CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203826Orig1s000

MEDICAL REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
HFD-170, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

CLINICAL REVIEW

Date:	December 10, 2012
To:	Christopher D. Breder, MD, PhD Clinical Leader, Anesthetics Drugs CDER/OND/DAAAP
From:	Leah H. Crisafi, MD Clinical Reviewer
Subject:	NDA 203826 Sponsor 11/28/2012 response to Complete Response
Date of Request:	December 5, 2012

Background

West-Ward Pharmaceutical Corp. (West-Ward) submitted a New Drug Application for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL, on December 27, 2011. On November 9, 2012, Food and Drug Administration issued a Complete Response Letter requesting that the sponsor conduct a pediatric study.

Discussion

The Sponsor agreed in the 11/28/2012 response to perform the study consistent with the description in the Complete Response. They wish to modify the suggested timeline because of a concern about patient recruitment, by adding "…an additional 6 months to the study and 2 months to subsequent final report submission date" and propose PMR milestones as follows:

PMR Final Protocol Submission:	December 20, 2013
PMR Study/Trial Completion Date:	December 20, 2016
PMR Final Report Submission Date:	February 23, 2017

This reviewer finds the addition of six months to the original proposed timeline for Study/Trial Completion acceptable. The original metric of six months post-study completion for the Final Report Submission Date shall be retained; The Sponsor may submit their final report earlier if able.

Recommendation

The Sponsor may be granted the requested additional six months for study completion, and the modified timeline follows:

PMR Final Protocol Submission:	December 20, 2013
PMR Study/Trial Completion Date:	December 20, 2016
PMR Final Report Submission Date:	May 23, 2017

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/s/

LEAH H CRISAFI
12/10/2012

CHRISTOPHER D BREDER
12/11/2012

Cross-Discipline Team Leader Review

Date	9/25//2012
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203826
Applicant	Westward Pharmaceuticals
Date of Submission	1/12/2012 (date received)
PDUFA Goal Date	11/9/2012
Proprietary Name / Established (USAN) names	Phenylephrine hydrochloride
Dosage forms / Strength	10 mg/mL injection
Proposed Indication(s)	Increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.
Recommended:	*Complete Response*

Purpose of Cross-Discipline Team Leader (CDTL) Review

The CDTL also conducted the primary medical review.

This review is based on the following reviews:

Chemistry, Manufacturing and: Wendy I. Wilson-Lee, Ph.D.
Pharmacology/Toxicology: Philip Gatti, Ph.D.
Clinical Pharmacology: Sudarshan Hariharan, Ph.D.
Statistics: Ququan Liu, M.D., M.S.
Microbiology: Erika Pfeiler, Ph.D.
SEALD: Eric Brodsky, M.d.
OSE: Eileen Wu, Pharm.D.
Clinical: Shari Targum, M.D.
ONDQA-Biopharmaceutics: Elsbeth Chikhale, Ph.D.

This NDA, a 505 (b) (2) application, used the published literature to support the nonclinical profile, clinical pharmacology, safety and efficacy; postmarketing databases, including AERS, provided an additional tool for assessing safety (albeit limited by the possibility of under-reporting). The primary medical and statistical reviews outlined a variety of general issues in considering publication evidence, such as lack of detail in publications; lack of access to protocols, datasets, or other source documents; selective reporting of outcomes; and potential publication bias. In addition, the phenylephrine publications were notable for their variable mention of a primary endpoint; presence of multiple endpoints without adjustment for multiplicity; and comparison with an unapproved agent (ephedrine).

Thus, the major issue in this application is whether there is enough evidence to conclude effectiveness, to adequately characterize the safety profile and to write instructions for use.

Cross Discipline Team Leader Review Template

1. Introduction

Phenylephrine is a selective alpha1-adrenergic receptor agonist that appears to have been available since before 1938; pre-1938 literature references to intravenous (IV) phenylephrine exist and IV phenylephrine never went through the formal NDA review process. In 2006, the Agency began an Unapproved Drugs Initiative and phenylephrine; consequently, the sponsor met with the Agency and submitted this application.

Dopamine hydrochloride (approved 1974) and norepinephrine bitartrate (approved 1950) comprise the other approved, marketed vasopressors. Norepinephrine bitartrate is indicated for blood pressure (BP) control in certain acute hypotensive states (with examples in the label).

2. Background

According to the current package insert, phenylephrine hydrochloride has been used as a vasopressor, mydriatic and decongestant. Phenylephrine has been administered via intravenous (continuous infusion or bolus injection), intramuscular and subcutaneous injection, as well as in oral, ophthalmic and intranasal dosage forms.

The proposed indication in this application is to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension, with the dose adjusted according to the pressor response.

Phenylephrine was approved in 1976 for nasal congestion. Phenylephrine is currently marketed as a decongestant: phenylephrine hydrochloride 1% nasal spray (OTC monograph) and in oral cold/cough combination products (e.g., Advil Congestion Relief, ibuprofen 200 mg/phenylephrine 10 mg film coated tablet, up to 6 tablets per day if needed).

The sponsor is seeking approval of phenylephrine hydrochloride injection under Section 505 (b) (2) of the Federal Food Drug and Cosmetic Act. The sponsor is relying on published literature, as of December, 2010 to support the nonclinical profile, clinical pharmacology, safety and efficacy of the product. In addition, the sponsor is relying on the long clinical use and two postmarketing databases (FDA and the sponsor's own database) to evaluate safety.

3. CMC/Device

The CMC reviewer, Wendy Wilson-Lee, Ph.D., has recommended a complete response action for phenylephrine hydrochloride injection based on outstanding CMC deficiencies. At the time of the CMC review (9/5/2012), the sponsor had not responded to an information request letter dated June 14, 2012. In addition, the Office of Compliance had not issued a final recommendation regarding manufacturing facilities associated with this application.

The CMC reviewer has not recommended Phase IV commitments.

- General product quality considerations
  Phenylephrine hydrochloride, USP, is an odorless, white, (b) (4) crystalline powder that is soluble in water and ethanol and not soluble in chloroform or ethyl ether. Phenylephrine is light sensitive.

  (b) (4) supplies drug substance that complies with the current USP monograph for phenylephrine hydrochloride. All drug substance analytical methods are appropriate and validated for their intended use except the HPLC method used for identification, assay, and related substances. The sponsor proposes a 24 month drug product expiry when stored in the commercial container closure at 25ºC, with excursions permitted to 15-30 ºC. However, the CMC reviewer was unable to provide a final determination of drug product expiry until the sponsor responds to their information request.

  The sponsor evaluated the drug substance impurity profile and showed no impurities above the ICH Q3A identification limit based on a maximum daily dose of 103.6 mg. However, the sponsor did not provide any information regarding potential heavy metals present in the drug substance.

  The sponsor also did not provide information on extractable/leachable results with the formulation. The sponsor did not identify or provide results for any container closure function tests. The sponsor also did not provide details regarding steps used to reprocess a batch or criteria used to evaluate reprocessed batches.

  The CMC reviewer found the sponsor's reliance on two different specification limits at release and during stability for testing pH, assay, phenylephrine content, individual unknown impurities and total impurities to be unacceptable. The sponsor was also asked to list all proposed regulatory drug product analytical procedures, providing a description for each method or, where appropriate, provide the compendial method reference.

- Facilities inspections have been completed and reviews of these facilities are pending.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer concluded that IV phenylephrine was approvable. No outstanding issues were identified.

- Of 624 articles, phenylephrine was shown to cause vasoconstriction and/or increased BP in 619 (99%).
- The dog model of endotoxic shock showed a high variability in the amount of endotoxin required and the dose of phenylephrine needed to raise BP to "normal."
- Two-year rat and mouse carcinogenicity studies were negative.

- Rabbit fetal growth retardation and onset of early labor was observed when phenylephrine was given in the last trimester (Shabanah 1969). However, human data do not show a safety signal when given to pregnant women at term.
- There is no mention of a renal safety signal.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology reviewed published literature in NDA 203826 and has recommended approval based on the BP effects observed with phenylephrine hydrochloride. No Phase 4 requirements or commitments are proposed at this time.

Per the OND-QA filing review, the to-be-marketed formulation was the same as the formulation in the pharmacokinetic (PK) studies. The evaluation and acceptability of human PK data were determined by the clinical pharmacology reviewer and the ONDQA-biopharmaceutics team was not further involved.

- When administered intravenously (IV), phenylephrine follows a bi-exponential decline with rapid distribution (α-phase half-life < 5 minutes) from the central compartment to peripheral tissues and end organs. The terminal elimination half-life is about an hour. Phenylephrine is extensively metabolized by the liver with only 12% of the dose excreted unchanged in the urine. Deamination by monoamino oxidase is the primary metabolic pathway, resulting in the formation of the major metabolite, m-hydroxymandelic acid. Following IV administration, phenylephrine and its metabolites are primarily eliminated in the urine.
- The metabolites of phenylephrine have been found to be inactive to α_1 and α_2-adrenergic receptors.
- Phenylephrine has a rapid onset of BP response (< 5 minutes). The time to offset the drug effect is about 10-15 minutes, which is consistent with the initial rapid elimination from the systemic circulation. Maintenance of BP around a target over a prolonged period of time will warrant an infusion regimen.
- There is a dose-dependent increase in the BP response of phenylephrine in healthy subjects. Heart rate decreases (reflex bradycardia) with increased exposures of phenylephrine (see Figure 4, clinical pharmacology review).
- There is an increase in BP with intravenous infusion or bolus of phenylephrine in subjects with hypotension due to induction of spinal anesthesia during elective cesarean delivery. However, the pharmacodynamic response to phenylephrine is dependent on the extent of spinal block.
    - Based on the available information, the reviewer felt that a reasonable initial IV bolus of phenylephrine was 100 μg, with additional rescue boluses depending on the extent of spinal block and BP target. Doses lower than 100 μg were often associated with higher frequencies of hypotensive episodes requiring more rescue boluses.
- Under general anesthesia, phenylephrine caused a dose-dependent increase in mean arterial pressure (MAP) in patients undergoing coronary artery bypass graft (CABG) surgery.

- A trend for dose-response of phenylephrine was observed in hypotensive or normotensive patients with sepsis.
- Based on the available information in septic patients, an initial infusion rate of 0.5-1.0 μg/kg/min is necessary to elicit a discernible pharmacologic response. The maximum mean change from baseline in MAP was achieved by a phenylephrine dose of about 6 μg/kg/min. Doses higher than 6 μg/kg/min might not result in significant incremental MAP response.
- Drug interactions with other co-medications primarily affect the pharmacodynamic response of phenylephrine. Specific dosing recommendations to address these interactions are not required because phenylephrine will be used in a controlled clinical setting and titrated to a target response.
- The phenylephrine dose-response curve is shifted to the left in end-stage renal disease patients and shifted to the right in liver cirrhosis patients, suggesting that lower and higher doses, respectively, might be required in these conditions (see Figure 6, clinical pharmacology review).

- Other notable issues (resolved or outstanding)

There was no TQT study in this application. However, I do not consider the lack of a TQT study to be an outstanding issue since IV phenylephrine is administered in a monitored environment.

6. Clinical Microbiology

The Clinical Microbiology reviewer recommended approval. The drug product undergoes (b) (4) sterilization and the manufacturing process was determined to be satisfactory.

7. Clinical/Statistical- Efficacy

- In this NDA, the basis of concluding efficacy came from published literature. The statistical reviewer felt that the clinical studies and meta-analyses from published literature seem to suggest that phenylephrine has an effect on increasing BP, measured by SBP, DBP, or MAP to treat or prevent hypotension in the acute peri-operative setting or septic shock. According to this reviewer, the evidence did not appear to be solid, because of potential biases from published literature and unresolved issues that hinder proper interpretation of the study results. Dr. Liu concluded that none of the literature studies "meet the standards for conducting a confirmatory trial. Statistical issues are found in all the studies, such as no predefined primary endpoint, no multiplicity adjustment, unapproved comparator as control, and selectively reporting study results." Therefore, results from the identified studies and analyses are considered to be exploratory.

- The CDTL concurs with the statistical reviewer concerning statistical issues in the publications. In addition, the reviewers were unable to review protocols, study reports,

datasets, case report forms, or visit sites. The reviewers were unable to determine what testing or design was pre-specified.

- However, evidence that phenylephrine raises BP is based on numerous studies (clinical and pre-clinical) with multiple investigators from various countries and conducted in various years.

- Most of the efficacy studies were carried out in the perioperative setting; a majority of the study population comprised low-risk (ASA 1 or 2) pregnant women with term singleton pregnancies. The studies in septic shock also showed an increase in MAP (and increase in systemic vascular resistance) with phenylephrine therapy (albeit vs. baseline). However, septic shock is a more complex disease state and there have been past concerns about effect of phenylephrine on regional hemodynamics.

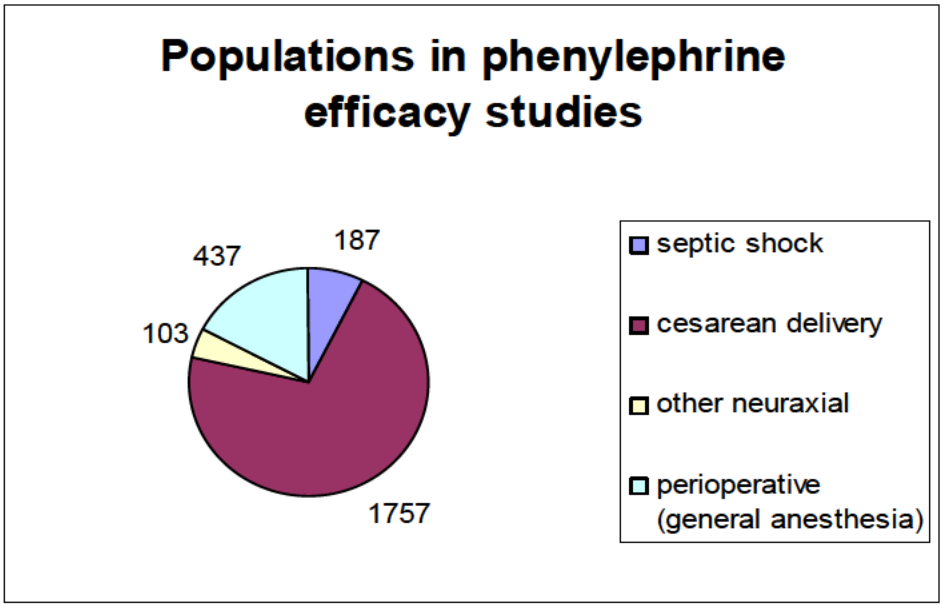

Figure 1. Phenylephrine efficacy study populations

- Other hemodynamic effects observed in the phenylephrine studies included:
  - Decreases in heart rate or an increase in the incidence of bradycardia
  - Decreases in cardiac output or cardiac index (except in the septic shock studies)
  - An increase in systemic vascular resistance
  - An increase in pulmonary vascular resistance

These hemodynamic effects are expected given the pharmacology of phenylephrine.

8. Safety

Three sources were used to evaluate safety: 1. published literature; 2. pharmacovigilance database; 3. FDA postmarketing databases (Spontaneous Reporting System: and Adverse Event Reporting System).

With the caveat of potential underreporting of adverse events, the most commonly reported events were largely consistent with the expected pharmacology of phenylephrine: bradycardia and hypertension. There were also cases of lung infiltration (see clinical review, Table 11); it is difficult to interpret whether these cases related to effects of phenylephrine (e.g., heart failure related to hypertension, increased wall stress, or decrease in cardiac output from phenylephrine) or coincident pneumonia with septic shock (unrelated to phenylephrine).

Maternal and fetal outcomes were evaluated in several studies, using maternal HR/BP monitoring, incidence of nausea/vomiting, and fetal Apgar scores and umbilical cord blood gases, and no signal of concern was observed. The study population comprised low-risk subjects, and the data do not include high-risk populations.

There were seven studies in septic shock and only two were prospective, randomized, double-blind, active-controlled studies. There has been concern regarding regional hemodynamic effects of phenylephrine (e.g., decreases in renal blood flow). In one of two randomized double-blind studies (Morelli), there was an imbalance unfavorable to phenylephrine in the number of patients requiring renal replacement therapy (7 vs. 2 on norepinephrine). In the other study (Jain), both groups (phenylephrine and norepinephrine-treated patients) showed a post-treatment increase in urine output; however, no assessment of renal function was reported.

It is difficult to interpret this renal finding in the Morelli publication. Laboratory tests were not consistently reported in the overall literature. A large renal signal, similar to what was observed with heart rate and BP changes, has not surfaced, at least in low-risk patients in the peri-operative setting. It is possible that phenylephrine effects on renal function have not been not fully characterized or those regional hemodynamic effects of phenylephrine are clinically apparent in only in patients with marginal renal function or that the Morelli publication is a solitary outlier.

9. Advisory Committee Meeting

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This NDA was presented at the Cardiovascular and Renal Products Advisory Committee meeting on September 13, 2012. Members of the panel included two anesthesiologists, two statisticians, several cardiologists, and consumer and industry representatives.

Discussion highlights included the following:

- Several committee members felt that a general indication for hypotension was too broad. One of the committee anesthesiologists voted for the sponsor's proposed indication.
- At least one panel member expressed concern about the small safety population in general anesthesia and septic shock studies.
- At least one panel member wanted to see additional data, pre-approval, in the septic shock setting.
- One panel anesthesiologist stated that the small study population in the general anesthesia and septic shock settings did not reflect clinical practice, where larger numbers have been treated with phenylephrine.
- At least one panel anesthesiologist commented on the medical need for phenylephrine in hypotensive patients undergoing general anesthesia, since phenylephrine, unlike norepinephrine or dopamine, can be administered through a peripheral IV line.
- Based on an informal "straw vote," the panel did not oppose approval of phenylephrine in neuraxial anesthesia during cesarean delivery.

The panel voted against a broad approval of phenylephrine in acute hypotension. Some panel members felt that phenylephrine should not be used in cardiogenic shock.

10. Pediatrics

To support use in pediatric patients, the sponsor submitted a case report (Kim), one retrospective cohort study (DiGennaro), one 4-patient open-label study in Tetralogy of Fallot (Shaddy) where no BP values were given, and an open-label tilt-table study in 16 patients with syncope (Strieper). Based on these studies, I do not feel that there is adequate data to characterize efficacy and safety in pediatric patients.

If phenylephrine is approved, the sponsor should characterize efficacy and dosing with a pharmacokinetic-pharmacodynamic study and evaluate safety in a pediatric population that would benefit from phenylephrine.

11. Other Relevant Regulatory Issues

OSE (Office of Surveillance and Epidemiology) has been asked to review medication errors in light of eight cases with Medication Error as the preferred term. Their review is pending.

12. Labeling

Labeling discussions are planned and proposed labeling will follow discussion with the review team. This reviewer would opt not to include specific clinical trials in the labeling, given the numerous statistical issues.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: The CDTL recommends a complete response pending resolution of CMC issues. If the CMC issues were to be resolved, then the CDTL would recommend approval to raise systolic BP in hypotension in peri-operative settings, including hypotension following neuraxial or general anesthesia. Based on the clinical and clinical pharmacology reviews, there is adequate information to conclude that phenylephrine increases BP. While there are data limitations and concerns about underreporting, the safety profile appears to be reasonably well characterized, at least in low-risk patients undergoing procedures. There is adequate information to guide instructions for use in adults.

- Risk Benefit Assessment

As mentioned in the primary clinical review, the benefit is maintenance of BP, which was present in all settings. In the neuraxial anesthesia setting, hypotension can result from loss of sympathetic tone. In several of the cesarean delivery studies, nausea and vomiting resulted from maternal hypotension. There is also a concern for fetal well-being in the face of maternal hypotension. IV phenylephrine appeared to maintain maternal BP, decreasing maternal nausea and vomiting. The side effects, bradycardia and hypertension, appeared to be easily monitored and treatable. Measures of neonatal outcome, such as umbilical cord blood gases and Apgar scores, provided reassurance regarding fetal safety.

In the general anesthesia, safety data were more limited. The available safety data did not raise concerns that would overcome phenylephrine's benefit. As mentioned in the advisory committee, phenylephrine has a benefit over dopamine or norepinephrine in its ability to be given via peripheral IV access; thus, there is an important role of phenylephrine in settings of acute hypotension where the main access is by peripheral IV line.

The CDTL does not recommend approval in pediatric patients or in general shock settings, due to insufficient data to adequately characterize dose-response or understand whether phenylephrine has a different safety profile in pediatric patients.

Septic shock represents a high cardiac output, low systemic vascular resistance state. Limited data in septic shock patients suggests improvement in BP and potential benefit with phenylephrine (e.g., decrease in serum lactate, improvement in measures of oxygen transport) but one study (Morelli) suggested an unfavorable imbalance in the need for renal replacement therapy. It is difficult to further interpret the limited data. In the primary medical review, this reviewer opted to not approve phenylephrine in septic shock until more renal safety data were obtained; this reviewer's position has not changed. However, an alternative approach would be approval in septic shock with a postmarketing requirement that the sponsor submit renal safety data, in order to better understand whether phenylephrine affects patients with renal dysfunction (with or without septic shock).

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None.

- Recommendation for other Postmarketing Requirements and Commitments

  1. A pediatric development program, under PREA, incorporating dose-response and pharmacokinetic sampling and safety in pediatric patients who require IV phenylephrine.
  2. If phenylephrine is approved in septic shock, the sponsor should submit renal safety data in this population, including phenylephrine effects in patients with baseline renal dysfunction.

- Recommended Comments to Applicant

If the Agency has received no response to the CMC information request letter by the PDUFA action date, a letter outlining outstanding CMC deficiencies and the lack of response should be sent to the Applicant.

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/s/

SHARI L TARGUM
09/25/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203826
Priority or Standard	Standard
Submit Date(s)	12/28/2011
Received Date(s)	1/12/2012
PDUFA Goal Date	11/9/2012
Division / Office	Division of Cardiovascular and Renal Products/ODE 1
Reviewer Name(s)	Shari Targum, M.D.
Review Completion Date	8/12/2012
Established Name	Phenylephrine hydrochloride
(Proposed) Trade Name	
Therapeutic Class	Vasoconstrictor, vasopressor
Applicant	West-Ward Pharmaceutical Corp.
Formulation(s)	Injection
Dosing Regimen	Intravenous infusion
Indication(s)	Increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension
Intended Population(s)	Adults, children

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHF	congestive heart failure
CO	cardiac output
CPB	cardiopulmonary bypass
CVP	central venous pressure
DBP	diastolic blood pressure
ED_{50}	dose eliciting 50% constriction, 50% of basal vein size, 50% of the maximum response
ED_{90}	90% effective dose
E_{max}	maximum dose response
ESRD	end-stage renal disease
FBF	forearm blood flow
FOI	Freedom of Information
FVR	forearm vascular resistance
IDDM	insulin-dependent diabetes mellitus
IM	intramuscular
IV	intravenous
LQTS	long QT syndrome
MAP	mean arterial pressure
OLT	orthotopic liver transplantation
QT_cd	corrected QT dispersion
QT_cmax	corrected maximum QTc interval
QTd	QT interval dispersion
QT_{end}	QT end interval
QTmax	maximal QT intervals
SBP	systolic blood pressure
SC	subcutaneous
SOC	system organ class
VF	ventricular fibrillation
VT	ventricular tachycardia

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of phenylephrine in the treatment of acute hypotension in patients undergoing neuraxial or general anesthesia. This reviewer does not recommend a broad approval in shock because of the limited data in septic shock and absence of data in other shock settings.

1.2 Risk Benefit Assessment

The evidence, based on known pharmacology and numerous clinical and preclinical studies, supports the conclusion that phenylephrine raises systolic and mean arterial blood pressure. Intravenous (IV) phenylephrine has a rapid onset of action (useful when rapid treatment is desirable), can be titrated toward a goal blood pressure, and has an effective duration of 15 minutes (also useful if one wishes to stop therapy).

Risks of hypotension are related to decreased perfusion (and consequent decreased delivery of oxygen and nutrients) to organs such as the brain, heart and kidney, with consequent organ dysfunction and/or damage.

Maintenance of adequate blood pressure (and adequate tissue perfusion and organ function) can then be considered a clinical benefit. One might then conclude that phenylephrine, by increasing or maintaining blood pressure (BP) and tissue perfusion, would benefit patients with symptomatic hypotension and shock, regardless of cause. One would then favor a broad approval for hypotension, regardless of cause. It would also be difficult to conduct placebo-controlled studies without rescue therapy, since there would be risks to leaving patients with symptomatic hypotension without treatment. Alternatively, one might conduct active-controlled studies against comparator agents. However, in the active-controlled setting, it is easier to interpret clinically meaningful evidence of superiority and more difficult to interpret “similarities” (or non-inferiority) in the absence of assay sensitivity and non-inferiority margins.

Half of the submitted publications were studies of low-risk parturients undergoing planned elective cesarean delivery under neuraxial anesthesia (also, most of the study population). Hypotension is a common complication of neuraxial anesthesia, with reported rates as high as 80%. The incidence of hypotension may vary depending on the definition used, position of the patient, rate of spinal anesthestic injection, IV fluid

loading, whether labor is occurring, or the presence of an associated morbidity such as pregnancy-induced hypertension.[1]

Risks of hypotension in pregnant women include maternal cerebral hypoperfusion, leading to nausea and vomiting, and reduced utero-placental blood flow, leading to fetal hypoxia and acidosis. One review and meta-analysis of 51 publications (over 400,000 infants) found an association between low arterial cord pH (<7.20) and neonatal outcomes (Malin 2010; Veeser 2012). Measures to prevent hypotension have included volume preloading, left uterine displacement, and the use of a pillow to support head/shoulders.

The phenylephrine studies in cesarean delivery consistently support phenylephrine's role in increasing blood pressure (BP) or maintaining BP within a specified goal. Even if one considers the review issues raised by the statistical reviewer, there was consistency of BP effect across studies, among different investigators in different countries, and over a span of decades. In addition, Ngan Kee (2004) reported a decrease in nausea/vomiting when systolic blood pressure (SBP) was maintained at baseline levels. The most common maternal side effects of phenylephrine were hypertension and bradycardia, which can be monitored and treated and are time-limited. The presence of such dose-related side effects would warrant frequent monitoring of vital signs and a low initial dosage with up-titration as needed. Of note, no neonatal safety signals (versus ephedrine, the main comparator) were observed (e.g., acid-base status or Apgar scores); however, no longer-term neonatal follow-up was reported. In general, the Apgar scores appeared high and seem reassuring.[2] Therefore, the benefit-risk assessment favors approval of phenylephrine in this population.

Increases in BP were also observed in the non-obstetric surgical population. In this setting, the main benefit of phenylephrine appears to be blood pressure support. There are little data to suggest other benefits and no outcome data relative to other agents. DiNardo reported better internal mammary artery (IMA) graft flow with norepinephrine and epinephrine than phenylephrine but did not correlate this finding to a clinical outcome. Goertz observed reduced indices of systolic function (e.g., median fractional area change and rate-corrected mean velocity of fiber shortening) and increased end-systolic wall stress in coronary artery disease (CAD) patients during phenylephrine treatment; phenylephrine did not impair left ventricular (LV) function in patients undergoing valve replacement. In one study (Smith), phenylephrine-treated patients had a 3-fold greater incidence of myocardial ischemia than patients with light anesthesia; however, this result seemed confounded by differences in anesthesia

[1] Source: Macarthur A and Riley ET. Obstetric anesthesia controversies: Vasopressor choice for postspinal hypotension during cesarean delivery.
[2] Guillon reported a lower range of 1-minute Apgar scores in neonates of women treated with phenylephrine in an unblinded study of QT/QTc intervals; the median one-minute Apgar score, however, was 9 and the mean umbilical artery and vein pH values were higher in the phenylephrine group compared to ephedrine (Guillon 2010).

regimen. The available data do not raise big safety concerns, especially with close vital sign monitoring and rapid offset of the drug after terminating therapy.

The benefits and risks of phenylephrine seems less clear-cut in the septic shock population, where there are fewer trials, mostly nonrandomized, in a sicker population with a high background mortality rate. Unlike the population undergoing cesarean delivery, there is a higher likelihood that phenylephrine will be administered for longer time periods (and longer exposure to phenylephrine) to maintain BP in patients with septic shock on multiple concomitant medications. Of the eight trials in septic shock, only two were randomized, double-blind active-controlled studies (Jain, Morelli) and we have no details related to protocols, study conduct, or analytic plan. While there may be a physiologic rationale to using phenylephrine in a population with low SVR, and phenylephrine appears to increase MAP and urine output, there are no data showing that phenylephrine significantly improves morbid-mortal outcomes versus comparators. It is not clear how to interpret "non-inferiority." On the other hand, the available data do not (thus far) suggest a gross adverse signal. One could make a case for approval in septic shock with a post-marketing commitment to collect renal safety/outcome data. However, while phenylephrine appears to increase blood pressure in septic shock, this reviewer would like to see more outcome and renal safety data in order to make an adequate benefit-risk assessment.

In the absence of data, can one extrapolate benefit and risk to other shock etiologies? Based on underlying physiology, phenylephrine might not be the drug of choice in a setting where patients present with high systemic vascular resistance and low cardiac output; one cannot state whether the benefits in this setting outweigh risks. One also cannot place phenylephrine in context, relative to another vasopressor such as dopamine. For these reasons, this reviewer would not recommend an approval in shock, regardless of etiology.

The three unblinded pediatric studies (Tetralogy of Fallot, neurocardiogenic syncope and a retrospective cohort study in traumatic brain injury) and one case report in pediatric patients are limited and do not allow an adequate characterization of benefit-risk or pharmacokinetic-pharmacodynamic relationship in children relative to adults. Based on these studies, this reviewer does not recommend approval in pediatric patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor should design a development program to characterize safety and the pharmacokinetic-pharmacodynamic relationship in pediatric patients.

If phenylephrine were to be approved for use in septic shock, this reviewer recommends that the sponsor evaluate renal safety.

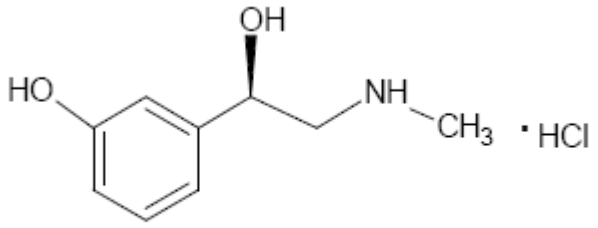
2 Introduction and Regulatory Background

Phenylephrine, available for several decades, has been used as a vasopressor, mydriatic and decongestant. Phenylephrine has been administered via intravenous (IV), intramuscular (IM), subcutaneous (SC) injections, as well as oral ophthalmic and intranasal dosage forms. The IV formulation has been commercially available for decades in the United States; an oral formulation was approved by the FDA in 1976 for nasal congestion and is available without a prescription in stores and pharmacies.

In June 2006, the Agency announced a new drug safety initiative to remove unapproved drugs from the market, including a final guidance entitled "Marketed Unapproved Drugs—Complicance Policy Guide (CPG)." Following the Agency initiative, the sponsor met with the Agency in 2010 (see section 2.5, below) and submitted this application for phenylephrine.

2.1 Product Information

Phenylephrine is a synthetic sympathomimetic agent and selective α_1 direct-acting adrenergic receptor agonist. Chemically, phenylephrine hydrochloride has the following structural formula:



Source: Ibrahim et al, 1983[1]

Figure 1. Phenylephrine chemical structure

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Vasopressors used in the United States

Drug	Indication
Dopamine HCl	Correction of hemodynamic imbalances present in the shock syndrome due to MI, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure
Norepinephrine bitartrate	1. For blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions). 2. As an adjunct in the treatment of cardiac arrest and profound hypotension
Metaraminol	Approved but not marketed; discontinued; no label available.
Vasopressin	Not approved for hypotension. Indicated for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.
Epinephrine	Epinephrine 1:10,000: May be of use in the treatment and prophylaxis of cardiac arrest due to various causes in the absence of ventricular fibrillation and attacks of transitory atrioventricular block with syncopal seizures but it is not used in cardiac failure or in hemorrhagic, traumatic or in cardiogenic shock. May be used to stimulate the heart in syncope due to complete heart block or carotid sinus hypersensitivity. Also used for resuscitation in cardiac arrest following anesthetic accidents. Seldom used as a vasopressor except in the treatment of anaphylactic shock and under certain conditions in insulin shock.
Ephedrine sulfate	Not approved for this indication. According to the label, “The drug has been used as a pressor agent, particularly during spinal anesthesia when hypotension frequently occurs.”

Source: www.dailymed.nlm.nih.gov/dailymed

2.3 Availability of Proposed Active Ingredient in the United States

Phenylephrine is available as an over-the-counter nasal decongestant, either alone or in combination with other cold remedies. Intravenous phenylephrine has been available and marketed for several decades.

In ophthalmology, ophthalmic preparations (e.g., drops) of phenylephrine or phenylephrine combinations have been used to induce mydriasis, as a provocative test for angle-closure glaucoma; and as an adjunct in the treatment of anterior uveitis and secondary glaucoma.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues with a pharmacologically similar drug, methoxamine (discontinued) included extravasation-related adverse events, bradycardia, hypertension, headache, anxiety, nausea and vomiting. Methoxamine was contraindicated in those with hypersensitivity to methoxamine and severe hypertension (source: www.medscape.com).

Other α_1-adrenergic receptor agonists include: mephentermine (discontinued), metaraminol (discontinued) and midodrine (Goodman and Gilman 2006). Hypertension has been a side effect common to these drugs. Mephentermine adverse effects were related to CNS simulation, excessive rises in blood pressure, and arrhythmias. (Goodman and Gilman 2006).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In a pre-IND meeting (November 10, 2010), the Agency felt that clinical literature alone will not support approval as treatment for any defined clinical condition because the studies do not appear to be adequately designed to demonstrate an improvement in clinical outcomes. However, the Agency believed that "it may be possible to approve phenylephrine to be marketed for increasing BP in certain hypotensive states." The sponsor could "make a case that increasing blood pressure in shock is desirable and so may serve as a basis for approval."

2.6 Other Relevant Background Information

Phenylephrine (PE) has been used in the treatment of hypotension/maintenance of BP during neuraxial/general anesthesia.
Besides use as a vasopressor, phenylephrine has been used to measure baroreflex sensitivity (BRS), with dosing via IV bolus to a blood pressure endpoint and measuring BRS. Other IV uses of phenylephrine have included: diagnostic evaluation of cardiac murmurs, treatment of paroxysmal supraventricular tachycardia, and treatment of priapism.

3 Ethics and Good Clinical Practices

This was a literature-based application. The studies in this submission were conducted in different countries and results were published over decades; this reviewer had no access to raw data or site inspections and cannot make any assertions or conclusions regarding integrity of an individual trial. There are no financial disclosures to review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review is pending and this reviewer is not aware of any outstanding issues that would preclude approval.

4.2 Clinical Microbiology

Erika Pfeiler, Ph.D., reviewed the sponsor's submission and recommended approval based on product quality microbiology. The drug product undergoes terminal moist heat sterilization and the manufacturing process was determined to be satisfactory. There were no deficiencies or Phase 4 commitments.

4.3 Preclinical Pharmacology/Toxicology

Philip J. Gatti, Ph.D. reviewed the sponsor's pharmacology/toxicology submission and recommended approval.

His conclusions were as follows:
1) Phenylephrine was shown not to produce arrhythmias in the rabbit and showed no direct effect on ventricular excitability or refractoriness in the dog
2) Large doses of PE can produce occasional extrasystoles and QT prolongation
3) PE does not produce torsades de pointes.
4) Of the 624 articles presenting the vasoconstriction/pressor action of PE, it effectively constricted blood vessels and/or raised blood pressure in 619 articles (99.2%).
5) PE has been shown to be neither mutagenic nor carcinogenic.
6) Preliminary results of the canine pharmacology study confirmed that IV PE increases blood pressure in a canine model of endotoxic shock. Pharmacokinetics (PK) of PE in dog closely mirrors PK in humans.

4.4 Clinical Pharmacology

The clinical pharmacology review is pending. Key findings include the following:

- There is an increase in blood pressure with intravenous infusion or bolus of phenylephrine in subjects with hypotension due to induction of spinal anesthesia during elective cesarean delivery. However, the pharmacodynamic (PD) response to phenylephrine is dependent on the extent of spinal block.

- There is a trend for dose-response of phenylephrine as seen in patients with sepsis who are hypotensive or normotensive.

- Drug interactions with other co-medications with phenylephrine exist, primarily affecting the pharmacodynamic response. Dosing recommendations to address these interactions are not warranted because phenylephrine will be used in a controlled clinical setting and titrated to a target response.

4.4.1 Mechanism of Action

Phenylephrine is a selective α_1-adrenergic receptor agonist. It increases mean arterial pressure (MAP) primarily through an increase in systemic vascular resistance. The elevated MAP, via baroreceptor reflexes, leads to bradycardia.

4.4.2 Pharmacodynamics

When phenylephrine was given to healthy volunteers as a short (5-20 minute) IV infusion (30 to 1500 µg/min) targeted to a 20-30 mm Hg systolic blood pressure (SBP) response, an increase in blood pressure (BP) and decrease in heart rate (HR) were observed with phenylephrine.

The onset of action is immediate and the offset around 10-15 minutes.

4.4.3 Pharmacokinetics

Pharmacokinetics for phenylephrine following intravenous administration follows a 2-compartment model with rapid distribution (α-phase half-life < 5 min) from the central compartment to peripheral tissues and end organs.

Phenylephrine is extensively metabolized by the liver, with only 12% of the dose excreted unchanged in the urine. The primary metabolic pathway is deamination by monoamine oxidase, forming the major metabolite, 3-hydroxymandelic acid. Following IV administration, phenylephrine and its metabolites are primarily eliminated in the urine. These metabolites are inactive to α1- and α2- adrenergic receptors.

5 Sources of Clinical Data

The source of clinical data was the published literature provided by the sponsor, based on the following:

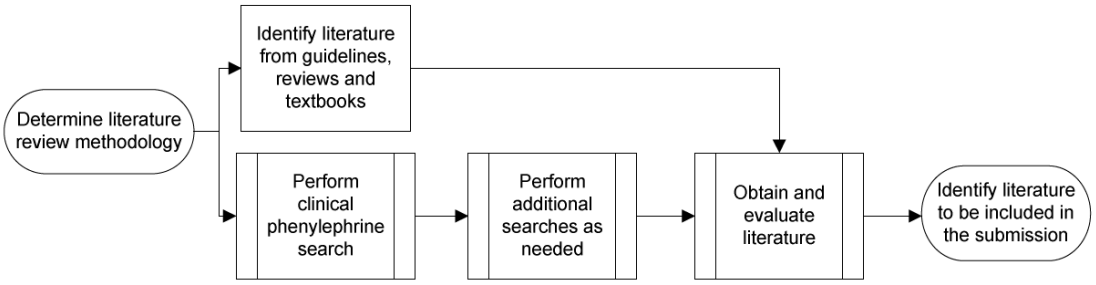


Table 2. Queried Databases

Database	Timeframe database covers	Content
BIOSIS Previews (Biological Abstracts)	1969-present	Life Sciences; including meeting literature
BIOSIS68	1945-1968	Life Sciences; including meeting literature
BIOSIS44	1926-1944	Life Sciences; including meeting literature
Chemical Abstracts Search	1907-present	All aspects of chemistry
Embase	1974-present	Clinical medicine
Embase73	1947-1973	Clinical medicine
Medline	1949-present	Clinical medicine
ToxFile	1900-present	Toxicology, pharmacology, biochemical & physiological effects of drugs & other chemicals

5.1 Tables of Studies/Clinical Trials

To support efficacy, the sponsor identified and submitted 50 publications; 42 were in the context of neuraxial or general anesthesia in adults undergoing surgery, and 8 reports, including one case report, in adults with septic shock. No data were submitted in patients with other types of shock. These 50 publications included a total of 2484 patients, of which 1682 were treated with phenylephrine.

Table 3. Summary of clinical efficacy studies

No. of Studies Presented	Section Supporting	Summary of Patient Population
42	Surgery settings	1538 patients treated perioperatively with phenylephrine; 29 studies used neuraxial blockage; 13 studies used general anesthesia
8	Use in setting of shock	144 patients in septic shock treated with phenylephrine to increase BP
4	Use in Pediatric Patients	68 children ages 7 days to 17 years were treated with phenylephrine to increase blood pressure for varied conditions

Table 4. Use during cesarean delivery under neuraxial anesthesia

Author	N	Dose (µg)	Administration	Control	Blinded
Ramanathan	74	100	IV bolus	Ephedrine	N
Moran	26	20-40	IV bolus	Ephedrine	N
Moran	60	80 initial; 40-80 repeat	IV bolus	Ephedrine	Y
Thomas	38	100	IV bolus	Ephedrine	Y
Ngan Kee 2008*	204	100	IV bolus	Ephedrine	Y
George	45	100 initial	IV bolus	None	Y
Gunda	100	100	IV bolus	Ephedrine	Y
Prakash	60	100	IV bolus	Ephedrine	Y
Alahuhta	17	100 + 16.6/min	IV bolus + infusion	Ephedrine	Y
Cooper	98	33/min	IV infusion	Ephedrine	Y
Ngan Kee 2004	74	100/min	IV infusion	None	N
Ngan Kee 2005	106	100/min	IV infusion	None	N
Cooper	54	33/min initial	IV infusion	Ephedrine	Y
Defossez	40	100 bolus or 20/min	IV bolus or infusion	Ephedrine	Y
Ngan Kee 2008**	122	0,25, 50, 75, 100/min	IV infusion	Ephedrine	Y
Tanaka	50	40 starting dose	IV bolus	None	Y
Adigun	62	100	IV bolus	Ephedrine	Y
Das Neves	120	0.15/kg/min or 50	IV infusion; bolus	None	N
Mohta	60	50/min	IV infusion	Mephentermine	Y
Sakuma	32	33/min	IV infusion	Ephedrine	N
Ngan Kee 2004	50	100	IV infusion	None: bolus vs. infusion	Y
Langesaeter	80	0.25/kg/min	IV infusion	Placebo	Y
Allen	101	25, 50, 75, 100	IV infusion	Placebo	Y
Ueyama	20	250 over 5 min	IV infusion	Ephedrine	Y
Saravanan	40	16.5/hr start	IV infusion	None	Y
Bjornestad	40	50 (x 3)	IV bolus	Elastic leg bandage	Y?

Total N 1773
* Nonelective Cesarean delivery
** combinations with ephedrine

Table 5. Use in patients undergoing non-obstetric surgical procedures under neuraxial anesthesia

Author	Surgical Procedure	Anesthesia Method	N[a]	Randomized	Dose/Mode of Administration	Control Group	Treatment of Hypotension	Prophylaxis Only	PE Rescue
Brooker[29]	Urologic; gynecologic, or orthopedic	Spinal	13	Yes (crossover)	40 µg IV bolus; 0.5 µg/kg/min IV CI (n = 13)	Epinephrine (n = 13)	Yes		NA
Cheng[31]	Inguinal hernia repair	Epidural	80	Yes	50 100, or 200 µg IV bolus (n = 20 for each dose)	Saline (n = 20)	No	Yes	no
Acosta[32]	Liver transplant	Spinal	10	No	0.1 mg IV bolus (n = 10)	NA	Yes		NA

Abbreviations: Random, randomized; IV, intravenous; CI, continuous infusion; NA, not applicable; PE, phenylephrine.
[a] Number of patients enrolled

Table 6. Use in patients undergoing CABG surgery under general anesthesia

Reference	N[a]	Dose	Mode of Admin.	Rand	Control Group
DiNardo[33]	28	0.87 µg/kg/min (mean) (n = 16)	IV CI	Yes	NE (n = 21); Eph (n = 19)
Baraka[34]	30	100 µg (n = 10)	IV bolus	Yes	NE (n = 10); Eph (n = 10)
Goertz[35]	24	1 µg/kg (n = 24)	IV bolus	Yes	NE (n = 24)
Nygren[36]	10	0.50 ± 0.22 µg/kg/min (n = 10)	IV CI	Yes	NE (n = 10)
Schwinn[37]	34	20 to 400 µg	IV bolus	No	—
Schwinn[39]	18	50, 100, 150, or 200 µg	IV bolus	No	—
Smith[38]	102	50 to 100 µg (n = 36)	IV bolus	No	—
Butterworth[40]	8	150, 300, and 450 ng/kg/min (n = 8)	IV CI	No	—
Lobato[41]	30	1 µg/kg per min (n = 30)	IV CI	No	—
Skubas[42]	30	Titrated; actual dose NR (n = 30)	IV CI	No	—

Abbreviations: CABG, cardiac bypass graft; Rand, randomized; CI, continuous infusion; Eph, ephedrine; IV, intravenous; NE, norepinephrine; NR, not reported; PE, phenylephrine
[a] Number of patients enrolled.

Table 7. Use in patients undergoing carotid endarterectomy under general anesthesia

Reference	N[a]	Dose	Mode of Admin	Rand	Control Group
Smith[61]	60	Titrated; actual dose NR (n = 29)	Bolus IV[b]	Yes	Anesthetic alone[c] (n = 31)
Mutch[44]	27	Titrated; actual dose NR (n = 27)	Bolus IV[b]	Yes	—
Borum[43]	36	0.2 µg/kg/min (n = 19)	IV CI	Yes[e]	PE + TEA pacing (n = 17)[d]

Abbreviations: CABG, cardiac bypass graft; CI, continuous infusion; CPB, cardiopulmonary bypass; Eph, ephedrine; IV, intravenous; NE, norepinephrine; NR, not reported; PE, phenylephrine; TEA, transesophageal atrial.
[a] Number of patients enrolled.
[b] Bolus injection; route to explicitly stated but presumed to be IV.
[c] Randomized treatments were high concentration anesthetic with PE and low concentration without phenylephrine.
[d] Patients were to receive phenylephrine as needed to increase blood pressure to 80% of baseline; the number of patients who actually received phenylephrine treatment was inferred to be 16 but the number was not explicitly stated in the manuscript.
[e] Patients were randomized with respect to anesthetic, but not with respect to phenylephrine.

Table 8. Use in septic shock

	Author	Population	Phenylephrine Administration	Rand	Control
Treatment	Morelli[45]	Hypotensive; N = 32 (21 M, 11 F) median age 70 yrs	IV CI; Titrated; mean at 12 h = 3 µg/kg/min (N = 16)	Yes	NE, titrated to effect (N = 16)
	Jain[46]	Hypotensive; N = 54 (28 M; 26 F); median age 44 yrs	IV CI; Titrated (range, 0.5-8.5 µg/kg/min) (N = 27)	Yes	NE, titrated to effect (N = 27)
	Gregory[47]	Hypotensive ; N = 13 (10 M, 3 F); mean age 67 yrs	IV CI; 0.5-9 µg/kg/min	No	NA
	Patel[48]	Hypotensive; N = 55 (age and sex NR)	IV CI; 25-200 µg/min, titrated to effect	No	NA
	Yamazaki[50]	Normotensive; N = 7 (all M); median age 65 yrs	IV CI; Titrated; approx 70 µg/min required	No	8 normotensive cardiac patients (6 M; 2 F); median age 68.5 y (same treatment as septic shock patients)
	Flancbaum[49]	Normotensive; N = 10 (9 M; 1 F); mean age 45 yrs	IV CI; Dose response: 0.5 to 8 µg/kg/min	No	NA
	Bonfiglio[62]	Hypotensive; N = 1 (1 M); age 75 yrs (Case report)	Initial bolus of 100 µg times 2; IV CI started at 40 µg/min and titrated to effect	No	NA
Prophylaxis	Morelli[51]	Normotensive; N = 15 (13 M, 2 F); mean age 60 yrs	IV CI; Titrated; mean 4.4 µg/kg/min	No	NA

Abbreviations: NA, not applicable; M, male; F, female; PE, phenylephrine; NE, norepinephrine; NR, not reported; M, male; F, female.

Pediatric population: To support use in pediatric patients, the sponsor submitted 3 studies (67 children), and 1 case report.

5.2 Review Strategy

This was a publication-based application, with the following limitations:
1. The reviewer was unable to scrutinize protocols or study conduct, perform additional analyses of the data, or inspect clinical sites.
2. The question of publication bias remains, since we do not know whether trials have been conducted and not published.
3. The publications in this application were not designed to support a claim. There were variable mentions of primary or secondary endpoints, sample size determination, dropouts, amendments, extent of follow-up, or extent of "prospectiveness" vs. post hoc. Definitions of hypotension and bradycardia, frequency of monitoring and criteria for intervention varied by study. Study and treatment duration were not always recorded.
4. In several studies, the study did not meet its primary endpoint: examples include two of three double-blind, placebo-controlled studies in this application (Allen, Cheng). Under the usual circumstances, the other endpoints would be deemed "exploratory."

The medical reviewer focused on randomized, double-blind, controlled studies. However, with the limitations of the publications, along with statistical issues, this review focused on BP/ other effects and evidence of benefit and risk.

5.3 Discussion of Individual Studies/Clinical Trials

Three studies were randomized, double-blind studies that compared phenylephrine to a placebo control (Allen, Langesaeter, Cheng) in the peri-operative setting. The sponsor submitted a fourth study (Ngan Kee 2004, n=50) as a placebo-controlled double-blind study; however, the statistical reviewer feels that this study evaluated different phenylephrine regimens. [3] Ngan Kee did not meet its primary endpoint. In addition, Cheng studied intrathecal administration of phenylephrine (e.g., a different route of administration than the proposed route of administration). Allen also did not meet its primary endpoint, which was the number of physician interventions (rather than the incidence of hypotension). .

Four randomized, double-blind, active-controlled studies (Gunda, Moran, Prakash, Thomas) evaluated patients undergoing elective C-section, and another study (Ngan Kee 2008) was a double-blind, active-controlled study evaluating patients undergoing non-elective C-section, using ephedrine as the active comparator.

[3] Given the risks, it would be unethical to leave hypotensive patients on placebo and this reviewer concurs with the idea of rescue therapy in these studies.

These studies did not stipulate whether they were designed to show "non-inferiority" (e.g., no discussion about margins). In addition, ephedrine is not approved for this indication, making comparisons more challenging.

The double-blind, placebo-controlled studies, under neuraxial anesthesia, will be discussed here. These studies also allowed for rescue doses of vasopressor (phenylephrine or ephedrine) in the event of hypotension.

1. Allen: This was a randomized, double-blind, placebo-controlled study of four fixed-dose phenylephrine infusions (thus PE 0, PE 25, PE 50, PE 75, PE 100) given immediately after spinal anesthesia. The study objective was to determine the prophylactic phenylephrine dose that, as a continuous fixed-rate infusion, is associated with the least number of interventions needed to maintain maternal SBP during cesarean delivery. Algorithms for SBP and HR management were specified in the publication; infusion was stopped (temporarily or permanently) when SBP > 20% baseline. The primary endpoint analyzed the number of interventions required to maintain SBP and treat bradycardia.

2. Langesaeter: This was a randomized, double-blind, placebo-controlled study comparing two different doses of bupivacaine for spinal anesthesia and effects of prophylactic intravenous phenylephrine infusion on hemodynamic variables. Study subjects were assigned to four groups, two different doses of bupivacaine and phenylephrine or placebo infusions.

3. Cheng: This was a placebo-controlled, double-blind study in adults undergoing inguinal herniorrhaphy under epidural anesthesia. The purpose of the study was to determine whether combining *epidural phenylephrine* with alkalinized lidocaine can reduce the incidence of hypotension. Patients were randomized to receive epidural alkalinized lidocaine with one of 4 doses of phenylephrine (0,50, 100, 200 µg). BP, HR and foot skin temperatures were measured 1 minute prior to the epidural and every 5 minutes thereafter for 1 hour. Rescue doses of ephedrine were administered in the event of hypotension.

Of the three studies in non-obstetric surgery under neuraxial anesthesia, two (Brooker and Cheng) were double-blind studies. Brooker evaluated 13 patients receiving sequential infusions of phenylephrine and epinephrine to manage hypotension after hyperbaric tetracaine spinal anesthesia. Cheng evaluated the hemodynamic effects of epidural alkalinized lidocaine with phenylephrine. Acosta was a non-randomized (open) study of phenylephrine effects in the treatment of postreperfusion syndrome (n=10) compared to patients without post-reperfusion syndrome (n=22).

All of the coronary artery bypass graft (CABG) studies were unblinded (or did not mention blinding). Four (or five including Schwinn, below) of the CABG studies were

randomized (DiNardo, Baraka, Goertz, Nygren). Of the randomized studies, only Goertz evaluated phenylephrine effects in hemodynamically unstable patients (e.g., patients with BP decreases during general anesthesia induction).

DiNardo measured the effect of vasoactive agents (including phenylephrine) on graft flows in hemodynamically stable patients post-cardiopulmonary bypass (CPB) (i.e., not for treatment or prophylaxis of hypotension). Baraka studied the hemodynamic effect of an IV bolus of norepinephrine, phenylephrine and epinephrine in 30 patients scheduled for CABG. Goertz (1993) studied the effect of phenylephrine bolus on left ventricular function in coronary artery disease (CAD) and aortic stenosis (AS) patients who, during anesthesia induction, developed mean arterial pressure more than 10% less than the lowest reading during the 24 hours prior to surgery during general anesthesia. Nygren studied the effect of phenylephrine on jeujuenal mucosal perfusion, gastric-arterial PCO2 gradient and the global splanchnic oxygen demand-supply relationship in 10 patients following uncomplicated CABG surgery.
Following induction, Schwinn (n=18) randomized patients to different IV boluses of phenylephrine and studied hemodynamic responses (this is listed as nonrandomized in the table below).

Schwinn (n=34) generated phenylephrine dose-response curves prior to induction; post-induction and prior to incision; and during CPB in patients with normal and impaired left ventricular (LV) function. Smith (n=102) evaluated the relationship between preoperative LV dysfunction and requirement for alpha-adrenoreceptor agonist drugs in CABG patients emerging from CPB. In this trial, IV phenylephrine boluses (50-100 µg) were administered alone or with inotropes to maintain mean arterial pressure (MAP) at preoperative levels (generally 60-80 mm Hg). Butterworth evaluated hemodynamic effects of 3 phenylephrine doses by infusion with and without calcium in 8 extubated intensive care unit (ICU) patients post-CABG surgery. Lobato (n=30) compared changes in internal mammary artery (IMA) graft flow post- CPB, with milrinone, nitroglycerin, a combination of milrinone and nitroglycerin, and after IV phenylephrine. Skubas measured the effect of phenylephrine on radial artery flow in 30 stable patients post-CPB.

None of the endarterectomy studies were blinded; however, phenylephrine was administered intraoperatively to maintain BP. Smith randomized 60 patients scheduled for elective carotid endarterectomy to different anesthesia regimens and studied effects on incidence of myocardial ischemia. Phenylephrine was not part of the randomization scheme, but appears to have been administered to patients in groups 2 and 4 to maintain BP (*this reviewer does not consider this study to be a randomized study of phenylephrine*). Mutch compared two anesthestic protocols for hemodynamic instability and administered phenylephrine infusions for post-induction MAP decreases > 20% below baseline. Borum (n=36) compared phenylephrine requirements in carotid endarterectomy patients randomized to phenylephrine infusion or phenylephrine infusion + transesophageal trial pacing to maintain SBP.

Of the septic shock studies, two (Morelli and Jain) were randomized and double-blind, using norepinephrine as a comparator. Jain evaluated multiple endpoints; Morelli studied effects on PDR (plasma disappearance rate of indocyanine green) and CBI (blood clearance of indocyanine green related to body surface area (CBI).

6 Review of Efficacy

6.1 Indication

The proposed indication is to increase blood pressure in acute hypotensive states, such as shock and in the perioperative setting.

6.1.1 Methods

The reviewer used the three double-blind, randomized, placebo-controlled studies as the highest level of evidence (Allen, Langesaeter, Cheng). The next level was double-blind, active-controlled superiority studies. Unblinded studies were assessed regarding endpoints and were used as supportive trials; however, the presence of measurement and other biases could not be excluded.

6.1.2 Demographics

There were four distinct populations in the efficacy studies:

1. Women of childbearing age undergoing cesarean delivery under neuraxial anesthesia (26 studies: n treated with phenylephrine approx. 1100);
2. Mostly male patients in a perioperative setting under neuraxial or general anesthesia, mean age 59 years and older (16 studies: n treated with phenylephrine approx. 300);
3. Sepsis/septic shock patients (n=144) majority male (n= 55 with unreported gender); mean age 45-67 years (7 studies and 1 case report).
4. Pediatric patients, gender mostly unreported, age 0-17 years (3 studies and 1 case report: n=68).

6.1.3 Subject Disposition

Few studies reported discontinuation rates and the sponsor did not conduct an analysis of pooled subjects who were discontinued from the trials. The most common reason for treatment discontinuation appeared to be hypertension.

6.1.4 Analysis of Primary Endpoint(s)

Evidence of Increase in BP:
In the double-blind, placebo-controlled studies (Allen, Langesaeter, Cheng), all in the context of neuraxial anesthesia, the primary endpoints were as follows:

1. Allen—number of physician interventions needed to maintain SBP within 20% of baseline and to treat bradycardia.
2. Langesaeter—group differences in SBP and cardiac output (CO)
3. Cheng-- incidence of hypotension

BP analyses were mostly focused on SBP (or, in the septic shock literature, MAP). Depending on the publication, endpoints included dose response, differences in BP, or outlier analyses (e.g., incidence of hypotension or hypertension, measured as SBP outside specified goals).

Many other studies either did not mention a primary endpoint, or contained a primary endpoint that differed from blood pressure measurement. Most of the studies were designed for titration to a BP goal and were not specifically designed (or mentioned) as BP "superiority studies."

Also, post-neuraxial BP monitoring varied among clinical trials (e.g., Cheng: every 5 minutes: Allen: every minute for the first 10 minutes and every 2.5 minutes thereafter; Langesaeter: continuous monitoring

While Allen failed to meet its primary endpoint (thus a "failed study"), one can observe a general increase in the incidence of hypertension, maximum percent change in SBP and bradycardia and decrease in hypotension, hypotensive episodes and minimum percent change in SBP with increasing doses of phenylephrine. The study design, with increasing fixed doses of phenylephrine and primary endpoint, number of interventions, reflects both treatment of hypotension as well as hypertension and bradycardia. In this study, the middle doses (PE 25, PE 50) show a higher proportion of patients within the target range.

Langesaeter and Cheng also did not meet BP endpoints, although one could argue that the trials were not adequately powered for BP effects; that the trials did not adequately control for multiplicity; that the analyses were not appropriate (e.g., Langesaeter not comparing apples to apples); or that the results (e.g., Cheng) involved a different route of administration and were confounded by ephedrine use.

However, taking into account these review issues, one can observe an increase in SBP after phenylephrine administration, that appears to be a consistent finding across studies, including Langeaeter and Cheng and including non-obstetric surgery and septic shock publications. Preclinical studies and pharmacological effects are consistent with evidence that phenylephrine raises BP.

The statistical review is pending; however, a preliminary recommendation is that the results from the identified studies and analyses are considered exploratory.

Other endpoints will be discussed in the next section.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1. Heart rate (HR):

A dose-related increase in the incidence of bradycardia can best be observed in Allen's study; other phenylephrine studies show consistent phenylephrine effects in decreasing heart rate.

6.1.5.2. Cardiac output (CO):

Cardiac output (CO) and/or cardiac index (CI) were not routinely measured in most cesarean delivery studies. Langesaeter found a decrease in CO in patients treated with phenylephrine vs. placebo. Other authors reporting a phenylephrine-related decrease in CO or CI included Ueyama; Brooker; Baraka, Nygren, DiNardo (reduction in CI). Taken together, the studies showed a consistent decrease in cardiac output with phenylephrine administration in the peri-operative setting.

In the septic shock population, Flancbaum, Morelli, Jain, Yamazaki and Gregory observed either no change or an increase in CO/CI.

6.1.5.3. Systemic vascular resistance (SVR):

In the septic shock studies, Morelli, Jain, Yamazaki, Gregory and Flancbaum observed an increase in systemic vascular resistance index (SVRI) with phenylephrine. Baraka and Nygren also observed an increase in SVR and SVRI, respectively, with phenylephrine. The increase in SVR and SVRI appears consistent with the known pharmacologic action of phenylephrine.

6.1.6 Other Endpoints

In the cesarean delivery trials, the following maternal/neonatal endpoints were measured:

6.1.6.1. Maternal nausea/vomiting:

The incidence of nausea/vomiting appeared to be mostly related to hypotension. In Allen, the incidence of nausea/vomiting decreased between placebo and highest doses. In the other trials, there did not appear to be a drug-related increase in nausea/vomiting with phenylephrine.

6.1.6.2. Fetal acidosis:

The incidence of fetal acidosis (umbilical artery pH < 7.2) appeared to be low; the median Apgar scores appeared to be high at 1 and 5 minutes in phenylephrine-treated neonates. The available data do not suggest a neonatal safety concern with phenylephrine treatment.

Prakash, Cooper (2002) are examples of double-blind, active controlled studies that met their primary fetal umbilical artery pH/fetal acidosis endpoints, showing a statistically significant higher umbilical artery pH in the phenylephrine group compared to ephedrine. It is not clear whether the difference in umbilical artery pH in these studies translates into a difference in neonatal outcomes. However, in another study (Cooper 2007) comparing phenylephrine and ephedrine, the study was stopped due to a high incidence of fetal acidosis in the ephedrine group.

Other trials such as Ngan Kee (2004) (IV phenylephrine infusion vs. saline infusion with rescue phenylephrine boluses) did not meet the umbilical cord pH primary endpoint, showing no statistically significant difference between treatments.

A limitation of these results is that no study reported a longer-term follow up (e.g., beyond hospital discharge).

Two meta-analyses in the literature showed less fetal acidosis with phenylephrine (at least no safety signal with regard to fetal acidosis).

Umbilical cord arterial pH:

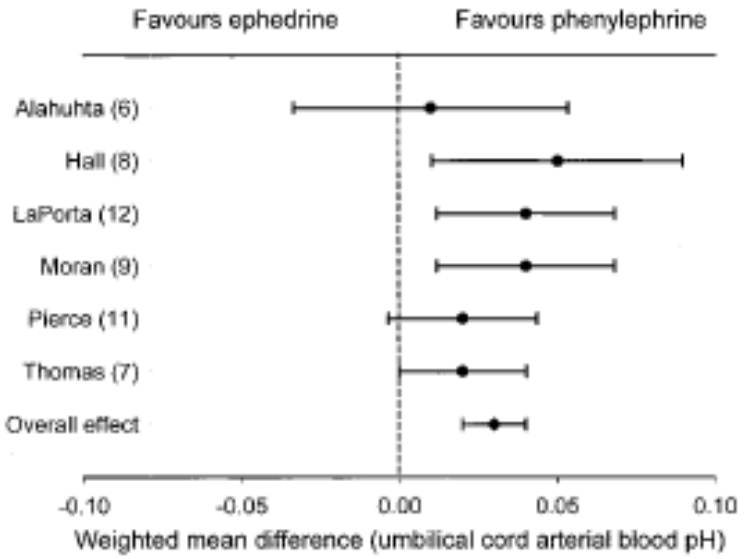


Figure 1. Meta-analysis of trials. The effect of phenylephrine versus ephedrine on umbilical cord arterial blood pH. Data are mean difference with 95% confidence intervals.

Figure 2. Umbilical cord pH: 6 trial meta-analysis: Lee (2002)

In this meta-analysis of 6 trials (Lee), there was one neonate with 1 minute Apgar score < 7 in the ephedrine group vs. 0 neonates in the phenylephrine group. At 5 minutes, no neonate in either group had an Apgar score < 7.

A more recent meta-analysis (Veeser 2012), including some (but not all) of the same trials, showed consistent results:

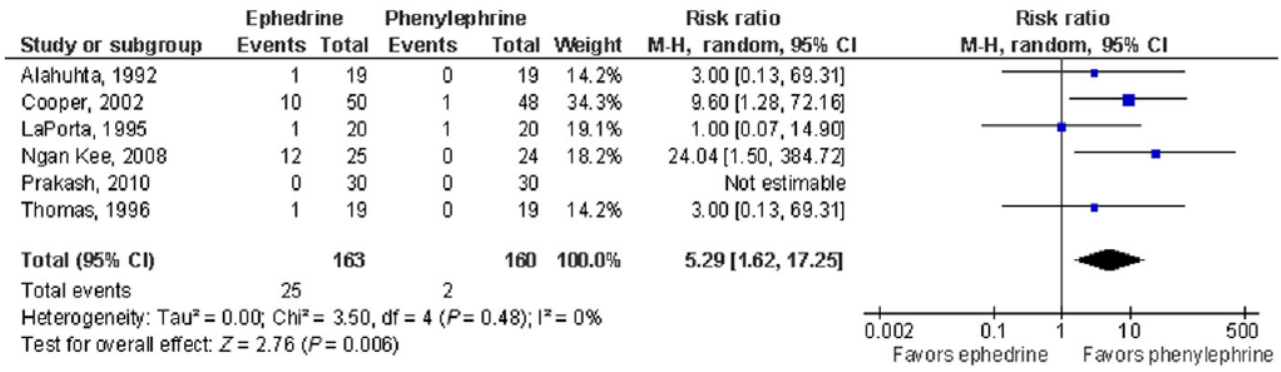


Fig. 2. Fetal acidosis after ephedrine or phenylephrine use. CI, confidence interval; M-H, Mantel-Haenszel Test.

Figure 3. Fetal acidosis: 6 trial meta-analysis: Veeser (2012)

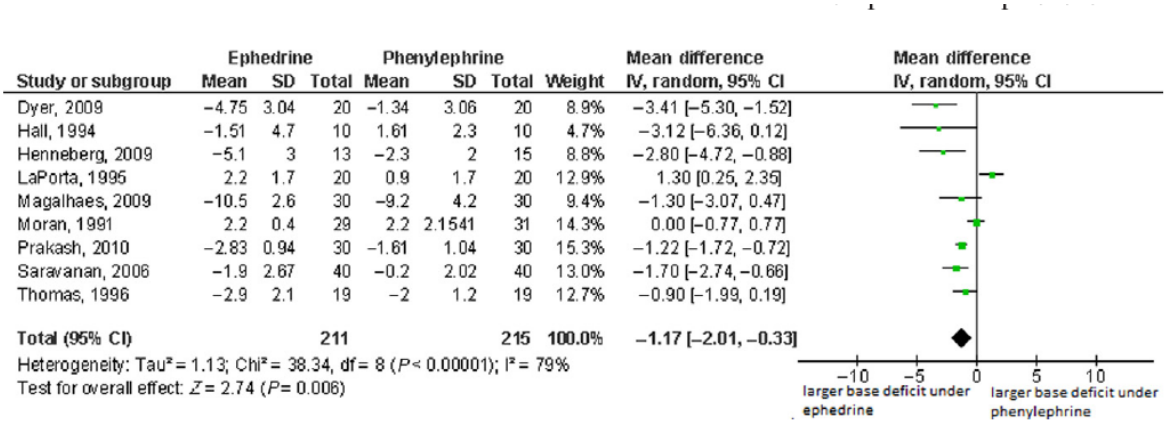


Fig. 3. Neonatal base excess after ephedrine or phenylephrine. CI, confidence interval; SD, standard deviation.

Figure 4. Neonatal base excess: 9 trial meta-analysis: Veeser (2012)

6.1.6.3. Apgar scores:

In general, median 1 and 5 minute Apgar scores in the publications appeared to be high in neonates of phenylephrine-treated patients.

A review of the literature revealed at least one meta-analysis of phenylephrine effects on Apgar scores, summarized below:

Table 1

Apgar data 1 and 5 min after delivery.

Author	APGAR 1 min			APGAR 5 min		
	Ephedrine	Phenylephrine	Significance	Ephedrine	Phenylephrine	Significance
Ayorinde et al., 2001[14]	9 (9–10)	9 (9–9)	n.s.	10 (9–10)	10 (9–10)	n.s.
Adigun et al., 2010[20*]	8.0 ± 0.56	9.0 ± 0.72	n.s.	10.0 ± 0.36	10.0 ± 0.17	n.s.
Guillon et al., 2010[23]	9 (5–10)	9 (2–10)	Not given	10 (8–10)	10 (5–10)	Not given
Prakash et al., 2010[24]	8 (7–9)	9 (8–9)	n.s.	9 (7–10)	10 (8–10)	n.s.
Dyer et al., 2009[4]	9 (7–10)	9 (6–9)	n.s.	9 (9–10)	9 (9–10)	n.s.
Hennebry et al., 2009[26]	9 (8–10)	9 (8–10)	Not given	10 (9–10)	9.5 (9–10)	Not given
Cooper et al., 2002[22]	9 (9–9)	9 (9–9)	n.s.	9 (9–10)	9 (9–9)	n.s.

Data are given as median and range.
*Standard deviation.
n.s., not significant.

Figure 5. Apgar scores: 7 trials: Veeser (2012)

The Apgar scores and neonatal acid-base and cord blood gas results appear to be reassuring regarding fetal/neonatal effects of phenylephrine.

6.1.7 Subpopulations

The submitted clinical trials did not distinguish between gender, age or race.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical pharmacology reviewer made the following suggestions:

- ❖ A reasonable initial starting dose when phenylephrine is administered in a bolus setting is 100 µg. Additional rescue boluses might be required depending on the extent of spinal block and the target maintenance of blood pressure.

- ❖ When administered as a continuous infusion, doses ranging from 12 µg/min to 50 µg/min seem to have a balance in reduction of hypotensive episodes and incidence of hypertension/bradycardia.

- There is a trend for dose-response of phenylephrine as seen in patients with sepsis who are hypotensive or normotensive.

  - ❖ An infusion rate of 0.5-1.0 µg/kg/min seems to be a reasonable initial phenylephrine dose to elicit a pharmacological response, followed by up titration to achieve the target mean arterial pressure. The mean response i.e., change from baseline in MAP maxes around 6 µg/kg/min, above which there might not be a significant incremental blood pressure response.

This reviewer concurs.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No systematic analysis has been provided to show persistence of efficacy and/or tolerance.

7 Review of Safety

7.1 Methods

The sources of safety information were: the available data from 1. Published literature; 2. The sponsor's Global Pharmcovigilance (PV) database (developed in 2005, AE through 4/25/2011), and 3. Freedom of Information (FOI) database.

The reviewer used the sponsor's literature review, supplemented by several Pubmed searches (terms included "phenylephrine;" "phenylephrine shock;" "phenylephrine blood pressure").

Because of the variable nature of adverse event reporting in the literature and spontaneous reporting, a quantitative assessment of event rates is limited. Furthermore, since phenylephrine has been used for decades, it is likely that adverse events and outcomes have been underreported. There is no adequate denominator to obtain incidence rates of adverse events.

As of April 25, 2011, the sponsor's PV database contained 146 cases where phenylephrine was reported as the suspect drug; of these cases, 2 had a fatal outcome and will be listed under Deaths (section 7.3.1).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 9. Phenylephrine postmarketing adverse event reports: Sponsor global PV database

Table 2.7.4.6-7.
Report Source—Phenylephrine Postmarketing Adverse Event Reports From West-Ward Global PV Database Through April 25, 2011

Report Source	
Literature	**Nonliterature**
(N = 107 cases, 135 adverse events)	(N = 39 cases, 68 adverse events)

Source: Module 5, Appendix 4

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In lieu of determining actual exposure to phenylephrine, the sponsor submitted marketing data for the past 2 years, in which the total units of phenylephrine sold have averaged about 2,000,000 units per quarter. However, this statistic may not reflect the actual amount or dosage used or numbers exposed (the drug could have been

purchased and remained on the shelf until its expiration date, and then discarded). Also, it is not clear whether use has been constant over time.

On the other hand, the 50 publications in the submission included 1682 subjects treated with phenylephrine. Since IV phenylephrine has been available for several decades and since there are likely to be additional publications in the "literature universe," not captured in this submission, it is likely that additional patients have been exposed to phenylephrine. For an acute treatment, over 1500 patients seem to be a reasonable exposure.

In a majority of the submitted publications, phenylephrine was used as intermittent IV boluses or short-term IV infusions. Phenylephrine doses were either given as fixed doses (Allen) with rescue boluses, prophylactic boluses or infusions with rescue boluses, or boluses/infusions titrated to achieve a blood pressure goal.

In many publications, the duration of phenylephrine exposure was not explicit. However, the induction of neuraxial anesthesia to delivery time appears to have been about 30 minutes.

The exposed patient populations include:
1. Low-risk pregnant women, with singleton pregnancies and elective cesarean delivery under neuraxial anesthesia (with one publication [Ngan Kee] that studied nonelective cesarean delivery). Other than anesthesia, these patients were on few or no concomitant medication. In addition, there is the potential of fetal exposure to phenylephrine.
2. Stable patients undergoing non-obstetric surgery, under neuraxial or general anesthesia
3. Septic shock patients, with a high background mortality rate and on multiple concomitant medications.

7.3 Major Safety Results

1. From the sponsor's global PV database (n = 146), 63.7% were female and 25.3% of patients had no reported or unknown gender; 83.6% of patients were of unknown age. The route of administration was recorded in 125/146 (86%) of patients; use was IV in 56% and intrathecal/epidural in 36% of patients. The most common indication was hypotension (61.6% of patients).

Table 10. Adverse events (serious and nonserious) by MedDRA SOC: sponsor PV database

Distribution of Adverse Events (Serious and Nonserious) by MedDRA SOC—Phenylephrine Postmarketing Adverse Event Reports From West-Ward Global PV Database Through April 25, 2011

MedDRA System Organ Class	No. (%) of Adverse Events (N = 203)
Injury, Poisoning and Procedural Complications	92 (45.3)
General Disorders and Administrative Site Conditions	32 (15.8)
Cardiac Disorders	31 (15.3)
Respiratory, Thoracic, and Mediastinal Disorders	12 (5.9)
Investigations	10 (4.9)
Vascular Disorders	9 (4.4)
Nervous System Disorders	8 (3.9)
Psychiatric Disorders	3 (1.5)
Skin and Subcutaneous Tissue Disorders	3 (1.5)
Musculoskeletal and Connective Tissue Disorders	2 (1.0)
Eye Disorders	1 (0.5)

Source: Module 5, Appendix 4

Table 11. Most frequently reported serious and nonserious adverse events: sponsor PV database

Most Frequently Reported (≥ 2 Adverse Event) Serious and Nonserious Adverse Events: Phenylephrine Postmarketing Adverse Event Reports From West-Ward Global PV Database Through April 25, 2011

MedDRA Preferred Term	No. (%) of Adverse Events (N = 203)
Drug exposure during pregnancy	85 (41.9)
Bradycardia	20 (9.9)
Drug ineffective	19 (9.4)
Lung infiltration	9 (4.4)
Blood lactic acid increased	3 (1.5)
Blood pressure decreased	3 (1.5)
Hypotension	3 (1.5)
Aphasia	2 (1.0)
Cardiac arrest	2 (1.0)
Chest pain	2 (1.0)
Hypertension	2 (1.0)
Medication error	2 (1.0)
Pulmonary edema	2 (1.0)
Ventricular extrasystoles	2 (1.0)

Source: Module 5, Appendix 4

Table 12. Adverse events by report source: sponsor PV database

Adverse Events by Report Source, Literature and Nonliterature Reports
Phenylephrine Postmarketing Adverse Event Reports
From West-Ward Global PV Database
Through April 25, 2011
146 Cases (203 Events)

MedDRA System Organ Class	No. (%) of Adverse Event		
	Literature (N = 135)	Nonliterature (N = 68)	Total (N = 203)
Cardiac Disorders	22	9	31 (15.3%)
Eye Disorders	1	0	1 (0.5%)
General Disorders and Administration Site Conditions	1	31	32 (15.8%)
Injury, Poisoning and Procedural Complications	85	7	92 (45.3%)
Investigations	5	5	10 (4.9%)
Musculoskeletal and Connective Tissue Disorders	1	1	2 (1.0%)
Nervous System Disorders	3	5	8 (3.9%)
Psychiatric Disorders	1	2	3 (1.5%)
Respiratory, Thoracic and Mediastinal Disorders	10	2	12 (5.9%)
Skin and Subcutaneous Tissue Disorders	0	3	3 (1.5%)
Vascular Disorders	6	3	9 (4.4%)

Source: Module 5, Appendix 4

2. Safety information from the published literature:

From the cesarean delivery publications, the most common maternal adverse events related to phenylephrine were bradycardia, reactive hypertension, and nausea and vomiting.

7.3.1 Deaths

Publications:

No deaths were reported in the publications of phenylephrine use in planned elective cesarean delivery. In addition, the authors of a Cochrane Collaboration review (Cyna 2009) of 75 trials (including phenylephrine trials) for preventing hypotension during spinal anesthesia for cesarean section noted that "mortality and serious morbidity in this population are rare…reviewed trials report no serious adverse events such as anaphylaxis, cerebral hemorrhage, or maternal death."

Since phenylephrine has been used in hypotension and shock, some deaths related to underlying disease and unrelated to phenylephrine may occur on or close to treatment. Therefore, comparison with background rates in matched populations would be important for detection of safety signals.

Cass (1979): published a case report of a 49 year-old women with hypertension treated with hydrochlorothiazide (50 mg BID) and propranolol (40 mg QID) who took 1 drop 10% phenylephrine solution in each eye during a routine ophthalmologic examination, developed sudden bitemporal pain and lost consciousness; angiography revealed a bleeding aneurysm of the anterior communicating artery and an intact aneurysm of the left middle cerebral artery. On autopsy, death was attributed to intracerebral hemorrhage due to a ruptured berry (congenital) aneurysm. The authors noted that the patient had received phenylephrine eye drops without incident on 2 previous occasions when she was not receiving other medications.

Sponsor's PV Database:
Of the 146 cases where phenylephrine was the suspect drug, there were two fatalities:

1.2010BH019785: 54 year-old male, 1 day s/p resuscitated cardiac arrest on phenylephrine to maintain BP. On 10/18/2009, the patient was on a phenylephrine drip via IVAC pump; on 10/19/2009 at 630, the pump displayed visual and aural alarms and delivery was interrupted for 1-2 minutes. During the swap out of the device, the patient became hypotensive and died following unsuccessful resuscitation efforts. The infusion pump was subsequently evaluated and no malfunction was found. Per the reporter, the death was possibly related to user error and the event was felt likely related to device failure.

2. 2011BH001296: 60 year-old female with acute on chronic liver failure and hypothermia, administered NaCl formula for irrigation via IV route of administration. Co-suspect medications given via same cannula included Prothromplex, ephedrine, esomeprazole, propofol, fentanyl, calcium chloride, phenylephrine and terlipressin. The patient died on an unknown date in the same month of the event, which was coded as "Blister; Incorrect route of drug administration; Necrosis; Rash Erythematous." The cause of death was unknown.

Another fatal event concerned an overdose related to medical error (see Overdose section).

FOI Adverse events:
The sponsor also submitted 33 FOI cases of fatal adverse events where phenylephrine was a suspect cause. Most of these cases involved multiple medications and are difficult to interpret without a patient medical history and narrative.

Table 13. Summary of FOI fatal adverse event reports

Table 2.7.4.6-19.
Summary of FOI Adverse Event Reports
Data Through December 2010
Number of Adverse Events Reports With a Fatal Outcome With Phenylephrine As a Suspect or Concomitant Drug by Route of Administration

Total No. of Reports With Fatal Outcome	**218**
Concomitant	**185**
IV or injectable	15
Not IV	2
Unknown or blank	168
Suspect	**33**
IV or injectable	9
Neuraxial	1
Not IV	11
Unknown or blank	12

Source: Module 5, Appendix 5

7.3.2 Nonfatal Serious Adverse Events

A review of literature reports and the FOI and sponsor databases revealed the following adverse events (not in the order of frequency): pulmonary edema; hypertension; ventricular arrhythmias; MI; stroke; anginal pain; bradycardia; tachycardia; and cardiac arrest. Some, but not all, of these events may be related to hypertension and bradycardia, known side effects of phenylephrine.

Hartstein and Deutsch (1991; ref 154) described a 26 year-old man with sarcoidosis who developed noncardiogenic pulmonary edema (with HR 110 bpm and BP 160/110 mm Hg) after receiving ophthalmic tropicamide, atropine and phenylephrine (10%, 100 mcL). Prior to the episode, he had a 10-day history of photophobia and fatigue, and fevers for several months.

Greger (1998: ref 155) described a 2 month-old female infant undergoing elective congenital cataract extraction who developed hypertension, LV failure and pulmonary edema after phenylephrine administration. The infant apparently received a high dose of PE and cyclopentolate, which was administered at a higher than recommended dose for infants. Of note, the infant developed ventricular couplets, decrease in HR to 95 bpm from initial HR 140 bpm, “off-scale” increase in BP, and decrease in peripheral oxygen saturation to 80%, with pale white skin indicating peripheral vasoconstriction. The infant was stabilized, moved to ICU, and subsequently had an uneventful hospital course.

The sponsor reports systemic absorption from ophthalmologic use of PE; rare AEs have included acute hypertension, ventricular arrhythmias, MI and stroke.

From the FOI serious cardiac adverse events (through December 2010), the most common events with IV administration (N=261 total) or all routes of administration (N=1586 total) were bradycardia and tachycardia, followed by cardiac arrest.

7.3.3 Dropouts and/or Discontinuations

It is difficult to estimate the percentage of patients who have been discontinued from phenylephrine. Reasons for discontinuation have included: reactive hypertension (e.g., Das Neves 2010) and anginal pain in CAD patients (Chapsal 1982; Heper 2004).

7.3.4 Significant Adverse Events

1. Cardiovascular Adverse Events:

Bradycardia:
The most commonly reported cardiovascular adverse event appears to be bradycardia, likely due to baroreceptor-mediated vagal stimulation and consistent with the pharmacological effect of phenylephrine.

Publications:
Criteria for bradycardia definition and need for interventions varied by publication. As an example, Thomas set the criteria for intervention as maternal HR < 60 bpm, regardless of blood pressure; Prakash set criteria for intervention when the maternal HR < 60 bpm and SBP below baseline or HR < 45 bpm regardless of BP.

Bradycardia or decreases in mean heart rates associated with phenylephrine were observed in several publications, including: Allen (dose-related), Langesaeter, Ngan Kee (2004; n=50), Gunda, Moran (1991), Prakash, Thomas, Alahuhta, Mohta, Adigun, George, Brooker, Baraka, Nygren and Flancbaum. Morelli observed statistically significant heart rate decreases from baseline in phenylephrine and norepinephrine-treated patients

In several other publications, bradycardia or heart rate decreases was not observed or not mentioned (e.g., Skubas, Gregory).

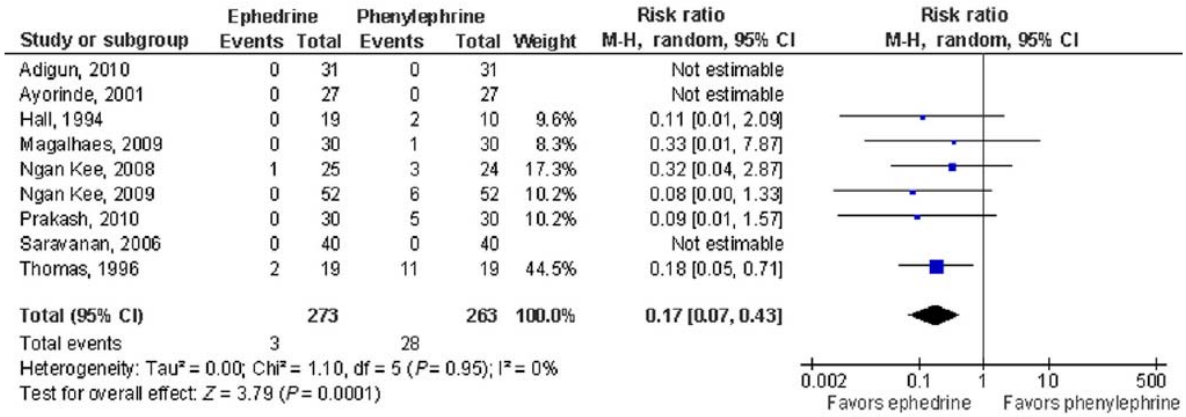


Fig. 4. Maternal bradycardia after ephedrine or phenylephrine. CI, confidence interval.

Figure 6. Maternal bradycardia: 9 trials (Veeser 2012)

Allen (2010): 3 patients experienced adverse events, two after receiving glycopyrrolate for bradycardia: 1 patient developed headache (2010BH030923) and 1 patient developed neck pain (2010BH030924) after receiving glycopyrrolate for bradycardia (glycopyrrolate 0.4 mg given if HR < 50 bpm). The third patient developed ventricular bigeminy which was unassociated with instability and which resolved spontaneously in the postanesthesia care unit (2010BH030920). It is difficult to determine whether these adverse events occurred as a consequence of bradycardia, abnormal blood pressure (or due to glycopyrrolate).

Allen reported glycopyrrolate use in 1 patient in placebo; 3 patients in the PE 25 group; 2 patients in the PE 75 group and 7 patients in the PE 100 group.

One 44 year-old man (2010BH010581) with intermittent bradycardia (50-60 bpm) before treatment developed persistent bradycardia (HR low 40s) with junctional escape rhythms; the patient was asymptomatic and had no ECG changes or cardiac enzyme elevation suggesting ischemia or injury. Two hours after discontinuing phenylephrine, his HR rose to 60-70 bpm.

Brooker (1995, 1997) compared double-blind, randomized crossover epinephrine vs. phenylephrine for treating hypotension after hyperbaric tetracaine spinal anesthesia for elective surgery. In 13 of 14 patients who completed the study, phenylephrine was associated with a decrease in HR ($p < 0.001$) and CO ($p < 0.003$) but no change in stroke volume (SV). At the end of the study 2 patients required rescue therapy for severe bradycardia (HR < 45 bpm) after phenylephrine infusion; in one case, epinephrine was given after the patient failed to respond to 0.8 mg atropine.
The sponsor's database revealed the following cardiovascular adverse events:

Table 14. Cardiovascular adverse events by route of administration

Cardiovascular Adverse Events by Route of Administration

Route of Administration	MedDRA SOC Preferred Term	No. (%) of Adverse Events
Intravenous N = 118 (58.1 %) adverse events	**Cardiac Disorders**	
	Bradycardia	14
	Atrioventricular block second degree	1
	Cardiac arrest	1
	Cardio-respiratory arrest	1
	Ventricular extrasystoles	1
	Investigations	
	Electrocardiogram T wave inversion	1
Neuraxial N = 38 (18.7%) adverse events	**Cardiac Disorders**	
	Bradycardia	2
Non-IV route of administration N = 8 (3.9 %) adverse events	**Cardiac Disorders**	
	Fetal heart rate disorder	1
Unknown route of administration N = 39 (19.2 %) adverse events	**Cardiac Disorders**	
	Bradycardia	4
	Cardiac Arrest	1
	Myocardial infarction	1
	Myocardial ischaemia	1
	Stress cardiomyopathy	1
	Tachycardia	1
	Ventricular extrasystoles	1

Other cardiovascular adverse events included the following:

Stress-induced cardiomyopathy/blindness/seizure-like activity:
Crimi (2008) reported a 31 year-old woman with acute, reversible, stress-induced cardiomyopathy (SIC) associated with cesarean delivery at 40 weeks gestation using spinal anesthesia; a prior cesarean delivery with epidural anesthesia was uneventful. She underwent spinal anesthesia with bupivacaine (12 mg); fentanyl (10 mcg) and morphine (0.2 mg). Fifteen minutes after spinal anesthesia initiation, she developed sinus bradycardia (36 bpm) and hypotension (60/40 mm Hg) and was treated with volume, multiple doses of IV ephedrine (total 50 mg) and two doses of IV atropine (total 0.8 mg), resulting in sinus tachycardia (150 bpm). Because of chest heaviness, she was given an infusion of phenylephrine to maintain BP. Ten minutes after atropine administration, the patient complained of blindness and felt anxious and developed seizure-like activity; she was intubated with propofol 150 mg and succinylcholine 100 mg. Surgery lasted about 1 hour; she was then extubated but required additional phenylephrine and oxygen. An echocardiogram 8 hours after surgery revealed moderated LV systolic dysfunction with isolated midventricle impairment, SIC was

diagnosed, the patient was treated with metoprolol and lisinopril, her symptoms subsided and a repeat echocardiogram showed complete normalization of her LV function. She was asymptomatic at her 4-week follow-up.

Ischemia/angina/Injury biomarker/T wave inversions:
One patient with a normal ECG (2010BH010529) developed a one-time elevation of CPK-MB to 3%, which normalized after phenylephrine was discontinued; rechallenge with phenylephrine did not elicit ECG changes or repeat rise in CPK-MB.

One patient (2010BH010580) developed T wave inversions, without chest pain or CPK-MB elevations, which resolved after 4 days.

Weber and Chapsal (1982) studied the effect of phenylephrine (50-200 mcg/min infusion, with infusion rate doubling Q5min) in 10 mean with chronic stable angina and angiographically-documented CAD and 10 age-matched controls. In 2 CAD patients, anginal pain occurred when the infusion rate reached 200 mcg/min (group mean SBP 190 mm Hg), requiring drug discontinuation.

Del Greco (1999): case report, 54 year-old man undergoing HR variability analysis and baroreflex sensitivity (BRS) evaluation with PE 8 days post-subacute anterior MI. After the two boluses of phenylephrine 2 mcg/kg), with each bolus separated by 10 minutes, the patient developed mild chest pain with ST elevations (angiography revealed 9% proximal LAD stenosis, total occlusion of the left circumflex artery and diffuse RCA narrowing).

Comment: There appears to be evidence that phenylephrine may induce or exacerbate ischemia/injury in some patients, especially those with underlying CAD and phenylephrine-induced hypertension (especially with SBP in 190 mm Hg range; see Weber and Chapsal, above). Frequent monitoring of vital signs and lower SBP criteria for stopping phenylephrine should be considered in this population.

Interstitial infiltrates/pulmonary edema:
Nine patients had mild-moderate interstitial infiltrates at some time during the study; 4 of these patients had transient increases in oxygen requirements and required at least one occasion of diuresis.

Kademani (2004) described pulmonary edema, acute hypertension and myocardial ischemia in a 16 year-old girl undergoing ENT surgery, given topical phenylephrine (0.5%, one spray each naris), topical lidocaine, IV glycopyrrolate 0.5 mg preinduction, prophylactic IV cefazolin 1 mg and dexamethasone 10 mg; induction with IV propofol 120 mg, lidocaine 80 mg and fentanyl 100 µg was uneventful. Muscle relaxation was achieved with IV vecuronium 5 mg. Ten minutes after the start of the procedure, the

patient became acutely hypertensive (200/100 mm Hg) with sinus tachycardia (150 bpm); CXR revealed pulmonary edema; postoperative troponin was 3.5 (normal < 0.3) and peaked at 8.3; echocardiogram the next day showed a global decrease in LV contractility with EF 35%. The authors related events to an idiosyncratic response to medications and suggested that the combination of α-agonists and the anticholinergic glycopyrrolate can, in some individuals, lead to hypertension and tachycardia.

Ashchi (1995) presented a case report of a 23 year-old woman given topical cocaine solution as a local anesthetic for elective ENT procedure who developed a non-Q wave MI with cardiac arrest and stunned myocardium after receiving topical phenylephrine packing for decongestion. The woman had no history of cardiac disease or risk factors. *Reviewer comment: cocaine use has been independently associated with MI and arrhythmias.*

Spontaneous reports:

1. There were 3 cases reported from 1 episode of drug exposure during pregnancy, including: reduction in fetal heart rate; and chest discomfort, resolving with nitroglycerin, after the mother was inadvertently given phenylephrine instead of metoclopramide;
2. One patient who developed PVCs after an unspecified perioperative dose of phenylephrine (no other information available);
3. A surgical patient who was administered phenylephrine for hypotension and developed bradycardia and continued drop in BP, but responded to ephedrine.

Arrhythmias:

Morelli (2008) reported tachyarrhythmias in 2/16 patients treated with phenylephrine. Also, there have been literature and spontaneous reports (see above) of ventricular ectopy following phenylephrine treatment (not clear if these events are related to effects on blood pressure or heart rate, or independent of those effects).

There have also been literature reports of AV block or heart block, presumably related to vagal effects.

One author reported the following adverse events when injecting phenylephrine 0.25 mg IV in mitral stenosis (n=12): bradycardia and increase in BP occurred, A2-OS interval was prolonged; mild transient headaches and slight nervousness (2), precordial discomfort (1), transient runs of bigeminy (3) and runs of AV junctional escape (1); these events least 3-4 minutes and resolved spontaneously (Tavel: 1969).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common maternal adverse events in studies of phenylephrine use in cesarean delivery under spinal or epidural anesthesia were bradycardia, reactive hypertension, nausea and vomiting. Other adverse events included: pruritis (Langesaeter); several studies included neonatal outcomes (Apgar scores, acid-base profiles) and did not reveal safety concerns related to phenylephrine.

Renal effects:
According to one publication, phenylephrine "constricts the renal vasculature and decreases renal blood flow….However, it increases renal perfusion pressure in the presence of a low SVR…." (Lee WCL 2004).

The studies in women undergoing cesarean delivery did not report effects on renal function. In one randomized, unblinded study of patients with abnormal renal function undergoing cardiopulmonary bypass (n=17), there was no evidence of worsening renal function with phenylephrine (dose titrated to maintain MAP $\geq$ 70 mm Hg) compared to dopamine 20 µg/kg/min infusion.

In the septic shock studies, Gregory (retrospective) observed stable creatinine concentrations and increases in urine output in 13 patients with septic shock. However, Morelli, in a crossover study of phenylephrine and norepinephrine in septic shock, observed renal function impairment with phenylephrine. In a randomized, double-blind study of phenylephrine vs. norepinephrine in 32 septic shock patients, with pressor doses titrated to maintain MAP at 70 $\pm$ 5 mm Hg, urine output and creatinine clearance were similar between the two groups when measured over a 12 hour period (Morelli). However, Morelli also reported more phenylephrine-treated patients (n=7) than norepinephrine-treated patients (n=2) requiring renal replacement therapy at the end of the 12-hour study period (p=NS). In a 52-patient double-blind study (phenylephrine vs. norepinephrine) in hypotensive septic shock patients (with background dopamine therapy), both groups showed increased urine output with pressor therapy (Jain).

There is one case report (below, Pediatric section) of a 29 day-old infant developing renal failure following indomethacin (for patent ductus arteriosus) and ophthalmic tropicamide-phenylephrine. It is not clear whether the indomethacin was a confounding factor, since indomethacin can cause renal impairment and renal failure.

In summary, the available data do not suggest a large renal safety signal, especially with short-term phenylephrine therapy. However, the effects of phenylephrine on renal

function, particularly in septic shock, are incompletely characterized and further safety data (e.g., measures of renal function and adverse events) should be collected.

Splanchnic Effects:
According to Beale (2004), sepsis is associated with redistribution of flow away from the intestinal mucosa, resulting in mucosal hypoxia. A variety of mechanisms, including a higher critical oxygen delivery threshold, constriction of the villus arteriole and reduced villus tip capillary density, impede oxygen transfer and increase the likelihood of gut ischemia, which increases intestinal permeability and translocation of bacteria or cytokines.

Nygren (2006), in a study of 10 patients post-CABG, suggested that phenylephrine reduced splanchnic blood flow but did not affect jejeunal mucosal perfusion. In a study of septic shock patients (n=32), Morelli (2008) did not observed a difference between phenylephrine and norepinephrine in indirect measures of regional hemodynamics, acid-base results, or arterial lactate concentrations.

Therefore, a theoretical concern remains, particularly in the septic shock population. There are limited available data with conflicting results. The two double-blind studies (Morelli and Jain), with the largest sample, do not suggest a safety signal.

Respiratory adverse events:
There was one spontaneous report of bronchospasm with phenylephrine administration in a patient admitted with MI (no other information was provided).

Nervous system disorders:
There was a spontaneous report of aphasia, delirium, mental status changes and transient unresponsiveness in a 69 year-old man with a history of cerebrovascular disease, diabetes, metabolic syndrome, chronic renal failure,

1. Non-Hodgkin's lymphoma requiring radiation and chemotherapy. His symptoms occurred 1 day post-CABG and he received multiple perioperative medications, including IV clevidipine, fentanyl, midazolam, nicardipine (for hypertension), phenylephrine 50 µg/min (21:20 to 22:00), and IV epinephrine 2 mg/min (for hypotension). A CT scan suggested a prior parietal infarct with no evidence of a new infarct (*not stated whether contrast was used*). Treatment and follow-up not specified.
2. Davila (2008) described a subarachnoid hemorrhage in a 23 year-old African-American male with sickle cell disease and a history of past sickle crises who presented with priapism, treated with phenylephrine solution, who developed a sudden headache with hypertension (180/100 mm Hg).

3. There was a spontaneous report of peripheral neuropathy in an 85 year-old man on lorazepam (primary suspect drug) and multiple other medications, including a combination oral formulation containing phenylephrine, guanifesin, chlorpheniramine and dextromethorphan.

Vascular disorders:

1. Taussig (1984) described a case of prostatic infarction in a 59 year-old man after CABG, who was given norepinephrine (and phenylephrine (60 µg/min) for postoperative hypotension associated with widening of the mediastinum. He remained hypotensive (SBP 50 mm Hg) and went back to surgery where a clot on the left ventricle and a small bloody pericardial effusion were noted. Attempts to remove the Foley catheter up to 96 hours postsurgery were unsuccessful; 8 days post-CABG, the patient underwent cystoscopy and transurethral prostatic resection, with extensive prostatic infarction found. A second case in this series was reported where the patient received norepinephrine.
2. Kalajian (2007) described a case of microvascular occlusion syndrome in a 45 year-old man with Factor V Leiden mutation, diabetes, hypertension, and family history of pulmonary embolism. This patient underwent C5-C6 vertebrectomy with postoperative spinal degeneration and infectious complications and required ventilatory and vasopressors support over a 4-month period. After a 2-day course of phenylephrine, discontinued one day prior to onset, he developed a purple discoloration of his hands and feet, with well-demarcated purpura, several tense hemorrhagic bullae on his hands and feet, and retiform purpura on his thighs and antecubital fossae; MOS was diagnosed and almost completely resolved 2 weeks later with no long-term sequelae.
3. From the UK regulatory authority came a spontaneous report of toxic endothelial cell destruction syndrome (20040300224) in an 83 year-old man with psoriasis receiving multiple medications, including calcipotriol, cyclopentolate, phenylephrine 2.5%, chloramphenicol, benoxinate, Alcon BSS (balanced salt solution), flurbiprofen, lidocaine, Betadine, hyaluronate and betamethasone..

Skin:

There was one spontaneous report of extravasation (HQ3788416NOV2000) from a health care professional. Also, Youmans (1949) reported tingling or skin coolness associated with phenylephrine use in treatment of supraventricular tachycardia.

Injury and procedure:

The most common injury and procedure complications were medication errors and drug exposure during pregnancy. Most of the use in pregnancy involved studies of women undergoing elective and nonelective cesarean delivery under spinal or epidural anesthesia.

7.4.2 Laboratory Findings

There were no reports of laboratory findings.

7.4.3 Vital Signs

Vital signs include BP increases (and increased hypertension) and HR decreases (with increased incidence of bradycardia). There were no additional data regarding vital signs.

7.4.4 Electrocardiograms (ECGs)

This submission did not include a thorough QT study.

One review article (Drake E; 2007) suggested avoidance of phenylephrine in congenital long QT syndrome, stating that phenylephrine increases the QTc in healthy volunteers and patients with LQTS but does not change the QT dispersion. Sun (1998) also found that phenylephrine infusion (1.4 mcg/kg/min) did not affect QT dispersion in 16 symptomatic LQTS patients and 9 healthy controls undergoing electrophysiologic studies.

Yee (2000) studied 10 normal male volunteers in a placebo-controlled, single-blind, crossover study with six 10-minute infusions 0.2 to 3.6 mcg/kg/min phenylephrine which stopped when 35-40 mm Hg increase in SBP was achieved. QTcmax by linear correction was increased but QTcmax (via Bazett) was unchanged with phenylephrine.

Magnano (2004) found no increase in QTcB in 25 healthy subjects given up to 1.6 µg/kg/min phenylephrine.

In the long history of phenylephrine use, there is no large signal for phenylephrine-related QT prolongation (other than what would be expected from the known pharmacologic effects of the drug). Intravenous phenylephrine has a rapid onset and peak and is usually administered in monitored setting; therefore, any arrhythmias of concern could be promptly diagnosed and treated.

7.5 Other Safety Explorations

As noted by the clinical pharmacology reviewer, there are reports of drug interactions with phenylephrine. However, phenylephrine will be administered in a monitored environment and titrated to a BP goal. Thus, dosing recommendations are not warranted.

7.6 Additional Safety Evaluations

Genetic toxicology studies, conducted by NTP, included: Ames test (negative with and without metabolic activation); mouse lymphoma (equivocal at toxic doses); CHO (chromosome aberration negative but induced sister chromatid exchanges without metabolic activation); and rat micronucleus (negative).

7.6.1 Human Carcinogenicity

Two-year mouse and rat carcinogenicity studies were negative.

7.6.2 Human Reproduction and Pregnancy Data

One Seg. II study reported rabbit fetal growth retardation and onset of early labor when given in the last trimester (Shabanah 1969).

In addition, the sponsor submitted 26 studies of phenylephrine use following neuraxial anesthesia in cesarean delivery and there appears to be no fetal/neonatal safety signal in terms of fetal acidosis, Apgar scores, or neonatal neurobehavioral development. However, no longer-term follow-up data on infants are available.

7.6.3 Pediatrics and Assessment of Effects on Growth

The submission included 2 pediatric literature case reports involving IV phenylephrine:

1. Carter (1987): 6 year-old female who underwent cardiac surgery with uneventful anesthesia and CPB, except for large doses of phenylephrine (67 mg) required to maintain perfusion pressure. Fixed and dilated pupils were observed at the end of the operation, despite satisfactory BP, HR and ABG. She was given dexamethasone 4 mg IV and transferred to the ICU out of concern for an intracerebral event. However, she made a full recovery with no neurologic deficit and her pupils returned to normal size 4 hours after surgery. The authors believed that the large dose of phenylephrine led to mydriasis.
2. Vutskits (2006): 40 month-old female with aromatic L-amino acid decarboxylase deficiency who developed severe bradycardia (HR <40 bpm) after phenylephrine 1 µg/kg for hypotension following anesthesia.

Additional case reports with ophthalmic phenylephrine formulations included the following (hypertension and bradycardia appear prominent):

1. Fraunfelder (2002): 11 cases following single exposure to topical ocular phenylephrine, including 2 pediatric cases: 4.5 year old with hypertension (BP 220/140 mm Hg) and pulmonary edema 1 day after exposure; and 1 year-old

patient with SBP > 200 mm Hg 3-4 minutes after exposure to 10% phenylephrine in pledget form.
2. Borromeo-McGrail (1973): Increases in SBP and DBP and eyelid skin blanching in 20 healthy low birth weight neonates (12 under double-blind conditions, 8 under open-label) receiving 10% phenylephrine ophthalmic solution.
3. Lees (1981): Increased BP following pupillary dilatation with 2.5% phenylephrine in 7 preterm infants.
4. Calenda (2007): Acute hypertension (SBP 180 mm Hg) without change in HR in a 5 month-old female who received 6 drops of 5% phenylephrine to the eye (indication or timing relative to surgery not stated) during general anesthesia for treatment of a posterior synechia; BP resolved without complication.
5. Vaughan (1973): Hypertension (BP increasing from 100/60 to 190/120 mm Hg) and ventricular ectopy/runs of ventricular tachycardia in an 8 year-old male who received 4-5 drops 10% ophthalmic phenylephrine applied to the eye because of conjunctival bleeding during surgery, under general anesthesia, for strabismus.
6. Van der Spek (1987): Cyanosis, HR slowing (60 bpm), ST depressions and T wave changes, and unobtainable BP in a 3 week-old female undergoing cataract extraction under general anesthesia who received halothane and phenylephrine eye drops.

There were additional reports of hypertension/arrhythmia and pulmonary edema in an 8 year-old male (Baldwin 2002); and reports of pulmonary edema (Varshney 2009; Greher 1998) in pediatric patients given ophthalmic phenylephrine.

Other adverse events related to ophthalmic administration of phenylephrine include:
1. Three cases of transient abdominal ileus causing abdominal distension in infants given cyclopentalate-phenylephrine combination to achieve mydriasis (Lim 2003; Sarici 2001).
2. One 29 day-old low birth weight female who received indomethacin IV for patent ductus arteriosus in addition to mydriatic eyedrops containing tropicamide and phenylephrine and subsequently developed renal failure (Shinomiya 2003).

Other than maternal-fetal exposure during pregnancy, the sponsor did not identify additional pediatric cases in the sponsor's Global PV database.

In the FDA FOI database, of 1595 unique cases, 896 provided age information; of these, 63 reported the age as 18 years or less. Phenylephrine was a suspect drug in 29 of these cases; in 7 cases, a route of administration was not reported. The 22 remaining cases involved ophthalmic (8), oral (6), nasal (2), transplacental (2), inhalational (1), or subconjunctival (1) routes of exposure. Of the 29 cases, adverse event terms reported in more than 1 case included pulmonary edema (5), apnea (2), and bradycardia (2).

There are no available data concerning effects of phenylephrine on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Drug Abuse Potential:
The sponsor submitted a case report (Snow 1980) of a 26 year-old patient "addicted" to phenylephrine nasal spray. There are no data concerning drug abuse potential related to the use of IV phenylephrine.

Withdrawal/rebound:
There have been no reports of withdrawal or rebound effects and the available data (stopping an infusion) do not suggest the presence of rebound.

Overdose:
From the literature:
1. An early report of IV phenylephrine overdose concerned a 59 year-old white female being treated for paroxysmal supraventricular tachycardia, who developed headache, neck pain, agitation, asystole, numerous PVCs superimposed on a sinus bradycardia after 10 mg inadvertently given, reverting to NSR after 10 minutes (Youmans, 1949).

2. Another case followed phenylephrine 0.5% instillation via dropper into the nasal cavity of a 4 year-old to stop bleeding following an outpatient adenoidectomy. Following phenylephrine instillation, severe hypertension occurred and a beta-blocker was injected intravenously. The heart rate dropped and the patient went into cardiac arrest with unsuccessful resuscitation.

There were three spontaneous reports of overdose related to medical error:

3. From the US Pharmacopeia Institute for Safe Medicine Practices (20050200038): This underage (unknown age) male patient undergoing elective orthopedic surgery was administered phenylephrine 10 mg IV (10 mg/mL vial) instead of metoclopramide 10 mg (10 mg/2 mL). The patient developed erratic vital signs, pulmonary edema and cardiac arrest, requiring resuscitation, cardioversion and mechanical ventilation. The patient was successfully resuscitated, underwent orthopedic surgery and was discharged from the hospital without complication. A second, similar report (possible duplicate) was submitted by a pharmacist (2008BH009197).

4. Spontaneous report 2008BH001154: A 65 year-old Asian male underwent elective angioplasty for stent placement of 90% right coronary artery stenosis. The physician ordered 50 µg phenylephrine during the stent placement; however, the nurse mistakenly gave 10 mg phenylephrine. Immediately, the patient's SBP increased to 265 mm Hg; he became hot and developed chest pain, diaphoresis, weakness and inability to talk. According to the report, no treatment was provided, the patient's BP dropped to 80 mm

Hg (not clear whether SBP, MAP or DBP), other symptoms resolved, a phenylephrine drip was started to maintain SBP around 108 mm Hg and the patient recovered.

5. Spontaneous report 2011BH002961: 78 year-old female with stage 4 laryngeal cancer received phenylephrine 0.5 mg IV in the ICU. However, the nurse thought that she was administering hydromorphone injection for pain; the hydromorphone "scanned" as phenylephrine. Shortly after phenylephrine administration, the patient's BP "went down" and the patient didn't require any more pain relief until the next hydromorphone dose was due. (*Reviewer: it is difficult know which drug was mislabeled, the phenylephrine or hydromorphone).*

Reviewer: The Office of Surveillance and Epidemiology will review phenylephrine for the potential for medical errors.

8 Postmarket Experience

The FDA Office of Surveillance and Epidemiology (OSE) reviewed the Adverse Event Reporting System (AERS) and Empirica Signal databases for an overview of postmarketing adverse event reporting with intravenous phenylephrine.

OSE searched the AERS database up to June 8, 2012 and the Empirica Signal database up to May 29, 2012.

As of June 8, 2012, the AERS database contained 148 reports (crude counts) with IV phenylephrine use; 78 reports had serious outcomes that included death (n=20), life-threatening (n=24) and hospitalization (n=34).

The most common 5 preferred terms were hypotension, hypertension, pulmonary edema, drug ineffective, and lung infiltration. These adverse event terms appear to be consistent with the known safety profile and the reports in the submission.

Table 15. Adverse Event Reporting System crude counts of preferred terms for IV phenylephrine

Table 3. AERS Crude Counts of Preferred Terms (N>3) for IV Phenylephrine as of June 8, 2012			
System Organ Class	Preferred Term	Count of PT (N)	Appears in the Draft Label *
Vascular disorders	Hypotension	20	
Vascular disorders	Hypertension	19	yes
Respiratory, thoracic and mediastinal disorders	Pulmonary edema	13	yes
General disorders and administration site conditions	Drug ineffective	9	
Respiratory, thoracic and mediastinal disorders	Lung infiltration	9	
Cardiac disorders	Bradycardia	8	yes
Injury, poisoning and procedural complications	Medication error	8	
Cardiac disorders	Tachycardia	8	yes (ventricular tachycardia)
Metabolism and nutrition disorders	Acidosis	7	
Nervous system disorders	Aphasia	7	
Nervous system disorders	Encephalopathy	6	
Metabolism and nutrition disorders	Lactic acidosis	6	
Injury, poisoning and procedural complications	Maternal exposure during pregnancy	6	
Cardiac disorders	Stress cardiomyopathy	6	
Cardiac disorders	Cardiac arrest	5	
Cardiac disorders	Cardio-respiratory arrest	5	
Psychiatric disorders	Delirium	5	
Investigations	Electrocardiogram ST segment elevation	5	yes (arrhythmia)
Injury, poisoning and procedural complications	Incorrect route of drug administration	5	
Skin and subcutaneous tissue disorders	Blister	4	
General disorders and administration	Necrosis	5	yes (skin necrosis)

Table 3. AERS Crude Counts of Preferred Terms (N>3) for IV Phenylephrine as of June 8, 2012			
System Organ Class	Preferred Term	Count of PT (N)	Appears in the Draft Label *
site conditions			
Cardiac disorders	Sinus tachycardia	5	yes (arrhythmia)
Nervous system disorders	Syncope	5	
Nervous system disorders	Unresponsive to stimuli	5	
Cardiac disorders	Arteriospasm coronary	4	
Psychiatric disorders	Anxiety	4	
Psychiatric disorders	Confusional state	4	
Investigations	Blood lactic acid increased	4	
Investigations	Blood pressure decreased	4	
Investigations	Blood pressure systolic increased	4	yes (hypertension)
Investigations	Electrocardiogram T wave inversion	4	yes (arrhythmia)
Skin and subcutaneous tissue disorders	Hyperhidrosis	4	
Metabolism and nutrition disorders	Metabolic acidosis	4	
Psychiatric disorders	Mental status changes	4	
Gastrointestinal disorders	Nausea	4	yes
Injury, poisoning and procedural complications	Procedural complication	4	
Metabolism and nutrition disorders	Propofol infusion syndrome	4	
Skin and subcutaneous tissue disorders	Rash erythematous	4	
Renal and urinary disorders	Renal failure	4	
* Phenylephrine Hydrochloride Injection, USP, 1 mg/mL, 1 mL Vial. 1.14.1.3 Draft Package Insert – Content of Labeling. Annotated Draft Phenylephrine Hydrochloride Injection, USP Package Insert in PLR format. West-Ward Pharmaceuticals, Eatontown, NJ 07724 USA. Revised December 2011 April, 2012. Amendment (Information request) submitted to FDA April 27, 2012.			

Table 16. Data mining drug-event pairs with IV phenylephrine

Table 4. Drug Event Pairs with IV Phenylephrine with EB05 scores >2 as of May 29, 2012				
Preferred term	**N**	**EB05**	**EBGM**	**EB95**
Stress cardiomyopathy	5	36.391	83.546	170.198
Propofol infusion syndrome	4	24.215	67.822	157.182
Lung infiltration	9	23.911	43.328	73.569
Acidosis	7	21.237	42.365	77.532
Lactic acidosis	6	5.643	24.463	52.716

Note: EB05 and EB95 refer to confidence intervals. The preferred term "stress cardiomyopathy" has small N and wide confidence intervals. Hypotension, hypertension, tachycardia and bradycardia are preferred terms with larger N and narrower confidence intervals.

Table 4. Drug Event Pairs with IV Phenylephrine with EB05 scores >2 as of May 29, 2012				
Preferred term	**N**	**EB05**	**EBGM**	**EB95**
Arteriospasm coronary	4	5.512	43.211	110.662
Hypertension	16	4.169	7.086	12.701
Electrocardiogram T wave inversion	4	3.841	34.902	96.146
Hypotension	16	3.682	5.89	9.86
Pulmonary oedema	8	3.511	10.146	24.852
Electrocardiogram ST segment elevation	4	3.056	27.259	83.025
Tachycardia	10	2.781	4.993	9.625
Bradycardia	8	2.754	5.96	15.818
Blood pressure systolic increased	4	2.06	12.323	54.177

9 Appendices

9.1 Literature Review/References

9.1.1. Elective cesarean delivery

9.1.1.1. Allen (2010)

Objective: Determine the dose of a prophylactic fixed rate continuous infusion of phenylephrine that is associated with the least number of physician interventions needed to maintain maternal SBP within set criteria during cesarean delivery under spinal anesthesia.

Population: ASA class I and II pregnant women > 36 weeks gestation undergoing elective caesarian under spinal anesthesia.

Exclusions: In labor; BMI > 45 kg/m2; type I DM; hypertensive or cardiac disease; history of MAOI use; fetus with severe congenital abnormalities; subjects in other anesthesia drug studies.

Dosing: Patients were randomly allocated to 2 liter fluid load with either placebo (PE 0) or phenylephrine infusion 25 (PE 25), 50 (PE 50), 75 (PE 75) or 100 (PE 100) µg/min immediately after spinal anesthesia. Maternal SBP was maintained within target range using a predetermined algorithm; however, PE was given as a fixed dose infusion and not titrated to BP response. To maintain blinding, infusions were prepared in identical syringes by a physician not involved in the study. Study drug infusion was started at 60 mL/hr; study drug was infused until 10 minutes after delivery, after which the study ended and further management was at the discretion of the anesthesiologist.

Spinal anesthesia: fentanyl 15 µg, morphine 150 µg and 0.75% hyperbaric bupivacaine 1.6 mL.

Methods: Noninvasive BP readings were taken every minute for the first 10 minutes after spinal injection and every 2.5 minutes thereafter. Cephalad extent of sensory block at 5, 10 and 20 minutes after spinal anesthetic was recorded using loss of pinprick sensation. Patients were asked to rate nausea severity at 5, 10 and 15 minutes post-spinal injection using an 11-point scale (0=no nausea, 11=worst possible nausea) and asked to report nausea occurring at any other time. Intraoperative nausea was treated with ondansetron 4 mg IV; intraoperative nausea occurring immediately before or after 20% decrease in material SBP was recorded as hypotension-induced nausea or

vomiting. Apgar scores (1 and 5 minutes) were recorded. Umbilical cord blood samples were collected for umbilical artery and vein blood gases.

Primary endpoint: The primary endpoint was the number of physician interventions needed to maintain SBP within 20% of baseline and to treat bradycardia.

Physician interventions were triggered by: decrease in SBP > 20% of baseline or SBP < 90 mm Hg (treated by 100 µg bolus of phenylephrine); increase in SBP to > 20% of baseline (stopping study drug infusion, restarting only when SBP decreased to below upper limit of target range, 20% above baseline); HR < 50 bpm (glycopyrrolate 0.4 mg administered). If study drug infusion had to be stopped on 3 occasions, it was discontinued permanently and BP was maintained with phenylephrine boluses for the remainder of the study.

Statistical analysis: The sample size was based on 18 patients/group, providing an 80% power to detect a mean difference of 2.5 interventions in pairwise comparisons at $\alpha = 0.05$ adjusted for multiple comparisons. Numeric measures were compared among treatment groups using Kruskal-Wallis rank tests. Categorical outcomes (e.g., incidence of hypotension or bradycardia) were compared using chi-squared tests. Times to first SBP outside 20% target range were analyzed using the log-rank test with a Kaplan-Meier analysis. The intent-to-treat population was used for analysis.

Results: 109 patients were recruited; 8 patients did not complete due to inadequate or failed spinal anesthesia. Insufficient samples were obtained for umbilical cord blood gases in 11 patients (1 placebo; 2 PE 25; 2 PE 50; 1 PE 75; and 5 PE 100).

There were no significant differences between groups in baseline demographics; maximum height of sensory block; skin incision to delivery time; uterine incision to delivery time; volume of Ringer's lactate infused; or estimated blood loss. The PE 100 groups received the largest total phenylephrine dose (mean 2179 $\pm$ 1070 µg) and the placebo group received the smallest total phenylephrine dose (mean 255 $\pm$ 248 µg).

Table 17. Allen: Hemodynamic variables

Table 2. Hemodynamic Variables

	PE 0 (n = 20)	PE 25 (n = 20)	PE 50 (n = 20)	PE 75 (n = 19)	PE 100 (n = 22)
No. of interventions	2 (1–3.5)	0.5 (0–4.5)	1.5 (0–3.5)	4 (1–6)	5 (4–6)*
Infusion permanently stopped	1 (5%)	5 (25%)	3 (15%)	9 (47%)	15 (68%)†
Predelivery hypotension	16 (80%)†	6 (30%)	3 (15%)	2 (11%)	0 (0%)
Predelivery hypertension	2 (10%)§	5 (25%)	8 (40%)	14 (74%)	18 (82%)‖
Postdelivery hypotension	9 (45%)	5 (25%)	1 (5%)	4 (21%)	2 (22%)
Postdelivery hypertension	0 (0%)	0 (0%)	5 (25%)	2 (11%)	8 (36%)
No. of hypotensive episodes	2 (1–3)¶	0 (0–2)	0 (0–0)	0 (0–1)	0 (0–0)
No. of hypertensive episodes	0 (0–0)#	0 (0–0)**	0.5 (0–2)††	2 (0–5)	3 (2–6)
Maximum percent change in SBP	8.3 (4.7–15.5)††	12.7 (5.0–19.8)§§	22 (14.4–27.1)	29.3 (19.9–37.2)	33.2 (23.9–46.5)
Minimum percent change in SBP	−26.9 (−30.5, −19.1)‖‖	−19.2 (−22.5, −13.1)	−9.8 (−15.1, −5.5)	−8.3 (−19.7, −0.4)	−11.8 (−17.6, −6.2)
Bradycardia	1 (5%)	3 (15%)	0 (0%)	6 (32%)	7 (32%)

PE = phenylephrine; SBP = systolic blood pressure.
Data are median (interquartile range) or number (%).
* P = 0.004 vs PE 50, P = 0.02 vs PE 25.
† $P < 0.001$ vs PE 0, P = 0.0096 vs PE 50.
† P = 0.001 vs PE 50, $P < 0.001$ vs PE 75 and PE 100.
§ $P < 0.001$ vs PE 75 and PE 100.
‖ P = 0.0081 vs PE 25.
¶ $P < 0.001$ vs PE 25, PE 50, PE 75, and PE 100.
# $P < 0.001$ vs PE 75 and PE 100.
** P = 0.0027 vs PE 75, $P < 0.001$ vs PE 100.
†† $P < 0.001$ vs PE 100.
†† $P < 0.001$ vs PE 75 and PE 100.
§§ $P < 0.001$ vs PE 100.
‖‖ $P < 0.001$ vs PE 50, PE 75, and PE 100.

The number of physician interventions needed to maintain maternal SBP within 20% of baseline was not significantly different between control and phenylephrine groups. PE 25 and PE 50 were associated with fewer interventions than PE 100. According to the sponsor, this finding was "confounded by the higher rate of hypertensive episodes in the PE 75 and 100 groups….Better maternal hemodynamic stability was achieved with the lower doses of PE."

However, one can observe a dose-related decrease in maternal hypotension and dose-related increases in maternal hypertension.

According to the authors, there were no differences in the incidence of bradycardia among the groups. There appears to be an increase in interventions for bradycardia in the PE 75 and 100 groups, suggesting a dose-response for bradycardia.

The highest incidence of hypotension-induced nausea occurred in PE 0 (n=7) and the lowest incidence in PE 100 (n=0; p 0.04 vs. PE 0). Otherwise, there were no significant differences across groups in intraoperative nausea, vomiting, or need for antiemetics.

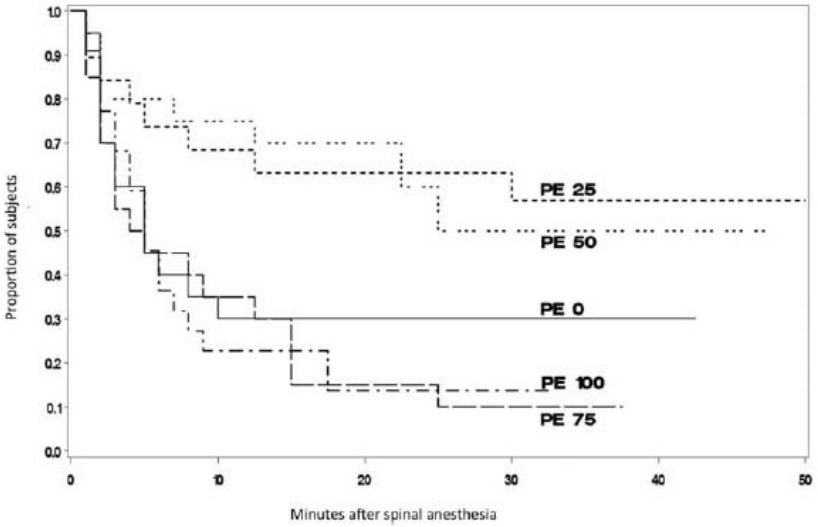


Figure 4. Kaplan-Meier survival curve—estimated time to first systolic blood pressure (SBP) outside the ±20% target range. Doses of phenylephrine of 25 and 50 μg/min were associated with a significantly longer time to a SBP outside the target range than doses of 75 (P = 0.006 vs PE 25, P = 0.004 vs PE 50) and 100 μg/min (P = 0.024 vs PE 25 and P = 0.021 vs PE 50). PE 0 = control group; PE 25 = phenylephrine 25 μg/min; PE 50 = phenylephrine 50 μg/min; PE 75 = phenylephrine 75 μg/min; PE 100 = phenylephrine 100 μg/min.

Figure 7. Allen: Kaplan-Meier curve: time to first SBP outside range

One patient (PE 50) developed an episode of ventricular bigeminy which was not associated with hemodynamic instability, persisted intraoperatively after the infusion was stopped and resolved spontaneously in the postanesthesthia care unit.
Two patients (both PE 100) developed headache and neck pain, respectively, after receiving glycopyrrolate for bradycardia and developing reactive hypertension.

There were no significant differences among groups in incidence of fetal acidosis, Apgar scores, or umbilical cord gases. All neonates in phenylephrine-treated groups had 1 and 5 minute Apgar scores $\geq$ 8. The median 1 minute Apgar score was 8 in the placebo group, with a range between 5-9; all neonates had a 5 minute Apgar score of 9.

The authors concluded that prophylactic phenylephrine infusions reduced the incidence and severity of maternal predelivery hypotension. Among the infusion regimens, PE 25 and PE 50 were associated with greater maternal hemodynamic stability.

9.1.1.2. Langesaeter (2008)

Objective: Compare effects of two different doses of bupivacaine for spinal anesthesia and effects of prophylactic intravenous phenylephrine infusion compared with placebo on invasive hemodynamic variables.

Design: Prospective, randomized, double-blind, parallel-group, placebo-controlled.

Population: 80 healthy women scheduled to undergo elective cesarean section delivery. The study was conducted at a single site in Oslo, Norway.

Exclusions: preexisting or gestational hypertension, preeclampsia, cardiovascular or cerebrovascular disease, height under 160 cm or over 180 cm; prepregnancy BMI > 32 kg/m2 or contraindications to spinal anesthesia.

129 women were eligible, 17 did not consent, and 32 were excluded. The remaining 80 were randomly assigned to one of four treatment groups (B10 + placebo; B10 + phenylephrine; B7 + placebo; B7 + phenylephrine). All patients were included in analyses.

Primary outcome: The primary outcome measures were group differences in SBP and CO (no apparent adjustment for multiplicity). Secondary outcomes were group differences in SVR, mean arterial pressure, DBP, SV, HR, duration of motor block, nausea, and umbilical cord pH and base excess. Additional data collected: Apgar scores, operation time, induction time, and pruritis. Analyses were based on the intent-to-treat population.

Methods: The senior author, who was not involved in the handling of the drugs or participants, performed the randomization in blocks of eight to four equal size groups using a list of random numbers according to an algorithm. To maintain blinding, syringes for each patient were prepared by personnel not involved in the treatment or assessment of the patients; test drugs were prepared according to information in opaque, sealed envelopes marked with a randomization number only. Unblinding of the investigators was tested by registering a guess at the treatment combination just after induction of spinal anesthesia and a second guess when the intravenous test drugs were stopped after 20 minutes.

A radial arterial line was placed; the LIDCO Plus monitor was used to measure BP continuously, with beat-to-beat measurements of CO, SV and SVR.

With induction of anesthesia, all women were given rapid intravenous infusion of 750 ml 0.9% normal saline. At the same time subjects received an intravenous infusion of placebo or 25 µg/kg phenylephrine via syringe pump for 20 minutes. A rescue 30 µg bolus of phenylephrine IV was given if hypotension (SBP < 90 mm Hg) developed; if hypotension developed with bradycardia (HR < 55 bpm) then ephedrine 5 mg bolus was given. The phenylephrine or placebo IV infusion would be stopped for MAP > 120 mm Hg.

A linear mixed model was used to analyze the change in hemodynamic variables over time; treatment groups and time was treated as fixed factors and baseline values were treated as covariate. The authors included rescue phenylephrine as a covariate in the analysis and did not correct for phenylephrine use in the raw data. Prior to breaking the randomization code, the authors decided to omit the first minute from statistical analysis due to disturbances in the beat-to-beat data associated with changes in body position.

Results: There were no baseline imbalances across treatment groups. The shortest time from induction of anesthesia to delivery was 11 minutes.

When the two phenylephrine groups were compared to the two placebo groups, statistically significant differences were observed with respect to cardiac output and heart rate, but not SBP. The bupivacaine 10/placebo group showed the lowest mean SBP and the largest number of patients requiring rescue pressor interventions.

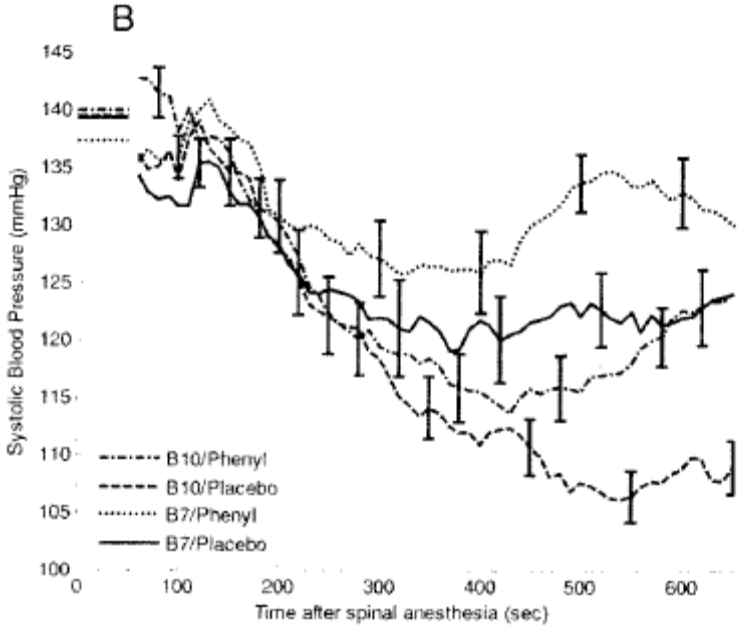


Figure 8. Langesaeter: SBP curves by group vs. time after spinal anesthesia

Table 18. Langesaeter: distribution of rescue pressor drugs

Table 5. Distribution of Rescue Pressor Drugs

	B10/Phenyl, n = 20	B10/Placebo, n = 20	B7/Phenyl, n = 20	B7/Placebo, n = 20
Phenylephrine	8	11	4	8
Ephedrine	3	6	4	2

Data are presented as number of patients in each treatment group. One patient (group 3) received ephedrine only. All other patients were given phenylephrine first, before ephedrine.

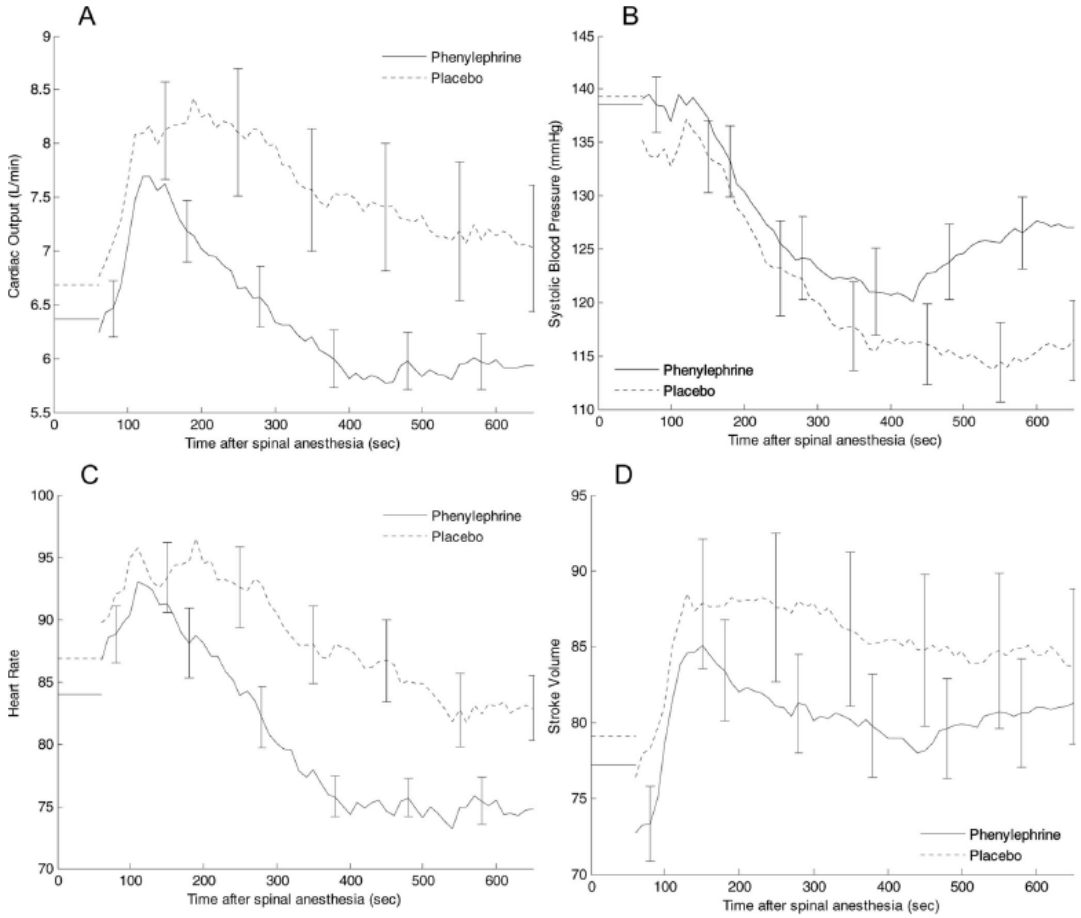


Fig. 3. Mean differences in hemodynamic variables between the phenylephrine groups and the placebo groups the first 11 min after spinal anesthesia. (*A*) Cardiac output. (*B*) Systolic blood pressure. (*C*) Heart rate. (*D*) Stroke volume. Baseline is marked on the y label. SE for each group is marked as error bars.

Figure 9. Langesaeter: Hemodynamic variables: phenylephrine and placebo

Analyses of the phenylephrine and placebo groups showed statistically significant differences in heart rate and CO; there was a mean increase in SBP in patients treated with phenylephrine that was not significantly different from placebo.

The mean minimum SBP values are higher in the bupivacaine/phenylephrine groups compared to their respective placebo counterparts (not shown in this review).

Other outcomes: Umbilical cord samples were missing in 15 cases; the umbilical artery base excess was lower in the high-dose vs. low-dose bupivacaine groups (p =NS). The investigators guessed the correct study group intervention in only 22/80 patients after spinal anesthesia induction and in 24/80 patients after completing the phenylephrine or placebo infusion, consistent with successful blinding.

The authors concluded that spinal anesthesia with 10 mg bupivacaine increased the risk of hypotension (RR 1.6 for 20% reduction of baseline SBP and RR 2.1 for 30% reduction of baseline SBP) and risk of Perioperative nausea. None of the patients in this study developed reactive hypertension, SBP > 120% baseline. There were lower heart rates and CO in the phenylephrine groups compared with placebo, but all groups developed an increase in HR and CO in the first minutes. The authors concluded that low-dose bupivacaine combined with low-dose infusion of phenylephrine and moderate co-hydration gave the best hemodynamic stability during spinal anesthesia for caesarean delivery.

The sponsor has claimed that the mean difference in SBP was statistically significant between Group 3 (7 mg bupivacaine + PE) and Group 2 (10 mg bupivacaine + placebo). However, this analysis brings to mind the comparison of an apple to an orange. A more appropriate analysis would have been 7 mg bupivacaine + PE vs. 7 mg bupivacaine + placebo or a similar analysis using 10 mg bupivacaine.

9.1.1.3. Ngan Kee (2004)

This study investigated a prophylactic infusion of IV phenylephrine vs. saline control (with rescue boluses of IV phenylephrine) for the prevention of hypotension. The study hypothesis was that there would be no detrimental effect on fetal acid-base balance despite the likelihood that large doses of phenylephrine would be administered by infusion.

Methods: This was a randomized, double-blind study of 100 µg/min phenylephrine IV infusion vs. saline control in 50 pregnant ASA I or II women scheduled for elective Caesarian section. Infusions were continued for a minimum of 3 minutes; after each 1 minute BP measurement, dosing was stopped if SAP was higher than baseline, and continued or restarted if SAP was less than or equal to baseline. If hypotension (SAP < 80% of baseline) occurred, patients received 1 mL IV bolus of study solution (patients in the phenylephrine group received saline bolus, and patients in the saline group received 100 µg bolus phenylephrine).

Outcomes: The primary outcome was umbilical cord arterial pH. Secondary outcomes included the incidence, frequency and magnitude of hypotension; incidence of reactive hypertension (SAP > 120% of baseline), nausea and vomiting. Power analysis was based on the primary outcome.

Results:

4. All patients completed the study; there were no baseline imbalances in patient characteristics and surgical times between groups; the median maximum block height was one segment lower in the infusion group vs. control (p=0.02).
5. Umbilical cord blood gases were similar between groups; only one patient in each group had an umbilical artery pH < 7.2. *(Reviewer: This trial did not meet its primary endpoint, which was based on umbilical artery pH)*. Two neonates in the infusion group had 1 minute Apgar scores of 6 with subsequent 5 minute Apgar scores of 10.
6. The SAP was significantly greater and HR significantly slower over time in the infusion group vs. control (p for both < 0.0001). Two patients in the infusion group had at least one episode of bradycardia (HR < 50 bpm) which improved when the infusion was stopped. No patient required atropine.

The proportion of patients who did not become hypotensive over time until delivery was greater in the infusion vs. control groups (p < 0.0001). Six (23%) of 26 patients in the infusion group and 21/24 (88%) in the control group (p < 0.0001) had at least one episode of hypotension.

7. The incidence of reactive hypertension (increase in SAP > 120% of baseline) was more frequent and the maximum SAP recorded was higher in the infusion vs. control group; no patient complaints of symptoms.

8. There was a nonsignificant trend toward lower incidence of transient nausea and vomiting related to the infusion group vs. control (4% vs. 21%, p = 0.09). No patient received metoclopramide.

9. Phenylephrine did not eliminate hypotension completely due to the study protocol, which included one set infusion rate and stop/start criterion. These authors used higher phenylephrine dosing and noted no “detrimental effect” on fetal acid-base status. The authors postulated that the slow HR with phenylephrine in 2 cases, unassociated with hypotension, was related to baroreceptor reflexes.

The authors additionally observed a higher level of block at 5 minutes in the control group vs. infusion; although the significance is uncertain, a higher block might result in a greater degree of sympathetic block and more frequent incidence of hypotension in the control group (potential confounder).

9.1.1.4. Gunda (2010):

The purpose of this randomized, double-blind study was to compare effectiveness and side effects of IV PE and ephedrine in treating maternal hypotension from spinal anesthesia in 100 patients undergoing elective cesarean section. Ephedrine 5 mg or 100 µg PE was given if hypotension (SBP fall ≤ 90 mm Hg and/or 30% less than baseline) was present. Atropine 0.5 mg IV was given for bradycardia (HR < 60 bpm). Oxygen saturation and vital signs were monitored every 2 minutes for the first 10 minutes, every 5 minutes from 10-30 minutes and every 15 minutes from 30-60 minutes. The publication did not mention primary and secondary endpoints or sample size calculation.

Results: The duration of surgery was longer in the group receiving ephedrine (mean 47.4 min) vs. PE (mean 45.3 min), $p < 0.001$; otherwise, there were no significant differences in demographic characteristics and operation data. The sensory level attained in both groups was comparable. All patients required vasopressors for hypotension; top-off doses for repeat hypotension were comparable between groups. A total of 92% of ephedrine-treated patients and 94% of phenylephrine-treated patients required a single bolus (ephedrine 5 mg or phenylephrine 100 µg, respectively); the rest received two boluses. There was a significant difference between groups in the time of vasopressor administration, suggesting an imbalance between groups in factor(s) other than a vasopressor drug (e.g., timing of hypotension or drug administration). There was a higher incidence of bradycardia in patients receiving PE (6 patients required atropine) and a higher incidence of tachycardia in those receiving ephedrine. More patients on ephedrine developed nausea and/or vomiting (below); all neonates had Apgar scores 8-9 at 1 minute and scores of 10 at 5 minutes, with no differences between treatments.

Table 19. Gunda: Complications between groups (ephedrine vs. phenylephrine).

Table IV. Number of complications between groups

	Ephedrine group, *n* (%)	Phenylephrine group, *n* (%)	*P*-value
Nausea	9 (18%)	4 (8%)	0.08
Vomiting	7 (14%)	0 (0%)	< 0.05
Bradycardia	1 (2%)	6 (12%)	0.05
Tachycardia	8 (16%)	0 (0%)	< 0.05
5 min Apgar < 7	0 (0%)	0 (0%)	1.0

Data expressed as number of patients (n) (%)

9.1.1.5. Moran (1991):

This was a randomized, double-blind study comparing prevention of maternal hypotension and nausea and vomiting following spinal anesthesia in 60 healthy patients scheduled for elective cesarean section. *The publication did not mention sample size calculations or primary outcome.* Patients were assigned to receive either ephedrine 10 mg IV bolus injection (n=29) or phenylephrine 80 µg IV bolus injection (n=31) for > 5 mm Hg decreases from baseline maternal SBP, followed by boluses of 5-10 mg ephedrine or 40-80 µg boluses, respectively, to maintain SBP > 100 mm Hg. Data were analyzed using Student's t-test, with $p < 0.05$ considered significant.

Results: There were no reported baseline imbalances between groups. The intraoperative mean heart rate increased in the ephedrine group and decreased in the phenylephrine group ($p = 0.001$) but no phenylephrine patient experienced a HR decrease to < 60 bpm. The mean ephedrine dose used was 41 mg and the mean phenylephrine dose was 335 µg. There were no significant differences between groups in maternal venous pH, umbilical vein pH, umbilical vein pO2, umbilical artery pO2. The frequency of maternal nausea or nausea and vomiting was 28% in the ephedrine group and 25% in the phenylephrine group. Significant differences were observed between groups in umbilical artery pH, pCO2 and base deficit, with higher mean pH, lower pCO2 and lower base deficit observed in the phenylephrine group. It is not clear whether these mean differences were driven by one infant in the ephedrine group with 1-minute Apgar score of 6 (the 5 minute score in this infant was 9); the remainder of the infants had 1 minute Apgar scores $\geq$ 7 and 5 minute scores of $\geq$ 9. There were no differences between the groups in early neonatal neurobehavioral testing.

9.1.1.6. Prakash (2010):

This was a randomized, double-blind study comparing maternal hemodynamic changes and neonatal well-being following boluses of ephedrine and phenylephrine in 60 pregnant women undergoing elective caesarian delivery under spinal anesthesia. Patients were assigned to receive a 1 mL bolus of either ephedrine 6 mg/mL or phenylephrine 100 µg/mL if the SBP decreased to 80% of baseline or less. Additional boluses were administered if the SBP remained at or below 80% of baseline. Atropine 0.3 mg was given for HR < 60 bpm associated with SBP below baseline or HR < 45 bpm irrespective of BP. Sample size was based on umbilical artery pH, the primary outcome, with 90% power at 5% significance level to detect a difference of 0.03 units between groups. Secondary outcomes included incidence of maternal bradycardia, tachycardia, reactive hypertension, nausea and vomiting, Apgar and Early Neonatal Neurobehavioral Scale (ENNS) scores. Student's unpaired t test (for continuous variables) and chi-squared (for categorical variables) tests were used to compare groups. $P < 0.05$ was considered statistically significant.

Results: 98 women were enrolled; 38 did not develop hypotension and were excluded from the study; the randomization code was not broken and further subjects were recruited. There were no gross baseline imbalances between the two groups. Patients received a mean of 2 vasopressor doses in both groups. There was a statistically significant increase in pH in umbilical artery pH in phenylephrine infants (7.32 ± 0.04) vs. ephedrine infants (7.29 ± 0.04), p = 0.01 and higher arterial base excess with phenylephrine (-1.61 ± 1.04) vs. ephedrine (-2.8 ± 0.94), p < 0.001. However, no neonate had fetal acidosis (umbilical artery pH < 7.20) and Apgar and neurobehavioral scores were similar between groups. 17% of patients on phenylephrine developed bradycardia (HR < 60 bpm) vs. 0 on ephedrine. No patient developed bradycardia with hypotension. 43% of patients on ephedrine and 6% on phenylephrine developed tachycardia (HR > 100). No patient developed reactive hypertension. (*Reviewer: Since the Apgar and neonatal neurobehavioral scores were similar between groups, the clinical meaning of the statistically significant differences in umbilical artery pH and base excess is not clear).*

9.1.1.7. Thomas (1996):

The purpose of this randomized, double-blind study was to compare effects of phenylephrine and ephedrine on maternal and fetal hemodynamic changes and umbilical artery pH in 40 healthy women undergoing elective cesarean section at term. While no primary endpoint was specified, the study was sized to detect a difference in umbilical artery pH of 0.05 units at the 5% level with 80% power, assuming a standard deviation of 0.05 pH units. Arterial pressure was measured by an automated oscillometric technique; BP was measured at 1 minute intervals; when SAP decreased to < 90% of baseline, 1 ml vasopressors was administered. Maternal heart rate was measured via finger pulse oximetry; atropine 0.3 mg IV was administered when maternal HR < 60. Maternal ascending aortic flow velocities and umbilical artery flow velocity were measured via Doppler. Group differences were compared using t-test (if normal) and Mann-Whitney test (if non-parametric).

Results: baseline SAP was higher in the phenylephrine group (mean 125 mm Hg) than ephedrine (mean 121 mm Hg) but the differences were not statistically significant. One subject in the ephedrine group had a uterine incision to delivery time of > 180 seconds, though the umbilical artery pH was normal (7.26). More patients in the phenylephrine group required atropine; the frequency of hypotension (SAP < 80% baseline) was similar between groups; there was no significant change in CO. Umbilical artery pH was significantly higher in the phenylephrine group (mean 7.29; 95% CI: 7.28, 7.30) vs. ephedrine (mean 7.27; 95% CI: 7.25, 7.28); however, only one infant in the ephedrine group had an umbilical artery pH < 7.2. There was also a statistically significant reduction on fetal HR in the phenylephrine group (mean -2.0; 95% CI: -2.6, -1.4) vs. ephedrine (mean + 0.8 bpm; 95% CI: -2.3, +3.8). All infants had Apgar scores ≥ 7 at 1

and 5 minutes. There was no significant correlation between the number of doses of either vasopressors and umbilical artery pH.

9.1.1.8. Alahuhta (1992):

This randomized, double-blind study evaluated blood flow velocity waveforms in the maternal and fetal circulation and fetal myocardial function by M-mode echocardiography during prophylactic IV vasopressor infusion (phenylephrine or ephedrine) during spinal anesthesia for cesarean section.

Nineteen healthy pregnant women undergoing elective cesarean section under spinal anesthesia were placed supine with left lateral tilt and the first ultrasound measurement was made before volume loading and spinal anesthesia. Flow velocity waveforms for the maternal uterine artery, placental arcuate artery and the fetal umbilical, middle cerebral and renal arteries were recorded via color Doppler.

Vasopressor bolus (1 ml, which contained 5 mg ephedrine or 100 µg phenylephrine) followed by solution (10 ml/hr) was given when pinprick analgesia reached T5 and continued until delivery. Hypotension (SBP decreased > 10 mm from baseline) was treated with 1 ml boluses of vasopressors and increasing the IV electrolyte infusion. After the initial bolus, the second ultrasound measurements were made.

The primary endpoint and sample size calculation were not mentioned in the publication.

Results: Two patients were excluded from the analyses, due to technical failure (1) and maternal bradycardia requiring atropine (1). It is not stated whether the patient developing bradycardia received phenylephrine.

Systolic and diastolic BP decreased in both groups during spinal anesthesia and prior to vasopressors administration, but increased with vasopressors infusion (Table 2 of publication, not shown in this review). Hypotension (SBP < 90 mm Hg) was recorded in 1 patient receiving phenylephrine and twice in 1 patient receiving ephedrine. There was no significant change in mean maternal HR in the ephedrine group, while PE administration was associated with a significant reduction in mean maternal HR.

There were no significant differences from baseline in any ultrasound measurement in the ephedrine group; the mean maternal uterine and placental arcuate PI values increased in those receiving PE. The mean PI values for fetal renal arteries decreased from baseline; fetal HR did not significantly change after PE administration. There were no statistically significant changes in LV or RV fractional shortening or mean circumferential shortening, or pulmonary trunk or ascending aorta systolic peak velocity. *The study did not define what constituted a meaningful change in any of the*

echocardiographic parameters, or whether it was adequately powered to detect a minimal clinically meaningful signal.

One neonate in each group had an UA pH < 7.15.
All neonates had Apgar scores > 8 at 1 and 5 minutes.
Reviewer comment: *Neither drug appeared to show a safety signal regarding fetal acidosis or low Apgar scores.*

9.1.1.9. Cooper (2002)

This randomized, double-blind study was designed to compare the incidence of fetal acidosis when an infusion of phenylephrine, norepinephrine, or a combination of both, was given to maintain maternal SBP at baseline during spinal anesthesia for elective cesarean delivery. The study also compared the incidence of maternal nausea and vomiting during spinal anesthesia.

The study population comprised ASA I and II women with a singleton pregnancy, no known fetal abnormality and no history of preeclampsia or diabetes.

Patients had three BP and HR readings recorded with an automated oscillometer at 3 minute intervals while sitting in bed; the lowest of the three readings was recorded as the baseline value for maternal SBP and HR. The highest nausea and vomiting score was recorded for 30 minutes before spinal anesthesia was induced (nausea and vomiting were scored as 0= none; 1= nausea without vomiting; 2= vomiting). Patients were randomly allocated by envelope selection to one of three vasopressor solutions to maintain SBP during spinal anesthesia. The groups received phenylephrine 100 µg/ml, ephedrine 3 mg/ml or phenylephrine 50 µg/ml combined with ephedrine 1.5 mg/ml; each solution was diluted with saline to a total volume of 40 ml. The anesthetist was allowed to choose the spinal anesthetic technique most familiar to them from one of four standard techniques; randomization was stratified using a separate set of randomization envelopes for each of the standard spinal anesthetic techniques. The height of neural blockade to cold sensation was measured at 10 minutes post-spinal and at skin incision; the target block height was above T5. An epidural top-up was only used if neural blockade was not sufficiently high or dense with spinal anesthesia alone.

Patients received 10 mg/kg rapid infusion of Hartmann solution before spinal anesthesia; the intravenous vasopressor was started immediately after spinal injection.

The study continued until delivery. Maternal HR was continuously measured via pulse oximeter. Intravenous glycopyrrolate 200 µg was given for inappropriate or severe bradycardia according to a protocol that included SBP.

The sample size was based on an 80% chance to detect a 15% incidence of fetal acidosis (umbilical artery pH < 7.20) in the ephedrine group and 80% chance of

detecting a mean difference of 0.03 in mean umbilical artery pH at two-sided p=0.05. The Kruskal-Wallis test was used to compare the three groups; if a difference was found, pairs were then compared using the Mann-Whitney U test.

Results: Forty-eight patients were studied in the PE group, 50 in the ephedrine group and 49 in the combination group. In four neonates, it was either not possible to obtain umbilical blood samples or the samples were almost identical. Baseline variables appeared similar across groups. Median block height at 10 minutes was T3; median spinal to skin incision time was 19 or 20 minutes (for the 3 groups); median skin incision to delivery time was 26 or 27 minutes; and median uterine incision to delivery time was 7 minutes.

There was a significant increase in fetal acidosis in the ephedrine-treated group (incidence 21%) compared to the phenylephrine (2%) or combination-treated (2%) groups (p = 0.0007). The mean umbilical artery and venous pH, V-A pH difference and A-V pCO2 difference were statistically significant, with a higher mean arterial pH (7.31) and lower V-A pH difference (0.05) and lower A-V pCO2 difference (11 mm Hg) in the PE group. Two fetuses in ephedrine-treated mothers had a base deficit > 10 mM. In the ephedrine group, decreases in umbilical artery pH correlated strongly with increasing A-V PCO2 difference.

The mean SBP from spinal to delivery and the incidence of hypotension (SBP < 80% of baseline) were similar for the three groups. There was a small, statistically significant difference between the groups at 20-25 minutes post-spinal anesthesia with lower mean SBP in PE group; however, the lowest SBP recorded was higher in the PE group and the proportion of SBP readings < 80% of baseline was lower in the PE group.

In 2 patients treated with ephedrine, the code had to be broken because of SBP < 75% of baseline despite vasopressors; each of these patients was successfully treated with 100 µg PE.

Mean HR in the combination group was lower than that in the ephedrine group (p < 0.0001) and higher than in the PE group (p=0.008). Interestingly, there was an increase in glycopyrrolate required in the ephedrine group (10%) compared to the PE group (4%) but this difference was not statistically significant.

The nausea and vomiting scores did not change from baseline for the PE group but increased in the ephedrine (p < 0.0001) and combination (p=0.007) groups.

The authors concluded that using a PE infusion to maintain SBP during spinal anesthesia for elective cesarean delivery can decrease fetal acidosis and maternal nausea and vomiting compared with ephedrine alone. There was no advantage to combining PE and ephedrine versus using PE alone.

9.1.1.10. Mohta (2010)

This was a randomized, double-blinded study comparing IV infusions of phenylephrine vs. mephentermine for the prevention of maternal hypotension and assessing neonatal outcome in 60 subjects undergoing spinal anesthesia for cesarean delivery.

Eligible patients were ASA 1 or 2 women with term, uncomplicated singleton pregnancy and planned elective cesarean delivery under subarachnoid block. Patients were excluded with pregnancy-induced hypertension, cardiovascular disease, cerebrovascular disease, placental or fetal abnormalities, contraindications to spinal anesthesia and SBP < 100 mm Hg.

Patients were randomly divided into two groups of 30, using a sealed envelope technique. The vasopressor solution was prepared by an assistant who was not involved in the study. Equipotent doses of the two vasopressors drugs were calculated on the basis of available literature; phenylephrine 50 µg/ml and 600 µg/ml of mephentermine was thus prepared. BP was measured at 2- minute intervals during the study period. Hypotension was defined as a decrease from baseline $\geq$ 20% or absolute value of < 100 mm Hg SBP, whichever was higher. Reactive hypertension was defined as an SBP increase > 20% from baseline.

Following spinal anesthesia, a prophylactic vasopressor infusion was started at 60 ml/hr (i.e., 50 µg/min for phenylephrine and 600 µg/min for mephentermine). If hypotension occurred, a 2 ml bolus of the respective vasopressor (i.e., 100 µg phenylephrine or 1.2 mg mephentermine) was administered through the infusion pump. If the SBP exceeded baseline, the infusion rate was decreased in steps of 6 ml/hr. Bradycardia, HR < 50 bpm, was treated with intravenous atropine.

Prospective power analysis was based on differences in umbilical cord blood gases; 22 subjects/group would be required to give 90% power at the 5% significance level to detect a difference in umbilical arterial pH of 0.05 units.

Results: There were no statistically significant differences between the two groups in cord blood gases (the base deficit appeared lower in phenylephrine-treated patients but $p > 0.05$).

There were no significant differences between the two groups in mean SBP or HR, although 7/30 (23%) phenylephrine-treated patients and no mephentermine-treated patients had bradycardia ($p=0.011$). Two patients in the phenylephrine group and one patient in the mephentermine group developed hypotension during the study period; the incidence of hypotension between groups was not significantly different.

Eight phenylephrine-treated patients developed reactive hypertension, and two developed hypertension after atropine used to treat bradycardia. Both of these patients

complained of headache; one vomited and developed ventricular ectopic beats. The phenylephrine infusion in both of these patients was stopped; the neonates "were not studied for the analysis." None of the mephentermine-treated patients developed hypertension.

Of the remaining 28 phenylephrine-treated patients and 30 mephentermine-treated patients, all neonates had Apgar scores of at least 7 and none had fetal acidosis (umbilical artery pH < 7.2). Two mephentermine-treated patients complained of nausea and one vomited. No other complications were reported.

The authors suggested that mephentermine was as effective as phenylephrine in preventing maternal hypotension following spinal anesthesia, had a similar effect on neonatal outcome, and was more economical in India. The authors also acknowledged certain limitations, e.g., BP measurements at 2-minute intervals, which may have contributed to the high incidence of reactive hypertension; and the use of an indirectly derived potency ratio of phenylephrine and mephentermine.

9.1.1.11. Adigun (2010):

This was a randomized, double-blind, active-controlled study of healthy women, ASA 1 and 2, with term singleton pregnancy and elective cesarean delivery.
The objective (aim) of this study was to compare the effect of bolus intravenous ephedrine and phenylephrine for the maintenance of BP under spinal anesthesia.

Patients were allocated to receive either ephedrine (group A, n=31) or phenylephrine (group B) using a coded sealed envelope technique. BP, HR, oxygen saturation and respiratory rate were measured every two minutes for the first 10 minutes and then at 5 minute intervals until the end of the procedure. Hypotension was defined as a decrease in SBP > 30% below baseline or < 100 mm Hg; hypertension was defined as an increase in SBP > 30% above baseline. When hypotension occurred, the randomized drug (IV ephedrine 5 mg or phenylephrine 100 µg) was administered and could be repeated as needed. Atropine was given whenever the pulse rate was < 60 bpm. Hypotension in the recovery room was treated with vasopressors and IV fluid; the study period continued for 30 minutes in the recovery room.

Comparison of means and proportions were performed using chi square; $p < 0.05$ was considered to be significant.

Results: The groups were comparable in age, weight, height, gestational age, BMI, preload volume, infant birth weights and median Apgar scores (1 and 5 minutes). No neonate had an Apgar score < 8 in either group and none required admission to a special care unit.

The incidence of hypotension in the 62 patients was 24%. Seven ephedrine-treated patients and 8 phenylephrine-treated patients developed hypotension. The groups were comparable in development of nausea; one ephedrine-treated patient developed hypertension. Post-vasopressor SBP changes were higher in the phenylephrine group but were only statistically significant at the 15th minute. Intraoperative mean heart rates were higher in ephedrine-treated patients (e.g., lower in phenylephrine-treated patients). The authors concluded that phenylephrine was as effective as ephedrine when there was a need to treat hypotension in obstetrics under spinal anesthesia.

9.1.1.12. Defossez (2007):

This was a randomized, double-blind study comparing ephedrine and phenylephrine, given either by bolus or continuous infusion, on maternal hemodynamics and fetal outcome during spinal anesthesia for cesarean delivery. No primary endpoint was identified.

Forty ASA physical status I or II patients were assigned to: ephedrine 5 mg/ml boluses (group 1); phenylephrine 100 µg/ml boluses (group 2); ephedrine 1 mg/min continuous infusion (group 3); and phenylephrine 20 µg/min continuous infusion (group 4). Patients were excluded if they had BP > 160/90, known hypertension, epilepsy, psychiatric illness, or age > 40. According to the authors, the groups were similar in age, weight and length (data not given). In each of these groups, IV boluses were given whenever the mean arterial BP < 70 mm Hg or < 75% pre-induction MAP value. In groups 3 and 4, vasopressors infusion was started immediately after spinal anesthesia and stopped at the end of the cesarean section. BP was measured every 2 minutes. Between groups differences were analyzed with t-test and one-way ANOVA ($p < 0.05$ was considered statistically significant). No primary analysis was mentioned.

Results: No significant differences were observed in maternal oxygen saturation, maternal blood loss, side effects, Apgar scores and umbilical blood gases (*no data given*). No actual data were given, but the publication stated that MAP was higher and HR lower in group 4, but not significant by one-way ANOVA. In the continuous infusion groups few patients (2 in group 3, 1 in group 4) required additional boluses. The paper did not mention how many boluses were needed in the other groups.
For both ephedrine and phenylephrine, the total dose was significantly higher in the groups given continuous infusion vs. boluses.

The authors concluded that hemodynamic stability was enhanced in the continuous infusion groups and that a larger population would likely “enhance these preliminary results.”

9.1.1.13. Cooper (2007)

This was a single-center randomized, double-blind study comparing infusions of phenylephrine 100 µg/ml (n=27) and ephedrine 4.5 mg/ml (n=27) during spinal anesthesia for cesarean delivery. The study tested the hypothesis that rostral spread of spinal hyperbaric bupivacaine is less during cesarean delivery when prophylactic IV phenylephrine is used, compared with ephedrine.

ASA 1 or 2 patients with term singleton pregnancy, no history of preeclampsia or diabetes, no known fetal abnormality and scheduled elective cesarean delivery were included. Patients were randomly allocated by a computer-generated code kept in a numbered envelope; patients, anesthetists and nurses involved with patient care were blinded to the patient grouping.

Patient received 14 mg (ED95 for blocking T5 to light touch) hyperbaric bupivacaine via spinal injection (L3-L4). Immediately afterward, patients received a rapid infusion of 10 ml/kg Hartmann's solution and trial solution at 20 ml/hr (either 33 µg/min phenylephrine or 1.5 mg/min ephedrine). The rate was doubled or halved, as necessary, to maintain SBP at baseline; the maximum infusion rate was 40 ml/hr and the minimum was 2.5 ml/hr. The infusion was stopped when SBP was 1.20 times baseline and restarted at half the rate when the SBP had decreased below that level. Additional boluses of trial solution were given, as required, according to a protocol, with an algorithm for rescue solution (phenylephrine 50µg/ml combined with ephedrine 2.25 mg/ml). The study continued for 90 minutes after spinal anesthesia or until the end of the operation, which was longer.

Analysis: The study was originally designed to have 80% power to detect a one-dermatome difference in block height to cold sensation at 15 minutes post-spinal at 2-sided p = 0.05 (total of 126 patients with SD of 2 for block height). However, the protocol was modified because of concerns about an unexpectedly high incidence of fetal acidosis. From patient 15 onwards, boluses of trial solution were replaced with the same volume boluses of rescue solution, only given if the SBP was less than 0.80 times baseline or 90 mm Hg, whichever was higher.

The study was stopped after an interim analysis (n=54) because of a high incidence of fetal acidosis in the ephedrine group.

Results: The groups appeared similar in baseline characteristics. Block height was similar in the two groups for both sensory modalities tested at all of the assessment times. There was no difference in pain scores or incidence of inadequate anesthesia.

There was a lower umbilical artery and venous pH in the ephedrine vs. phenylephrine groups (p=0.001). Compared to phenylephrine, umbilical arterial and venous base deficits and P_{CO2} were higher in the ephedrine group.

One-minute Apgar scores were similar among groups. While the authors observed higher 5- minute Apgar scores in the phenylephrine group [10 (9-10)] than in the ephedrine group [9 (9-9)] (p=NS), neonates in both groups appeared to have scores > 8. Increasing spinal-delivery intervals were strongly associated with decreasing umbilical artery pH, but only in the ephedrine group. According to the authors, spinal-delivery time and total dose of ephedrine, via multiple regression analysis, were significant factors for fetal acidosis.

During the 0-15 minute time period, SBP was not significantly different between groups. During the 15-30 minute time period, more hypotension was observed in the phenylephrine group and a higher infusion volume was required.

9.1.1.14. Ueyama (2002):

The objective of this randomized, double-blind study was to clarify the effects of prophylactic ephedrine and phenylephrine on the change in cardiac output in 20 pregnant women undergoing spinal anesthesia for elective cesarean section.

Five minute infusions of either 40 mg of ephedrine (n=10) or 250 µg phenylephrine were administered immediately after spinal anesthesia. Cardiac output was measured, via indocyanine green dilution (ICG) method and ICG blood concentrations were monitored by pulse spectrophotometry. After baseline measurements, patients received lactated Ringer's solution at 100 ml/hr; spinal anesthesia was performed with bupivacaine 10 mg and morphine 100 µg; BP was measured at one minute intervals. When hypotension (SBP < 20% or < 100 mm Hg) occurred, ephedrine 10 mg and ICG (5 mg) was administered simultaneously and both CO and BP were measured. When patients did not develop hypotension, CO was measured when the level of sensory block was achieved at T4-6 level; hypotension was treated with 5 mg ephedrine at 1-minute intervals. CO was measured before delivery in all patients. *No analytic plan was specified in this abstract.*

Results: The incidence of hypotension was 0 in PE and 10% (e.g., 1 patient) in ephedrine. *No data were given for the incidence of hypertension or bradycardia.* In both groups, the decrease in CO was accompanied by a significant increase in TVR (total vascular resistance). *No data were given for CI (e.g., correcting for BSA).* A significant ($p < 0.01$) increase in HR was noted in the ephedrine group.

9.1.1.15. LaPorta (1995):

This randomized, double-blind study evaluated the effects of ephedrine and PE on Apgar scores, maternal and neonatal catecholamine concentrations, and acid-base

status in patients undergoing elective cesarean section under spinal anesthesia. Forty patients were treated with incremental doses of either ephedrine 5 mg/ml or PE 40 µg/ml to maintain SBP > 100 mm Hg following initial boluses of 10 mg ephedrine or 80 µg PE followed by 1-2 ml boluses as needed. Oxygen (5 L/min) was administered via plastic disposable face mask from induction until delivery. Maternal venous blood was obtained at the time of delivery. *No primary endpoint was mentioned.*

Results: The mean doses of ephedrine and phenylephrine used were 39.5 ± 18.5 mg and 364 ± 149 µg, respectively. Mean skin incision to delivery time was 18 minutes for both groups. Neonates in the ephedrine group had lower umbilical artery pH (mean 7.28 vs. 7.32 PE, p=0.01); higher pCO2 (mean 7.32 vs. 6.68 PE, p=0.03) and higher base excess (mean 2.2 mmol/l vs. 0.9 mmol/l PE, p=0.04). A significant correlation was observed between UA pH and noradrenaline values in both groups. None of the neonates in either group had Apgar < 7 at one or five minutes. *No BP or HR results were given and there was no mention of any adverse effects.*

9.1.1.16. Ngan Kee (2004)

The objective of this study was to compare IV PE infusion regimens based on three different BP thresholds in patients undergoing spinal anesthesia for elective cesarean delivery.

The main outcome measure was the umbilical artery pH.

This was a single-blind, randomized trial of 75 ASA physical status I and II women with term singleton pregnancies scheduled for elective cesarean delivery under spinal anesthesia. Patients were excluded if they had pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormalities or contraindications to spinal anesthesia.

The authors chose not to administer prehydration before induction of spinal anesthesia. Patients received PE 100 µg/min infusion, immediately post-spinal injection, and continued for a minimum of 2 minutes. Subsequently, until uterine incision, the infusion was adjusted according to each 1 minute measurement of SBP. PE was infused at 100 µg/min each minute if SBP was less than or equal to a randomly assigned percentage of baseline: 100% (Group 100), 90% (Group 90) or 80% (Group 80). The infusion was turned off if the SBP was greater than the assigned value. Patients were randomized according to computer-generated randomization codes contained in sealed, sequentially numbered envelopes.

Prospective power analysis was based on the primary outcome, umbilical artery pH; a sample size of 23/group would have 90% power at the 5% significance level to detect a

difference in umbilical artery pH of 0.03 units among groups. Secondary outcomes included incidence, frequency and magnitude of hypotension (decrease below baseline in SBP by > 20%), incidence of bradycardia and incidence of nausea or vomiting. Data were compared using one-way ANOVA, repeated-measures ANOVA, and Kruskal-Wallis test, with post hoc comparisons via Tukey's HSD test and the Mann-Whitney U test. Modified Bonferroni corrections were applied for post hoc multiple comparisons as appropriate.

Results: Spinal anesthesia was successful in all patients. One patient in Group 100 was excluded because severe shivering prevented accurate BP measurement. Umbilical cord blood gases could not be measured for technical reasons in 2 Group 80 and 3 Group 100 patients. There was a difference across groups in baseline height (Group 80 > Group 100 > Group 90; p = 0.007). The total dose of PE was different among groups, Group 80 (mean 790 µg) < Group 90 (mean 1070 µg) < Group 100 (mean 1520 µg) (p=0.001). There was no difference between groups in other patient characteristics.

There was a statistically significant difference between the three groups in umbilical artery pH (mean 7.30 in Groups 80 and 90; mean 7.32 in Group 100; p = 0.036). No neonate had an umbilical artery pH < 7.2.

Only one neonate (Group 100) had a 1 minute Apgar score of 6 and all neonates had 5 minute Apgar scores $\geq$ 9.

Changes in SBP and maternal HR over time were significantly different among groups. The number of patients with hypotension and number of episodes was smallest in Group 100 and largest in Group 80. The incidence of reactive hypertension and bradycardia were similar among groups; only 2 patients required treatment with atropine. The incidence of nausea and vomiting was different among groups (p=0.006) and smaller in Group 100 than in Group 80.

The authors concluded that when PE is infused to maintain maternal BP during spinal anesthesia for cesarean delivery, the optimal regimen is to titrate it to maintain maternal BP at values near baseline.

9.1.1.17. Tanaka (2009)

The objective of this trial was to determine the 95% effective dose (ED95) of phenylephrine by intermittent IV bolus to prevent spinal-induced hypotension and/or nausea at elective cesarean delivery.

This was a double-blind study in 50 patients underlying elective cesarean delivery under spinal anesthesia. Inclusion criteria were age > 18 years, ASA I or II, and term singleton pregnancy. Exclusion criteria included allergy to phenylephrine, pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormalities, and contraindications to spinal anesthesia.
The observation period was from induction of spinal anesthesia to uterine incision. Patients received lactated Ringer's solution 10 ml/kg immediately before induction. Immediately following intrathecal injection, without assessment of SBP, a prophylactic bolus of study solution was administered; thereafter, 1 mL study solution was given every time SBP $\leq$ baseline, in order to maintain SBP at 100% baseline.
The phenylephrine dose was determined using up-down sequential allocation according to an algorithm determined by responses of previous patients. The first patient was assigned a 40 µg dose and the dose to subsequent patients varied by 10 µg increments or decrements. SBP and HR were assessed every minute until uterine incision. An adequate response was defined as absence of hypotension (SBP < 80% baseline) and nausea. If hypotension occurred at any time during the study period, the treatment was considered a failure, study solution was abandoned and the patient received 100 µg bolus doses as per the practice of that institution. Hypertension was defined as SBP > 120% baseline. Bradycardia was defined as HR < 50 bpm for two consecutive measurements 1 minute apart. The ED95 was determined by a logistic model with non-log-transformed doses.

Results: 79 patients were approached and 29 refused to participate. The 50 study patients received phenylephrine doses from 40-120 µg. The bolus ED95 of phenylephrine to produce an effective response (no hypotension or nausea) was determined to be 159 µg (95% CI 122-371 µg). The ED95 for prevention of hypotension alone was 135 µg (95% CI 106-257 µg). Fourteen patients (doses of 60-120 µg) developed a single episode of hypertension; no patients complained of headache, chest pain or shortness of breath. Bradycardia was not observed. Nausea was reported in 11 patients; in 7 cases the nausea was accompanied by hypotension. No vomiting was observed. Umbilical cord blood could not be obtained in 4 patients due to technical reasons. Umbilical artery pH values were < 7.2 in two neonates, although the 1 and 5 minute Apgar scores were > 7 for both. The phenylephrine doses (40 and 50 µg, respectively) were deemed ineffective in these two cases.

9.1.1.18. Das Neves (2010):

The study investigated efficacy of phenylephrine when administered therapeutically and prophylactically for BP maintenance in patients undergoing spinal anesthesia for elective cesarean section.

This was a prospective, randomized, double-blind study in 120 ASA 1 women with a term pregnancy, single fetus, and indication for elective cesarean delivery. Patients were excluded with: history of hypertension or pregnancy-induced hypertension,

cardiovascular or cerebrovascular disease, fetal abnormalities, history of hypersensitivity to study drugs, and contraindications to spinal block.

Patients were randomly distributed in 3 groups, using sequential sealed envelopes containing random computer-generated numbers. The result of the distribution was not revealed and it was not known by patients or physicians responsible for collection and analysis of the data. The size of the study population was based on prior studies (*no sample size calculation was mentioned).* Phenylephrine was administered as follows: Group 1: continuous IV infusion, using an infusion pump, at 15 µg/kg/min, starting immediately after the spinal block; Group 2: a single dose of phenylephrine 50 µg IV, administered immediately after the spinal block; Group 3: a single dose of phenylephrine 50 µg IV, administered in case of hypotension, defined as a decrease in SBP and/or DBP of up to 20% of mean baseline levels.

In all groups, a bolus of 30 µg phenylephrine IV repeated every 2 minutes was allowed for a BP decrease > 20%, not controlled with the allowed therapeutic regimen.

Results:
A statistically significant baseline difference was observed in initial DBP ($p < 0.05$) among the three groups (lowest in Group 1, highest in Group 3); however, baseline SBP, age, weight, height or HR was not significantly different between groups.

The incidence of hypotension was significantly different among the 3 groups, with the highest percentage in Group 3 (85%) and the lowest in Group 1 (17.5%); $p < 0.001$. In addition, the incidence of nausea, vomiting and rescue doses was highest in Group 3 and lowest in Group 1. One patient in Group1 developed reactive hypertension, which was treated with discontinuation of the infusion. Transient bradycardia, not requiring treatment, was observed in 1 patient in Group 2. One-minute Apgar scores showed a higher proportion with values ≤ 8 in Group 3 (40%) compared to Groups 1 and 2 ($p=0.01$). The 5-minute Apgar scores (all with scores ≥ 9) did not show differences between the groups.

The authors chose the minimal doses for direct IV administration (50-200 µg) and continuous infusion (0.15-0.75 µg/kg/min) while "the optimal dose has yet to be determined." The authors concluded that, according to the methodology used, the study showed that continuous infusion of prophylactic phenylephrine, initiated immediately after spinal block, is more effective in reducing the incidence of hypotension and maternal and fetal side effects.

9.1.1.19. Saravanan (2006):

The aim of this randomized, double-blind, sequential allocation study was to calculate the dose ratio for clinical equivalence between ephedrine and phenylephrine in patients undergoing elective cesarean section under combined spinal-epidural anesthesia.

Patients were randomized to receive ephedrine 50 mg or PE 500 µg via infusion pump (same rate) with an arbitrary initial dose for dilution. Hypotension was defined as decrease in SBP to < 75% baseline or 100 mm Hg SBP. Tachycardia was defined as rise in HR to > 130 bpm and bradycardia as fall to < 60 bpm. Hypotension during the study period meant that the infusion dose was ineffective. The vasopressor dose for the subsequent patient was determined by efficacy in the previous patient, according to up-down sequential allocation. After an effective outcome, the next patient in that group received a dose reduced by 5 mg ephedrine or 50 µg PE; after an ineffective outcome, the dose for the next patient was increased by the same amount in the respective groups. Hypotension was treated with a bolus of ephedrine 6 mg unless the HR > 100, in which case PE 40 µg bolus was given, with repeat dosing if needed.

The primary outcome was the minimum vasopressor dose for ephedrine and PE in prevention of hypotension; data were analyzed with unpaired t-test, Mann-Whitney U-test and Fisher's Exact tests as appropriate; two-sided $p < 0.05$ was defined as significant. Results: Four ephedrine and two PE patients were withdrawn from the study because the block did not reach the T5 level or infusion pump failure. The minimum vasopressor dose for PE was 532.9 µg (95% CI 506.0-559.8) and for ephedrine 43.3 mg (95% CI 39.2-47.3); this gave a potency ratio for PE: E of 81.2:1 (95% CI 73.0-89.7). Using the mean doses gave a dose ratio of 1:80. Umbilical artery blood gases showed higher pH for PE (7.30 [0.06]) than ephedrine 7.25[0.09]) (p=0.01). Among patients with effective BP control, there was a similar incidence of nausea and vomiting; in the subgroup with ineffective BP control, there was significantly less vomiting (p=0.01) in PE. No patients required treatment for bradycardia and no tachycardia was observed.

9.1.1.20. Pierce (1994):

The purpose of this study was to evaluate the effects of ephedrine and PE on fetal and maternal plasma ANP levels in 26 patients undergoing elective cesarean section under spinal anesthesia. Immediately following delivery, umbilical artery ANP concentrations were higher than umbilical vein concentrations for both groups with no differences between groups. Postpartum maternal, umbilical artery and vein blood gas variables (pH, OCO2, and PO2) were not significantly different between groups. *No BP or HR results were given and there was no mention of any adverse effects.*

9.1.1.21. George (2010):

The purpose of this double-blind up-down study was to estimate the 90% effective dose (ED90) of IV phenylephrine.

The mean of 3 SBP readings prior to entering the operating room, before anesthesia, was considered the baseline SBP. Hypotension was defined as SBP < 20% baseline or SBP < 90 mm Hg. After spinal anesthesia induction, BP was measured every minute

for 10 minutes and then every 2.5 minutes for the duration of the study. If SBP decreased > 20% baseline or to SBP < 90 mm Hg, a 5 mL bolus was administered; an anesthesiologist not involved with the study prepared the coded syringes of phenylephrine. If study medication was administered, BP was measured every minute until SBP returned to within 20% of baseline. Treatment success meant that SBP returned to within 20% of baseline or > 90 mm Hg within 1 minute. Resultant hypertension (SBP > 20% above baseline) was noted but not considered as a treatment failure. Hypotension lasting longer than 1 minute was considered as a failure and treated with a vasopressor of the anesthesiologist's choice. The study concluded with the response to blinded phenylephrine bolus or delivery, whichever occurred first.

The initial phenylephrine dose was 100 µg; each subsequent dose was based on the response of the preceding subject, with dosing changes in 20 µg increments.

Results: Sixty-nine subjects were screened, 3 were excluded prior to consenting and 1 was withdrawn before spinal anesthesia. Of the 65 subjects who completed the trial, 20 (31%) did not experience hypotension and were withdrawn from the study. Forty-five subjects (69%) experienced hypotension and were treated with phenylephrine. Of these 45 subjects, the mean reduction in SBP was 25% from baseline and the mean time from spinal anesthesia administration to hypotension was 5.8 min. No subject experienced hypertension after receiving their allocated phenylephrine dose. Two subjects required treatment for bradycardia. One subject, a treatment failure after 140 µg phenylephrine, received atropine for HR 55 with hypotension (with resolution). The second subject was a treatment success with phenylephrine 160 µg and received glycopyrrolate for HR 49 bpm without hypotension.

The authors concluded that the ED90 of phenylephrine bolus to reverse hypotension induced by spinal anesthesia in cesarean delivery to be 147 µg (95% CI 98-220 µg).

9.1.1.22. Bjornestad (2009):

This was a randomized, double-blind study comparing two groups: tight leg wrapping with an elastic bandage before the epidural block + placebo iv injections; and repeated phenylephrine 50 µg boluses immediately and at 5 and 10 minutes post-epidural block + loose placebo wrapping. (*Reviewer: Since the comparison was between "loose" and "tight" leg wrapping, it is not clear how the blinding was maintained)*. Hypotension, 30% decrease from baseline in SBP or SBP < 90 mm Hg, was treated with 5 mg IV doses of ephedrine and repeated after 2 minutes if not effective; mild hypotension was defined as requiring 1 ephedrine dose, moderate = requiring 2 doses, and severe as more than 3 ephedrine doses. The primary outcome was the incidence of hypotension, with an incidence > 50% with leg wrapping demonstrating significant inferiority and similarity to hypotension without prophylaxis.

Results: There were no statistically significant differences in the frequency or severity of hypotension between the two groups: 70% of phenylephrine patients and 65% of leg wrapping patients (NS) were normotensive all the time; there was no difference in ephedrine dosing between groups. No bradycardia, tachycardia or hypertension was observed in either of the two study groups. Only one patient in the leg wrapping group developed nausea requiring IV metoclopramide treatment; otherwise, no patient developed nausea or vomiting. Apgar scores and umbilical cord (artery and venous) pH results were similar between groups; one neonate in each group had an Apgar score < 7 only at 1 minute (none at 5 minutes). This study attempts to make a case for tight leg wrapping as a cheap, easy to use prophylaxis against hypotension; however, the incidence of hypotension in both groups seemed relatively high (e.g., 65-70%). The authors also point out that they used a smaller PE dose than that of Moran (1991) or Ngan Kee (2005) but also did not achieve hypertension or bradycardia.

9.1.1.23. Ngan Kee (2005)

This was a randomized open study in patients undergoing spinal anesthesia for elective cesarean delivery. The study investigated whether rapid crystalloid co-hydration with high-dose PE infusion was more effective at preventing hypotension than PE alone and whether this technique would prove effective for eliminating hypotension.

Women with ASA physical status I or II and singleton pregnancies, scheduled to undergo elective cesarean delivery during spinal anesthesia, were included. Patients were excluded if they had preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, known fetal abnormalities, contraindications to spinal anesthesia, or any signs of labor onset.

BP was measured every 1-2 min. BP measurements were continued until they became consistent; baseline SBP and HR were calculated as the mean of the 3 recordings.

No IV prehydration was given. Bupivacaine and fentanyl were injected intrathecally and the patient was placed in a tilted supine position. BP was measured at 1-minute intervals beginning 1 minute after spinal injection. Patients were allocated to one of 2 groups according to computer-generated randomization codes contained in sealed, sequentially numbered envelopes. In group 1, rapid crystalloid infusion was given to a maximum of 2 liters until uterine incision, and then adjusted to a minimal rate to maintain vein patency; in group 0, the infusion was continued at a minimal rate to maintain vein patency. Patients and investigators were not blinded to group allocation. Immediately after intrathecal injection, patients received a PE 100 µg/min infusion for 2 minutes (stopped if SBP > 120% baseline); subsequently, until uterine incision, the infusion was adjusted according to the SBP value measured at 1-minute intervals (infusion either continued if SBP $\leq$ baseline or stopped if SBP > baseline). If there were

3 successive episodes of hypotension, patients received a “rescue” IV bolus of 100 µg PE from a separate syringe. Bradycardia was defined as HR < 50 bpm and treated by stopping PE infusion or, if accompanied by hypotension, with 0.6 mg IV atropine. Oxygen was administered if the arterial oxyhemoglobin saturation decreased to < 95%.

The primary outcome was the incidence of hypotension. An effective method was defined as one that would reduce the incidence of hypotension to ≤ 5%.

A sample size of 53 patients/group was assumed to have 80% power (two tailed) to detect a reduction in the incidence of hypotension to ≤ 5% in group 1. To allow of a dropout rate of 5%, a total of 112 were recruited. Secondary outcomes included change in BP and HR, incidence of reactive hypertension, bradycardia, nausea or vomiting, umbilical blood gases and Apgar scores. Data were compared using the Student t test, Mann-Whitney U test, chi-square test and the Fisher exact test. Serial changes in SBP, DBP and HR were analyzed using two-way ANOVA for repeated measures.

Results: 55 patients were randomly assigned to group 0 and 57 to group 1. Two patients in group 0 and 4 patients in group 1 were excluded (due to inadequate spinal block, shivering, and replacement of the IV cannula). Insufficient umbilical arterial blood was obtained in 1 patient in each group and insufficient umbilical venous blood was obtained in 1 group 0 patient.

Baseline characteristics and surgical times appeared similar between groups.

The incidence of hypotension was 15 (28.3%) in group 0 and 1 (1.9%) in group 1 (p=0.0001). Also, the median minimum recorded SBP was lower in Group 0 (95 mm Hg) vs. Group 1 (107 mm Hg; p=0.0002). There was no difference in the incidence of hypertension (47%) or median maximum recorded SBP.

The median minimum HR was lower in Group 0 (53 bpm) than Group 1 (58 bpm) (p =0.013); however, no atropine was required in either group. There was no significant difference between groups in umbilical cord blood gases. One neonate in each group had a 1-minute Apgar score < 7 and no neonate had a 5-minute Apgar score < 7. Two patients in each group experienced nausea and, of these, 1 patient in each group vomited.

The authors concluded that high-dose PE infusion combined with rapid IV crystalloid co hydration effectively prevented hypotension during spinal anesthesia for elective cesarean delivery.

9.1.1.24. Sakuma (2010):

This was a randomized study (*no blinding mentioned*) in 32 women with singleton pregnancies and planned cesarean delivery. Cases of fetal distress, preeclampsia, gestational diabetes/hypertension and hyper-obesity (*not defined in the paper*) were excluded. The objective of the study was to compare effects of the type of vasopressor on circulatory function, anesthesia level, blood cord pH and "the like" (*as stated in the paper*) during spinal anesthetic block in low-risk cesarean section patients using hyperbaric bupivacaine, 2.0 ml. *No primary outcome, analysis, or sample size calculation was mentioned.*

Immediately following spinal anesthesia, continuous infusion of vasopressors was started at 20 ml/hr at a concentration of 4.5 mg/ml in ephedrine (Group E, n=16) and 100 µg/ml in phenylephrine (Group P, n=16). If BP was $\geq$ 1.2 times the baseline BP or if SPB was $\geq$ 90 mm Hg, then the speed of administration was halved, and if BP was 0.8 times the baseline BP, the speed of administration was doubled. If the SBP was < 90 mm Hg, a 1-2 ml bolus was administered. The maximum continuous infusion was 40 ml/hr and the minimum was 2.5 ml/hr. The shortest infusion was administered until birth. BP was measured every minute and anesthesia territory was evaluated using cold sensation loss at 5, 10 and 15 minutes after spinal anesthetic block.

Results: There were no differences between groups in reported baseline characteristics. The time from spinal anesthesia to incision was about 16 minutes and the time from induction to delivery was about 23-24 minutes. Cord blood pH was significantly lower in Group E (mean cord blood pH 7.25 $\pm$ 0.03 SD vs. 7.31 $\pm$ 0.07 SD in Group P; p value = 0.0074). There were no significant differences in neonatal Apgar scores. There were no patients in either group who did not achieve BP control. Graphs of mean SBP and HR showed a trend toward lower HR and SBP in phenylephrine-treated patients (p = NS). There was also a statistically significant difference between the groups in median anesthesia level at 15 minutes; with a higher level in Group E vs. Group P (*it is not clear whether the difference in anesthesia level confounded the difference in BP between groups*).

9.1.1.25. Ramanathan (1988):

This study assessed whether phenylephrine for treating maternal hypotension interferes with fetal oxygenation; whether transient maternal hypotension is associated with fetal lactic acidosis; and by what mechanism vasopressors increase BP when used for treating hypotension induced by epidural anesthesia.

This was an unblinded study of 137 healthy patients scheduled for repeat elective cesarean section. Patients were given 1200 ml lactated Ringers solution IV over 30 minutes, followed by epidural anesthesia induced to a T6-T4 level. Maternal BP and

HR were recorded every minute with an automatic instrument; MAP was calculated by adding 1/3 pulse pressure to DBP. Fetal HR was monitored continuously via Doppler until surgery. Patients inhaled 50% oxygen via disposable mask. An impedance cardiograph was used to measure SV, PEP, and VET. Patients were divided into three groups: Group 1 (n=57) received no vasopressors because SBP remained > 100 mm Hg. Eighty patients with SBP < 100 mm Hg after epidural anesthesia were randomly allocated to Group 2 (5 mg IV ephedrine) or Group 3 (100 µg IV phenylephrine) as soon as systolic hypotension was detected.

No primary endpoint or sample size calculation was mentioned. ANOVA was used to compare baseline hemodynamic data and post-delivery acid-base indices among the three groups. It is not stated whether the statistics were prespecified.

Results: Four patients in Group 1 and three each in Groups 2 and 3 were omitted from the study because of poor quality impedance or ECG tracings.

9.1.1.26. Moran (1989):

This abstract compared ephedrine and phenylephrine as vasopressors in women having spinal anesthesia for cesarean delivery.

Twenty-six patients scheduled for elective cesarean delivery under spinal anesthesia received 2 liters lactated Ringer's solution followed by hyperbaric bupivacaine 0.75% dosed according to patient height. Maternal BP and HR were monitored every minute until delivery and then every 3 minutes thereafter. Patients were randomized to receive boluses of IV ephedrine 5-10 mg (n=11) or phenylephrine 20-40 µg (n=15) to maintain SBP. At delivery, maternal venous pH, umbilical vein and artery pH, pCO2, pO2 were measured and base excess. Uterine incision to delivery time, Apgar scores, and the presence or absence of maternal nausea was noted; Scanlon neonatal neurobehavioral exams were performed.

Results: All patients required at least one dose of vasopressor. *The abstract did not state how much dosing was required.* One patient in the ephedrine group developed nausea. There were no significant differences between the two groups in maternal venous pH, umbilical vein pH, umbilical artery blood gases or base deficit. Infants of mothers receiving phenylephrine had higher neurobehavioral scores on two items (slightly more rapid habituation to light and slightly greater sucking reflex). All infants had Apgar scores $\geq$ 7 at one minute and 9 at 5 minutes.

The authors concluded that with adequate prehydration and proper spinal anesthesia, the treatment of hypotension with phenylephrine appeared to be as safe and efficacious as ephedrine on the basis of maternal/fetal acid-base status, Apgar scores and neurobehavioral exams.

9.1.2. Non-elective cesarean delivery

9.1.2.1. Ngan Kee (2008*):*

This was a randomized, double-blind study comparing boluses of phenylephrine 100 µg and ephedrine 10 mg for treating hypotension (SBP < 100 mm Hg) in 204 ASA 1 and 2 patients having non-elective Caesarean section under spinal anesthesia. Patients with hypertension, cardiovascular or cerebrovascular disease, multiple gestation, known fetal abnormality or medical contraindication to spinal anesthesia were excluded from the study. Patients were only recruited during office hours when the members of the investigating team were available.

After receiving neuraxial anesthesia, the patient was placed in the left-tilted supine position and received rapid IV hydration with up to 2L lactated Ringer's solution. BP was measured at 1-minute intervals beginning 1 minute after spinal injection. Patients were randomized to receive an IV bolus of either PE or ephedrine immediately after each episode of hypotension. To maintain blinding, the vasopressors were prepared in identical syringes by an anesthetist or investigator who was not involved in subsequent patient care. The upper sensory level of anesthesia was measured by pinprick 5 minutes after spinal injection. The vasopressor protocol terminated at the time of uterine incision. Bradycardia was defined as HR < 50 bpm and, if associated with hypotension, was treated with IV atropine 0.6 mg.

The primary outcome was umbilical artery pH, with an effect size of 0.03 units. The sample size calculation of 85 patients per group provided 90% power at 0.05 significance to detect a difference between groups; the sample size was increased by 20% to compensate for anticipated dropouts and difficulties with data collection. The primary analysis was performed on an intent-to-treat population, with a secondary per-protocol analysis to compare only protocol-compliant patients who actually required vasopressor treatment. A blinded obstetrician reviewed all notes after study conclusion to identify cases where factors were present indicating potential fetal compromise. Univariate intergroup comparisons used the unpaired Student's t-test or Mann-Whitney U-test as appropriate; nominal data were compared using the Chi-Square or Fisher's exact test. P < 0.05 was considered statistically significant.

Results: Of 869 patients who consented, 204 (102/group) were enrolled into the study; 73% of patients in each group had at least one episode of hypotension requiring hypotension; the number of hypotension episodes and total volume of IV fluid were similar between groups. There were no significant differences between groups in block height at 5 minutes, uterine incision to delivery time, or induction to delivery time.

The minimum recorded HR was lower in the phenylephrine group; there was no difference in maximum HR or minimum or maximum SBP and no patient required atropine. More patients in the ephedrine group had nausea or vomiting compared to phenylephrine (12.7% vs. 3.9%, p = 0.02).

There was no significant difference between the two groups in umbilical artery pH (median 7.28). There were 2 cases in the ephedrine group and none in the phenylephrine group with umbilical artery pH < 7.0. Lactate concentration was higher in the ephedrine vs. phenylephrine group for both umbilical artery and vein blood. Fetal compromise was considered potentially present in a total of 48 patients, with a similar proportion in the two groups.

There were no differences between groups in the clinical outcome of the neonates. One neonate in the ephedrine group had an Apgar score < 7 at 1 and 5 minutes; one neonate in the PE group had an Apgar score < 7 at 1 minute but ≥ 7 at 5 minutes. 17% of neonates in the phenylephrine group and 21% of neonates in the ephedrine group were admitted to the special care baby unit; there was no difference in duration of stay between groups. One neonate in the ephedrine group was admitted to the NICU because of feto-maternal transfusion syndrome, with a total duration of stay of 22 days, including transfusion and treatment of convulsions.

9.1.3. Non-obstetric surgery: Neuraxial anesthesia

9.1.3.1. Cheng (1999):

Objective: Alkalinization of local anesthetics has gained acceptance as a method of shortening the onset of epidural anesthesia, but with concern of hastened onset of sympathetic block and worsened hypotension. The purpose of this study was to determine whether combining epidural PE with alkalinized lidocaine can reduce the incidence of hypotension in epidural anesthesia.

Reviewer comment: This is a different route of administration than the other publications.

81 adult patients, ASA I or II, undergoing inguinal herniorrhaphy under lumbar epidural anesthesia were randomized to receive epidural alkalinized lidocaine with one of 4 doses of PE (0, 50, 100 or 200 µg in Groups 1-4, respectively). Patients received 500 mL of lactated Ringer's solution prior to anesthesia. BP, HR and foot skin temperature were measured 1 minute prior to the epidural injection and every 5 minutes thereafter for 1 hour. Pinprick testing was performed at 20- and 30-minute intervals post-epidural injection to determine highest level of sensory block. Incremental doses of 4-8 mg ephedrine IV were administered to restore BP if systolic BP was <80% of baseline or < 100 mm Hg. Hypotension was defined as MAP < 80% of baseline. MAP was

calculated by adding 1/3 of the pulse pressure to the DBP. To determine whether PE-induced vasoconstriction would be reflected in lower limb skin blood flow, foot skin temperature was measured with a thermoprobe attached to the dorsum of the first interdigital space of the right foot.

Comments: 1. Ephedrine as rescue might confound whether phenylephrine was inadequately dosed using this route;
2. BP measured every 5 minutes might miss transient signals.

Patient characteristics and baseline hemodynamic variables were compared using one-way ANOVA. Sequential MAP and HR measurements were tested for the main effects of dose, time and dose x time using repeated measures ANOVA. Kruskal-Wallis test was used to compare the highest sensory block level among groups. Spearman rank correlations were used to test associations between PE doses and the presence of hypotension or ephedrine use. One-sided Fisher's exact tests were used to test for pairwise differences among groups and their effects. Bonferroni corrections were made for multiple comparisons only when the overall effects for the Spearman rank correlation or ANOVA analyses were not significant. $P < 0.05$ was considered statistically significant.

Comment: The primary and secondary outcomes and sample size calculations are not explicitly stated. It is not clear whether these analyses were prespecified.

Results:
One patient experienced an episode of severe hypertension (BP 212/146 mm Hg) and confusion; it was suspected the 200 µg PE-alkalinized lidocaine mixture was directly absorbed through a lacerated epidural vessel. IV droperidol was injected and the patient gradually recovered with sequelae, but this patient was not included in the data analysis.

There were no significant differences in baseline characteristics, hemodynamic variables and highest sensory block across groups. The study population was mostly male; mean age was about 65 years.

Repeated-measures ANOVAs found the overall effect of time to be significant for both MAP and HR ($p = 0.0001$). Overall dose effects were not significant for MAP or HR, and dose x time interaction was not significant for MAP.
However, the authors noted confounding of the repeated-measured ANOVAs because some patients were "rescued" with ephedrine for hypotension, and the "true MAP differences" might be greater than reported.

Several post hoc analyses were significant, including MAP between Groups 2 (PE 50) and 4 (PE 200) at 15 minutes ($p = 0.0005$) and Groups 1 (PE 0) and 4 (PE 200) at 20

minutes (p= 0.0006). Hypotension and ephedrine use were negatively correlated with PE dose (hypotension r = -0.254, p = 0.023; ephedrine use r = -0.275, p = 0.013).

HR analysis showed a significant dose x time interaction (p =0.0148); at no time did the mean HR for any group differ by > 10% of baseline.

There were no significant differences in foot temperatures between groups.

Comments: 1. one case of severe hypotension and transient confusion in a patient receiving 200 µg PE dose. 2. Phenylephrine ADME characteristics, and consequent BP effects, might differ with different route of administration.

9.1.3.2. Brooker (1997):

This prospective, double-blind, randomized, crossover trial tested the hypothesis that epinephrine would more completely and effectively restore BP and CO after spinal anesthesia than phenylephrine. Patients were excluded for: anticoagulation, symptomatic coronary artery disease, cardiac valvular regurgitation or stenosis, pregnancy, or unwillingness to have a spinal anesthetic. Patients were also excluded if satisfactory images of the mitral valve could not be obtained during preoperative screening.

After tetracaine spinal anesthesia, when a 15% reduction in SBP was observed, treatment was initiated with a bolus of either epinephrine 4.0 µg or phenylephrine 40.0 µg followed by an infusion of either epinephrine 0.05 µg /kg/min or phenylephrine 0.5 µg /kg/min, respectively. If SBP did not increase with the initial infusion, repeat boluses could be given and the infusion rate could be doubled until SBP increased to pre-anesthesia value. Then, after measurements were completed, the infusion was discontinued. A 10-minute washout period was used, and the second drug was given in the same manner. The drugs were given in a random order. SV was determined by echocardiography, and CO was determined from the formula SV x HR. *Comment: There was no mention of rescue therapy or maximal duration of infusion.*

No primary or secondary endpoints or sample size calculation were mentioned. A mixed-model double-repeated ANOVA was used to determine differences between time-points and between treatment groups. Corrections were made for multiple comparisons using Bonferroni technique as appropriate using Fisher's protected LSD approach. Statistical significance was set at an alpha of 0.05.

Results: Thirteen of 14 patients completed the study; one patient was excluded because SBP did not decrease by 15% after spinal anesthesia. The extent of spinal anesthesia was measured by pinprick 10 minutes after tetracaine injection; the median level of spinal analgesia was T7, with a range of T12-T4. The study population was ASA I-III, mostly male, median age 62.5 years. Surgical procedures performed included 5 orthopedic, 6 urologic and 2 gynecologic operations. Five minutes after tetracaine

injection, SBP decreased from 143 ± 6 mm Hg to 125 ± 5 mm Hg (p < 0.001); MAP decreased from 102 ± 4 mm Hg to 89 ± 3 mm Hg (p < 0.001) and DBP decreased from 81 ± 3 mm Hg to 71 ± 3 mm Hg (p < 0.001) before treatment.

Increases in SBP and MAP were observed with both phenylephrine and epinephrine.

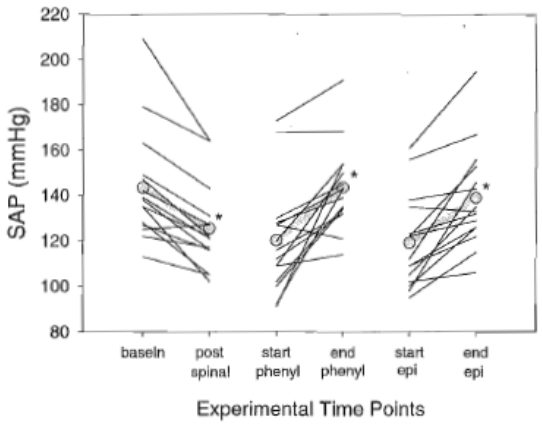


Fig. 1. Management of hypotension after spinal anesthesia: effect on systolic blood pressure at the following points: 1) baseline (baseln); 2) five min after injection of tetracaine (post spinal); 3) before treatment of hypotension with phenylephrine (start phenyl); 4) after treatment of hypotension with phenylephrine (end phenyl); 5) before treatment of hypotension with epinephrine (start epi); 6) after treatment of hypotension with epinephrine (end epi). Figure shows raw data from all patients. The thicker line denotes the group mean. *P < 0.001 for connected data points.

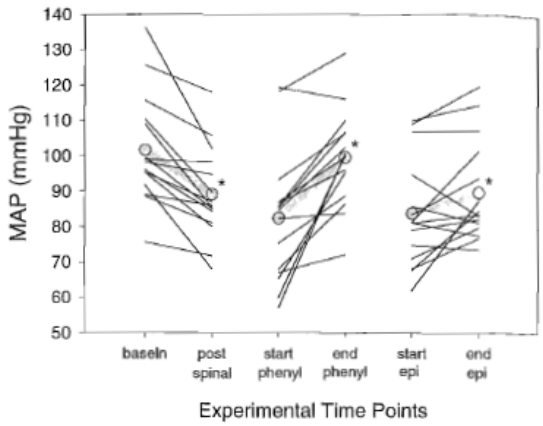


Fig. 2. Management of hypotension after spinal anesthesia: effect on mean arterial pressure at the following points: 1) baseline (baseln); 2) five min after injection of tetracaine (post spinal); 3) before treatment of hypotension with phenylephrine (start phenyl); 4) after treatment of hypotension with phenylephrine (end phenyl); 5) before treatment of hypotension with epinephrine (start epi); 6) after treatment of hypotension with epinephrine (end epi). Figure shows the raw data from all patients. The thicker line denotes the group mean. *P < 0.001 for connected data points.

Figure 10. Brooker: BP at experimental time points.

An increase in DBP was observed with phenylephrine but not epinephrine. HR increased with epinephrine and decreased with phenylephrine. SV did not change after spinal anesthesia or after phenylephrine but increased with epinephrine. CO was unchanged after spinal anesthesia; CO decreased with phenylephrine (8.5 to 6.2 L/min, p < 0.003) and increased with epinephrine (7.8 to 10.8 L/min, p < 0.001).

The largest doses of epinephrine and phenylephrine required to manage hypotension were 136 µg and 1,1132 µg, respectively.

There were few arrhythmias at any time during the study and no significant differences between phenylephrine and epinephrine; no ST changes consistent with ischemia during continuous 2-lead ECG monitoring (II, V5) and no new segmental wall motion abnormality on echocardiographic images.

9.1.3.3. Acosta (1999):

This was a nonrandomized open trial studying the effect of 0.1 mg PE boluses in cirrhotic patients who developed postreperfusion syndrome (PRS) (n=10) during

orthotopic liver transplantation compared with patients without PRS (n=22). The MAP was lower in patients with PRS than in those without PRS, after unclamping the portal vein; five minutes after the start of reperfusion, there were no hemodynamic differences between the two groups and systolic function, expressed as RVSWI/CVP and LVSWI/PCWP were normal during reperfusion. The authors mention that "it was not possible to determine CI and related variables after unclamping the vena cava *and after unclamping the portal vein;" the extent of missing variables is not specified in the publication. Also, multiple variables were explored without a specified primary efficacy variable. However, the available results are consistent with a BP-raising effect of PE.*

9.1.4. Non-obstetric surgery: General anesthesia:

9.1.4.1. Goertz (1993):

The aim of this study was to continuously assess LV function, using TEE, after phenylephrine bolus injection.

The study population evaluated patients with severe coronary artery disease and normal LV global function (Group 1: n=14) and patients with valvular aortic stenosis (Group 2: n=10) who developed hypotension during general anesthesia. BP was monitored via femoral artery catheter in 19 patients and radial artery catheter in 5 patients. A 7-lead ECG was used for monitoring. Patients with mean BP > 10% less than lowest recorded value during the 24 hours prior to operation received phenylephrine 1 µg/kg or norepinephrine 0.05 µg/kg in random order, with the second substance administered when BP and HR had returned to baseline levels. Hemodynamic measurements started immediately before injection and continued for 3 minutes after administration.

Because some hemodynamic parameters were skewed, nonparametric tests were selected for statistical analysis (*not clear from the publication whether this was prospective or post hoc*). *Also, no primary outcome or sample size calculation was specified.*

Results: Significant increases in MAP from time 0 to 3 minutes post-dosing were observed in both groups and on both drugs. In all patients, MAP returned to baseline 2-5 minutes after injection; there was no difference in the maximal MAP and duration of MAP increase following drugs. Decreases in HR were observed in both groups and with both drugs with no significant difference between drugs. In the CAD patients treated with phenylephrine, there was an observed reduction in the Fractional Area Change and mean HR-corrected VCF and increase in end-systolic wall stress (not seen in the AS group treated with phenylephrine). The authors postulated that the increase in LV wall stress caused the impairment of LV function post-phenylephrine

administration. According to the authors, these effects were transient; it was unknown if there was an effect on clinical outcome. There was no report of ECG changes.

9.1.4.2. DiNardo (1991):

This was a randomized (*no mention of blinding*) study of 26 males and 2 females, EF > 40%, undergoing elective CABG with LIMA to LAD, hemodynamically stable post-CPB, mean age 61.7 years, assigned to receive one of six 2-drug combinations of PE, norepinephrine, and epinephrine. After termination of CPB baseline, control hemodynamic and graft flow measurements were made. The first vasoactive drug was administered as an infusion to elevate MAP 20 mm Hg; when necessary, pacing was used to maintain HR at the control rate. After a 5-minute period of stability at the increased MAP, hemodynamic and graft flow measurements were repeated. The vasoactive agent was then discontinued. After 5 minutes of stability a second set of control hemodynamic and graft flow measurements were made, the second vasoactive drug was administered in a similar fashion (to elevate MAP 20 mm Hg) and, after a 5-minute period of stability at the increased MAP with a steady-state infusion of vasoactive agent, repeat measurements were made. Changes in hemodynamic and graft flow were analyzed by paired t-test; group differences were tested by ANOVA. Results: 16 patients received a PE infusion; 21 a norepinephrine infusion; and 19 an epinephrine infusion. For all patients, the second set of control measurements was not significantly different from the first set. The mean dose of PE required to elevate MAP was 76 $\pm$ 31 µg/min or 0.87 $\pm$ 0.37 µg/kg/min. PE infusion induced an increase in mean flow through SV grafts (p=NS) from 68 to 81 ml/min; and a decrease in mean LIMA graft flow from 40 to 32 ml/min (p=0.008). Norepinephrine and epinephrine infusions increased mean SV and LIMA flows. PE increased MAP from 75 to 94 mm Hg (p=0.0001), reduced CI (3 to 2.6 L/min/m2, p=0.0003) and increased LVSWI from 33.3 to 38.8 gm-m/beat/m2 (p=0.0002); PE infusion was not associated with significant changes in HR, PCW, or CVP. The authors concluded that PE, compared with epinephrine and norepinephrine, adversely affects IMA graft flow.

9.1.4.3. Baraka (1991):

This study investigated hemodynamic effects of an IV bolus of norepinephrine, PE and epinephrine in patients with ischemic heart disease. 30 patients with CAD, without CHF or LV EF < 40%, scheduled for elective CABG were randomized to receive norepinephrine 10 µg (n=10), epinephrine 10 µg (n=10) or PE 100 µg (n=10) administered 10-20 minutes following induction of anesthesia and before skin incision. There is no mention of blinding, primary endpoint, or sample size calculation. When the mean MAP following epinephrine was reached, the other hemodynamic parameters were measured. PE and norepinephrine resulted in significant increases in MAP, SVR and PCWP; the HR decreased and the CO showed a decrease that was not statistically significant. These results seem consistent with effects of PE in other studies.

Table 20. Baraka: hemodynamic effects of phenylephrine

Table 2
The Hemodynamic Effects of Phenylephrine 100 μg

	Control	PH 100 μg	% Change	P
MAP (mmHg)	72.7 ± 9.5	97.7 ± 10.4	35.0 ± 9.0	<0.0001
CO (L/min)	3.74 ± 0.53	3.48 ± 0.68	−6.3 ± 16.7	NS
PCWP (mmHg)	10.1 ± 3.8	12.5 ± 5.2	30.0 ± 34.4	0.03
SVR dyne-sec.cm^{-5}	1420 ± 296	2260 ± 280	57.7 ± 23.3	0.002
HR/min	66 ± 13	60 ± 11	−8.6 ± 7.6	0.01

9.1.4.4. Nygren (2006):

This was a randomized, unblinded crossover study to evaluate the effects of norepinephrine and PE on jejeunal mucosal perfusion, gastric-arterial PCO2 gradient, and the global splanchnic oxygen demand-supply relationship after cardiac surgery. Nine males and one female, mean age 66 and normal EF, underwent propofol sedation and mechanical ventilation after uncomplicated CABG. All patients received atenolol or metoprolol on the morning of surgery. In the intensive care unit, patients were sedated with propofol to provide MAP 65-75 mm Hg according to a standard protocol. Measurements started 345 + 40 minutes after the end of CPB; patients received randomly and sequentially norepinephrine 0.052 $\pm$ 0.009 μg/kg/min and PE 0.50 $\pm$ 0.22 μg/kg/min to increase MAP by 30%, titrated to the target MAP of 90 mm Hg. The highest acceptable SBP during the treatment periods was 150 mm Hg. There was a 60 minute washout between the two treatments. Results: Both drugs increased MAP, SVRI, PCWP (PAOP) and CVP. There were also decreases in CI and HR with PE administration (p=NS). PE administration led to an increase in splanchnic oxygen extraction that was more pronounced than with norepinephrine ($p < 0.05$); PE also increased the mixed venous-hepatic venous oxygen saturation gradient to a greater extent than norepinephrine ($p < 0.05$). Arterial lactate levels increased significantly with PE ($p<0.01$) but not with norepinephrine. However, intestinal mucosal perfusion or gastric-arterial PCO2 gradient was not changed by either drug when used to increase MAP by 30-35% and the authors "accepted the null hypothesis." The authors also concluded that PE induced more pronounced global α1-mediated splanchnic vasoconstriction compared with norepinephrine; however, neither drug affected jejeunal mucosal perfusion or gastric mucosal PCO2 gradient.

9.1.4.5. Smith (1990):

The objective of this nonrandomized study was to characterize the relationship between preoperative LV dysfunction and requirement for alpha-adrenoreceptor agonist drugs in

CABG patients during emergence from CPB. 102 patients undergoing elective CABG were studied; 34 had normal LV function, 41 had mild dysfunction, 19 had moderate dysfunction and 8 had severe dysfunction. Group 1 consisted of 75 patients with normal or mild LV impairment; group 2 consisted of 27 patients with moderate or severe LV dysfunction. Patients were excluded if they required combined vascular or valvular surgery or were unstable. All patients were maintained on their usual dose of beta-blockers/calcium channel-blockers up to the morning of surgery. Results: Group 2 had a higher incidence of myocardial infarction prior to surgery than Group 1. A total of 49.3% of patients in group 1 and 39.2% in group 2 required some form of inotropic and/or vasopressor support after CPB (p=NS). Group 2 patients required significantly greater cumulative doses of PE after CPB than group 1 patients.

9.1.4.6. Schwinn (1988) :

The authors tested the hypothesis that α1-adrenergic responsiveness decreases in patients with impaired ventricular function, compared with patients with normal ventricular function, who undergo coronary artery revascularization.

This was a nonrandomized, open study of 34 patients for elective aortocoronary bypass surgery. Patients with unstable angina, receiving intraaortic balloon counterpulsation, requiring IV nitroglycerin or inotropic agents, or receiving alpha-adrenergic blocking medication were excluded from the study. Impaired ventricular function was prospectively defined as LVEF $\leq$ 40% during cardiac catheterization within 1 month of surgery. Group I comprised 12 patients with LVEF < 40% (range 20-40%) and group II comprised 22 patients with LVEF > 40% (range 43-68%).

A phenylephrine dose response curve was generated prior to anesthesia induction with an initial 20 µg bolus injection (via internal jugular vein); the peak MAP in the first 2 minutes, along with HR, PAD, PCWP and CVP, were recorded. Once MAP had returned to baseline, at least 5 minutes after the first phenylephrine bolus dose, the next bolus dose (40 µg) was injected and hemodynamic parameters measured as before. Bolus doses were given in the following sequence: 20, 40, 80, 120, 160, 200, 240, 280, 320, 360, and 400 µg, until peak MAP increased 20% above baseline MAP. At this point, the phenylephrine dose response curve was considered complete. In most patients, the dose response was completed within the first 6 bolus doses of phenylephrine. A second blinded investigator confirmed the peak mean BP readings in every patient.

Anesthesia was induced; 10 minutes post-intubation and prior to incision, baseline hemodynamics were obtained and a second phenylephrine dose-response curve was generated. A third dose-response was generated during cardiopulmonary bypass, after aortic cross-clamp and stabilization of temperatures.

Results: In addition to expected baseline differences in EF, there were baseline imbalances between the two groups with respect to myocardial infarction and congestive heart failure (higher in Group I) and use of beta-blockers (higher in group II). In addition, patients in group I had lower MAP pre-anesthesia. It is not known whether baseline imbalances confounded the results. The results suggested that fentanyl anesthesia was associated with decreased α1-adrenergic responsiveness in patients with impaired ventricular function, compared to those with normal ventricular function; and that less phenylephrine was required during CPB and aortic cross-clamp than during awake state to produce the same pressor effect.

9.1.4.7. Schwinn (1989):

The purpose of this unblinded study was to assess the time course and hemodynamic effects of IV bolus phenylephrine in 18 patients undergoing elective CABG. Patients were randomized to receive 50, 100, 150 or 200 µg IV bolus phenylephrine following anesthesia induction. There was no placebo control or unanesthetized control.

Results: Mean patient age was 63.2 years; race and gender information were not recorded. The mean baseline EF was 50.8% mean MAP was 74.4 mm Hg; CO 3.9 L/min.

All patients had significant increases in MAP and calculated SVR and significant decrease in CO during bolus phenylephrine administration. Peak hemodynamic effects occurred simultaneously about 42 seconds after phenylephrine administration. Significant BP differences between groups (50 vs. 200 µg phenylephrine) occurred at 115 seconds. The maximal increase in MAP (+ 18 mm Hg) occurred in patients receiving 200 µg phenylephrine. Significant HR decreases were also observed following phenylephrine administration. There were no ischemic events (PVCs or ECG changes) or sustained hemodynamic changes associated with IV phenylephrine administration in any patient.

9.1.4.8. Butterworth (1990):

The purpose of this study was to determine whether a clinically significant interaction occurs between calcium and phenylephrine. Eight patients, 48-73 years old (mean 61 years) recovering from aortocoronary bypass surgery, were studied in the ICU. After baseline measurements were obtained, patients received a placebo infusion, repeat hemodynamic measurements, and three 8-minute incremental infusions of phenylephrine 150, 300 and 450 ng/kg/min. Hemodynamic data were collected at 4 and 8 minute into each infusion. After a 20 minute rest period and new baseline measurements, calcium chloride 5 mg/kg IV bolus was administered followed by 2 mg/kg/h IV infusion; measurements were repeated 10 and 20 minutes into the calcium infusion. Then the same phenylephrine sequence was administered.

Results: There was no placebo effect on any measured hemodynamic variable. Calcium administration increased ionized calcium levels and MAP. Phenylephrine increased MAP (from 83 ± 2 to 97 ± 2 mm Hg, an average increase of 14 mm Hg) and was not synergistic with calcium.

9.1.4.9. Lobato (2001):

The objective of this randomized, unblinded study was to compare changes in internal mammary artery (IMA) flow after CPB in response to milrinone or nitroglycerin and to establish effects of α-adrenergic stimulation.

Thirty adults scheduled for elective CABG surgery were randomized to: Group 1: continuous IV nitroglycerin (2 µg/kg/min; n=10); Group 2: standard loading dose of milrinone (50 µg/kg over 10 minutes; n=10); Group 3: combination of both drugs (continuous IV nitroglycerin infusion followed by milrinone loading dose; n=10). IMA flow was measured 10 minutes after completion of milrinone dose or 5 minutes after the start of the nitroglycerin infusion. Patients subsequently received continuous IV phenylephrine infusion (1 µg/kg/min) with stepwise increments to increase MAP to 20% of baseline value after CPB. The IMA flow was measured again and the study concluded.

Results: The 3 groups appeared similar in age, LVEF and CPB data. Phenylephrine significantly increased IMA flow in all patients receiving milrinone alone or milrinone in combination with nitroglycerin. Post-CPB blood flow with milrinone was greater than with nitroglycerin at the doses studied.

9.1.4.10. Skubas (2005):

This study evaluated the effect of phenylephrine on radial artery flow when used as a coronary artery bypass conduit in the presence or absence of a vasodilator drug.

Thirty patients undergoing CABG with arterial conduits in which the radial artery was used as a T-graft were randomly assigned to receive IV normal saline (n=10); nitroglycerin 0.5 µg/kg/min (n=11) or nicardipine 0.5 µg/kg/min (n=9) early in the operation. After discontinuation of CPB and stable hemodynamics, control measurements were obtained followed by phenylephrine infusion to achieve 20% increase in MAP, after which measurements were repeated.

Following phenylephrine infusion, MAP and SVR increased in all three groups, consistent with a BP-increasing effect of phenylephrine. Mean HR appeared similar pre- and post-phenylephrine infusions.

9.1.4.11. Borum (2000):

This unblinded study evaluated whether transesophageal atrial pacing reduces phenylephrine requirement for BP support during general anesthesia for carotid endarterectomy.

Thirty-six patients undergoing carotid endarterectomy under general anesthesia were randomized to phenylephrine infusion (group 1; n=19) or phenylephrine infusion plus transesophageal atrial pacing (group 2; n=17) to maintain SBP within 20% of baseline SBP. Outcome measures included: amount of phenylephrine required in each group; variance of SBP outside the desired range; occurrence of postoperative ECG or myocardial enzyme changes suggesting ischemia (or injury).

The average requirement for phenylephrine was significantly less for group 2 compared with group 1 patients. In group 1, 8 or 19 patients (CHECK< DOES NOT MAKE SENSE) required atropine for bradycardia with hypotension (criteria for atropine = HR < 50 bpm associated with hypotension). No patients in group 2 required atropine. The percent of time in SBP below target was similar between groups. There was no evidence in either group of postoperative myocardial ischemia or injury.

9.1.4.12. Mutch (1995):

The purpose of this unblinded nonrandomized study was to compare two anesthetic protocols for hemodynamic instability (HR or MAP < 80% or > 120% baseline values) measured at 1-minute intervals during carotid endarterectomy. The authors hypothesized that patients given a continuous IV infusion of propofol, compared to inhaled isoflurane, would have less hemodynamic instability and a decreased incidence of myocardial ischemia.

One group received propofol/alfentanil (Group Prop; n=14) and the other isoflurane/alfentanil (Group Iso; n=13). Phenylephrine was infused to support MAP at 110 $\pm$ 10% of baseline values during cross-clamp of the internal carotid artery in both groups.

The power calculation was based on a 50% reduction in antihypertensive therapy as an index of hemodynamic stability. However, a single primary outcome was not specified.

Thirty patients were studied; three patients were removed from analysis due to technical reasons (e.g., failed Holter monitoring records, data acquisition). A total of 8/13 patients in Group Iso and 6/14 patients in Group Prop developed hypotension; most were treated with bolus ephedrine and persistent hypotension was treated with continuous IV infusion of phenylephrine. During cross-clamping of the internal carotid artery, all patients received IV phenylephrine for BP support and no patient in either group had MAP values out of range during this period.

9.1.5. Septic shock population:

9.1.5.1. Jain (2010):

Objective: Compare norepinephrine and phenylephrine in the management of dopamine-resistant septic shock.

Inclusion criteria: persistent hypotension, evidence of at least one end-organ dysfunction, infection plus at least two of the following: elevated or decreased body temperature; HR > 90 bpm; respiratory rate > 20/min or arterial CO2 < 32 mm Hg; WBC > 12,000/mm3 or < 4000/mm3 or > 10% immature bands. Persistent hypotension was defined as: SBP < 90 mm Hg or MAP < 60 mm Hg and CVP > 12 mm Hg or PA occlusion pressure > 18 mm Hg, despite adequate fluid resuscitation and continuous dopamine at 25 µg/kg/min for 1 hour. Exclusion criteria included: cardiac dysfunction, acute mesenteric ischemia, severe liver disease, chronic renal failure, and uncorrected shock due to blood loss. All subjects were mechanically ventilated to maintain PaO2 > 60 mm Hg and Pa CO2 35-40 mm Hg.

Patients were randomly allocated to two groups using computer-generated random numbers. The operator who manipulated the syringe pump was aware of the allocation; the assessment of outcome was conducted by another physician who was blinded to study drug. Dopamine infusion was continued at 25 µg/kg/min throughout the study duration; in addition, serial IV fluid challenges were given through the study.

Table 21. Jain: study design

Table I: Study design

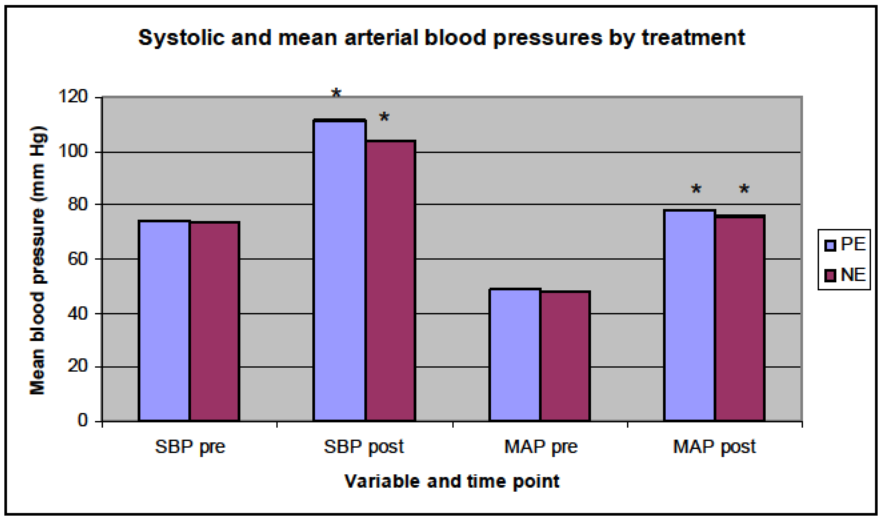
	Group-I (27 patients)	Group-II (27 patients)
Drug used	Norepinephrine	Phenylephrine
Dose range	0.5–3.5 µg/kg/min	0.5–8.5 µg/kg/min
Increments	0.5 µg/kg/min	I µg/kg/min
Time interval	30 min	30 min

The study allowed for 8 up-titrations for phenylephrine and 6 up-titrations for norepinephrine; it is not clear how these up-titrations were managed in terms of blinding. The duration of infusion is also not explicit although of "short duration." The target of therapy was to achieve all the following parameters: SBP > 90 mm Hg; MAP > 75 mm Hg; SVRI > 1100 dynes.s/cm5m2; CI > 2.8 L/min/m2; DO2I > 550 ml/min/m2; VO2I > 150 ml/min/m2. All parameters were recorded every 30 minutes, with a dose increment if the targets were not achieved. A responder was defined as the subject who achieved and maintained all the predefined targets of therapy for a period of continuous 6 hours in the specified dose range.

The sample size calculation, 25 cases/group, was based on detecting a 20% difference in the measured variables with a standard deviation of 25%, 80% power and 95% Confidence Intervals. The duration of the study was 12 months, from August 2008 to July 2009. Comparison of APACHE II scoring and sex distribution was done using Fisher's exact test. Other parameters were compared by one-way ANOVA. A $p < 0.05$ was considered statistically significant.

Results: Of 98 screened, 60 subjects met inclusion criteria and were initially randomized; three subjects in each group were excluded due to protocol violation and 54 completed the study. There were no statistically significant differences between the two groups in age, weight, APACHE II score (mean 18 in the norepinephrine group and 19.04 in the phenylephrine group), ARDS, cause of shock, and pretreatment parameters. Mean blood pressure and urine output results are displayed graphically below. In addition, statistically significant increases were observed in post-treatment SVRI and decreases in serum lactate in both groups. There also increases in post-treatment DO2I and VO2I parameters in both groups. There were no statistically significant differences between the two groups in responders or survivors; however, the length of follow-up for survival is not clear in the publication.
In the discussion, the authors stated that "one must consider the fact that delayed administration of phenylephrine in sepsis may negatively affect renal function as compared to norepinephrine," referencing the pilot crossover study by Morelli. However, the publication did not mention whether vasopressor treatment in this study affected creatinine clearance or liver function.

Figure 11. Jain: Blood pressure by treatment and time point



The maximal infusion rate of phenylephrine required to achieve the target was 3.28 ± 1.02 µg/kg/min and maximal infusion rate of norepinephrine was 2.96 µg/kg/min.

9.1.5.2. Morelli (2008):

Objective: Investigate the effects of first-line therapy with phenylephrine or norepinephrine on systemic and regional hemodynamics in patients with septic shock.

This was a prospective, randomized, double-blind, active-controlled trial at a single site in Rome, Italy. Thirty-two patients with septic shock, MAP < 65 mm Hg despite volume resuscitation (PAOP 12-18 mm Hg and CVP 8-15 mm Hg) were enrolled and randomized to a 12-hour infusion of norepinephrine or phenylephrine (n=16 each) titrated to achieve MAP between 65 and 75 mm Hg. All patients received mechanical ventilation using a volume-controlled mode with plateau pressure maintained below 30 cmH2O. Patients were monitored via pulmonary and radial artery catheters; MAP, RAP, MPAP and PAOP were measured at end expiration. HR and ST segments were monitored via continuous ECG recording; CI was measured using thermodilution. Regional hemodynamic monitoring was performed via femoral artery thermodye dilution catheter for determination of plasma disappearance rate of indocyanine green (PDR) and blood clearance of indocyanine green related to body surface area (CBI). An air tonometer was inserted via nasogastric route to measure gastric mucosal CO2 tension.

Patients also received serial fluid challenges to maintain CVP at 8-15 mm Hg and PAOP 12-18 mm Hg during the intervention period; packed RBC were transfused when hemoglobin concentrations decreased < 8 g/dl.

At the end of the 12-hour study period, study drugs were gradually reduced and patients were switched to open-label norepinephrine.

The primary endpoint(s) was (were) the modifications of the PDR and CBI after phenylephrine compared with norepinephrine. A sample size of 16/group was required to detect a 30% difference in one of the measured variables (PDR or CBI) with an expected SD of 30%, power of 80% and α of 0.05. Differences within and between groups were analyzed using two-way ANOVA for repeated measurements with group and time as factors. Time-independent variables were compared with one-way ANOVA. In the case of significant group differences over time, post hoc comparisons were performed. Categorical data were compared using the chi-square test. A $p < 0.05$ was considered statistically significant.

Results: Of 62 screened patients, 30 were excluded due to prior catecholamine therapy, low CO or chronic renal failure. Thirty-two patients, 16/group, were enrolled and randomized. Except for a higher weight in the norepinephrine group, there were no significant differences between groups in baseline characteristics. The amount of fluids infused during the study period was similar. The MAP goal (65-75 mm Hg) was reached in all subjects; twelve hours post-randomization, the MAP was significantly

higher in the norepinephrine group compared to phenylephrine (p = 0.011) but this difference was within the predefined MAP threshold. In both groups there was a statistically significant decrease in heart rate and statistically significant increase in SVRI and LVSWI. The PVRI increased with time only in the phenylephrine group. Six patients in the norepinephrine group and eight patients in the phenylephrine group received dobutamine during the study period with similar dobutamine requirements between groups. The incidence of new-onset tachyarrhythmias was similar between both groups (2/16 for phenylephrine, 1/16 for norepinephrine).

There was no significant overall difference between groups in any variable of regional hemodynamics, acid-base homeostasis or oxygen transport. Urine output, creatinine clearance and troponin I were not significantly different between the two groups. The length of ICU stay and ICU mortality were similar between groups.

The number of patients who required renal replacement therapy at the end of the 12-hour study period was higher in the phenylephrine group (n= 7) vs. norepinephrine group (n= 2) (**p= NS, but unfavorable for phenylephrine**).

9.1.5.3. Gregory (1991):

This was a retrospective analysis of 13 surgical ICU patients with septic shock (MAP < 65 mm Hg; SVRI < 1500 dyne-sec/cm5/m2; evidence of hypoperfusion: mental status changes, urine output < 0.5 mL/kg.hr or blood lactate > 1.7 mmol/L) who were treated with phenylephrine between July and December, 1989. Clinical criteria for sepsis included positive blood or peritoneal cultures or obvious peritonitis, hyperthermia or hypothermia, and WBC count > 12,000/mm3. All patients underwent invasive arterial and pulmonary artery catheter monitoring. Patients were resuscitated with blood or crystalloid to achieve PAOP > 10 mm Hg and hemoglobin > 10 g/dL; patients with persistent vasodilatation and hypotension received phenylephrine which was initiated at an infusion rate of 0.5 µg/kg/min and titrated to maintain MAP > 70 mm Hg. Dobutamine was started if the CI was < 3.0 L/min/m2 and titrated until V0x reached a plateau or adverse effects (arrhythmias or heart rate increase > 15%) were noted. Dopamine, when used, was limited to < 5 µg/kg/min for its purported renal vasodilatory properties. Urine output, blood lactate concentration and serum creatinine were monitored as indicators of tissue perfusion. Patients were “weaned” from phenylephrine when deemed clinically stable (MAP > 70 mm Hg). HR, BP, PAOP and CO were recorded immediately before and within 1 hour of phenylephrine administration.

Mean age was 67 (± 11.1) years; mean APACHE II score was 24 (± 4.7). Increases in MAP were observed in all patients within 5-10 minutes of initiation of phenylephrine. Mean MAP, SVRI, SVI, LVSWI were increased from baseline; HR and PAOP were unchanged from baseline during phenylephrine therapy; oxygen extraction ratio and

mixed venous oxygen saturation were unchanged at the time of maximal VO2. Increases in mean urine output and decreases in mean blood lactate were observed; 11 of 12 evaluable patient maintained urine flow > 0.5 mL/kg.hr during phenylephrine; however, 5 of these patients were receiving concomitant dopamine. No clinical evidence of impaired organ function during phenylephrine therapy was noted; mean serum creatinine concentration was 1.7 ± 1.1 mg/dL at baseline and was 1.8 ± 1.4 mg/dL at the final day of treatment; the paper did not record creatinine clearance. Two patients developed tachyarrhythmias which resolved on infusion reduction or discontinuation of dopamine (apparently not attributed to phenylephrine). In 4 patients, the MAP decreased to < 65 mm Hg with dobutamine, and phenylephrine was then used to maintain MAP > 70 mm Hg. Six patients died in the hospital; four patients died from sepsis; one developed a fatal hemorrhage at 43 days; and one died of unresectable metastatic carcinoma at 47 days post-phenylephrine.

Comment: This retrospective study could be subject to bias. However, the results appear consistent with an effect on raising blood pressure.

9.1.5.4. Patel (2010):

The objective of this single-center, prospective, randomized open-label study was to determine if there was an efficacy or safety benefit to dopamine vs. norepinephrine (NE) as the initial vasopressor in patients with septic shock.
Inclusion criteria were: age 18 or older; diagnosis of systemic inflammatory response syndrome (SIRS) plus suspected or documented source of infection and admitted to ICU; MAP < 60 mm Hg and/or SBP < 90 mm Hg after adequate fluid resuscitation; and requiring vasopressors for management. Patients were excluded with alternative causes of their shock or SIRS; patients allergic to DA or NE; or patients on vasopressors for > 6 hours before enrollment.

Randomization was based on whether the patient presented on an odd or even calendar day of the month (e.g., third day = dopamine; fourth day = NE) *(Note: the authors acknowledged that this randomization scheme has the potential to introduce bias)*. Patients with MAP < 60 mm Hg or SBP < 90 mm Hg were randomized to receive vasopressor; if the predetermined maximum dose was reached for the initial vasopressors (DA 20 mcg/kg/min or NE 20 mcg/min) then vasopressin was added at a continuous infusion dose (0.04 U/min). Patients who required additional hemodynamic support were started on phenylephrine 25-200 mcg/min, titrated to reach goal hemodynamic parameters. *Phenylephrine was thus given as "third-line" therapy.*

The primary endpoint was 28-day all-cause mortality.

The sample size was based on the assumption of expected mortality of 40-60% due to septic shock; the assumed effect was 20% reduction in mortality rate, requiring n=240

to achieve 80% power. The primary outcome was compared using chi-square test. Statistical significance was set at $p \leq 0.05$.

Results: A total of 252 patients were enrolled over a 5-year period. Baseline characteristics (e.g., APACHE II scores, SOFA scores, fluid administration, gender, steroid use, Gram positive/negative/culture negative; sites of infection, use of recombinant activated protein C) appeared similar between groups; however, mean age or age distribution was not reported *(age is a well-known confounder with respect to mortality)*. There was no significant difference between the two groups in the primary endpoint, 28-day mortality rate, which was 50% for dopamine-treated patients and 43% for norepinephrine-treated patients. Thirty-two dopamine-treated and 23 norepinephrine-treated patients required vasopressin and phenylephrine treatment. **While the sponsor claims that "third-line treatment with phenylephrine resulted in increased blood pressure in 52 patients in septic shock with persistent hypotension (MAP < 60 mm Hg or SBP < 90 mm Hg) after fluid resuscitation" (NDA 203826, Integrated Summary of Efficacy, section 2.7.3.2.2.3.1.2, page 16), this reviewer sees no documentation of a treatment effect.**

9.1.5.5. Flancbaum (1997)

This was a prospective, open-label study of 10 septic non-hypotensive patients in the surgical ICU. The study objective was to determine effects of increasing doses of phenylephrine on hemodynamic parameters; all patients had invasive arterial and pulmonary artery thermodilution catheters in place prior to infusion. Patients received increasing doses of phenylephrine (0.5, 1.0, 2.0, 3.0, 4.0, 8.0 µg/kg/min) in 30-minute increments to achieve a steady state. Hemodynamic and oxygen transport parameters were measured at baseline and end of each infusion period; the study was terminated if MAP > 110 mm Hg or arrhythmias developed. The length of evaluation did not exceed 180 minutes. Five patients were receiving low-dose dopamine (2.5 µg/kg/min) and/or nitroglycerin ($\leq$ 33 µg/min) with these other infusions kept at a constant rate during the study.

The relationship between phenylephrine dose and the various cardiovascular variables were tested by univariate repeated-measures analysis of variance; dose-response relationships were further analyzed by linear regression. A p-value < 0.05 was considered statistically significant. A difference in cardiovascular variables vs. baseline of at least 15% was considered clinically significant.

Nine men and one woman, mean age 45 (SD 19) years were enrolled (APACHE II mean score 21.4). There were no fatalities, arrhythmias, hemodynamic instability or signs of myocardial ischemia during phenylephrine infusion. Mean baseline CI 5.6 L/min/m2; SVRI 863 dyn s/cm/m2, MAP 70 (SD 7) mm Hg. There were dose-related increases in MAP, SVRI, and PVRI and decrease in HR. There was no statistically significant dose-related effect on CI (although an increase in CI is observed when phenylephrine is increased from 4.0 to 8.0 µg/kg/min). There did not appear to be

dose-related changes in VO2 or DO2; mean serum lactate concentration decreased with therapy. There was no mention of effects on urine output or renal function.

Comment: This is a nonrandomized study, and one cannot exclude measurement bias or selection bias (the paper does not report whether patients were excluded from enrollment or analysis); however, the data are consistent with a dose-effect relationship with increases in mean blood pressure and small mean negative chronotropic effect.

9.1.5.6. Yamazaki (1982)

Cardiac function by acute pressure loading with phenylephrine was assessed in 7 patients with hyperdynamic sepsis and 8 patients with heart disease. *No study objective, sample size calculation, randomization or blinding method was mentioned.* The study was conducted at one site (Osaka University Hospital) between October 1987 and April 1980. The criteria for hyperdynamic sepsis were a positive Limulus lysate test, presence of a septic focus, and CO > 6.0 L/min. Eight patients with heart disease (6 with ischemic heart disease, 2 with rheumatic heart disease) admitted to the ICU were used as a control group.

Hemodynamic studies were performed before and during phenylephrine administration. Phenylephrine (25 mg diluted in 300 ml 5% fructose in water) was infused over 5-10 min to raise SAP by approximately 30 mm Hg. An infusion rate of about 70 µg/min was required to maintain SAP at this level throughout the study period. CO was determined by the dye dilution method. Hemodynamic values before and during phenylephrine administration were compared using the paired or unpaired t-test.

Results: Baseline hemodynamic measurements (e.g., CI, SVRI, MAP, CVP, HR) were different between the two groups (sepsis vs. heart disease); however, this could be an expected finding given the different conditions.
In both groups, the mean MAP, SAP, and CVP increased from baseline and the mean HR decreased from baseline. In the group with sepsis, mean CI and SWI increased from baseline but these values decreased from baseline in the group with cardiac disease. There is no mention of renal, GI or liver testing.

9.1.5.7. Morelli (pilot 2008)

This was a prospective, 15-patient crossover pilot study comparing the effects of norepinephrine and phenylephrine on systemic and regional hemodynamics in patients with catecholamine-dependent septic shock.

Patients were enrolled who fulfilled criteria of septic shock and required norepinephrine to maintain MAP between 65 and 75 mm Hg despite adequate volume resuscitation.

Exclusion criteria were age younger than 18 years, pregnancy, and present or suspected acute coronary artery disease or mesenteric ischemia.

Systemic hemodynamic monitoring included pulmonary and radial artery catheters; heart rate was analyzed from continuous electrocardiogram recordings. Cardiac index was measured via thermodilution. Arterial and mixed venous blood samples were taken for measuring blood gases and oxygen saturations, as well as base excess, pH and arterial lactate concentrations. Regional hemodynamic monitoring was performed via femoral artery catheter for determination of PDR (plasma disappearance rate of indocyanine green) and CBI (blood clearance of indocyanine green related to body surface area). An air tonometer was inserted via the nasogastric route for gastric mucosal CO2 tension measurement.

Measurements were taken at baseline; after 8 hours during stable conditions, a second set of data was obtained (NE I). Norepinephrine infusion was then replaced by continuous IV phenylephrine, and the dosage rate was adjusted to maintain the same threshold MAP as before (65-75 mm Hg). After another 8 hours during stable conditions, a third set of data was obtained (phenylephrine). Then, the treatment was switched back to norepinephrine to maintain MAP 65-75 mm Hg and, after another 8 hour period under stable conditions, a final set of data was obtained (NE II). Fluid challenge (hydroxyethyl starch 6%) was performed to maintain PAOP and CVP at baseline $\pm$ 3 mm Hg during the 24-h study period. Packed red blood cells were transfused when hemoglobin concentrations decreased to < 8 g/dL. All other medications were held constant.

Paired data before and during phenylephrine infusion were compared using Student t test. Significance was assumed when $p < 0.05$.

Two females and 13 males, mean age 60.3 years, were studied. There was a statistically significant decrease in mean HR following phenylephrine treatment (e.g., mean baseline HR 92 $\pm$ 18 bpm, mean HR following phenylephrine 89 $\pm$ 18 bpm, $p < 0.05$); and systemic and pulmonary hemodynamic parameters (e.g., MAP, SVRI, RAP, PAOP) and CI appeared similar between baseline and norepinephrine or phenylephrine treatments. PDR and CBI, considered by the authors to be surrogates of hepatosplanchnic perfusion and function, decreased significantly with phenylephrine infusion ($p < 0.05$ vs. NE I); in addition, phenylephrine infusion decreased creatinine clearance vs. NE 1 (81.3 $\pm$ 78.4 vs. 94.3 $\pm$ 93.5 mL/min; $p < 0.05$). Phenylephrine increased lactate, did not affect gastric mucosal perfusion and did not affect pH. The authors were unable to distinguish between increased splanchnic lactate production versus decreased hepatic, renal or myocardial lactate clearance.

The authors also noted that, 8 hours after treatment had been switched back to NE II, all variables returned back to values obtained before phenylephrine infusion except creatinine clearance and gastric mucosal perfusion. In addition, because of the study

design, the authors were unable to exclude time-dependent effects unrelated to treatment or carryover effects.

9.1.5.8. Bonfiglio (1990):

This was a case report of a 75 year-old male with pancreatic adenocarcinoma who underwent an exploratory laparotomy, lysis of adhesions and gastrojejeunostomy. His postoperative course was complicated by acute renal failure, systemic candidiasis, respiratory failure and hypotension, treated initially with fluids and dopamine. Following a cholangiogram, he became hypotensive, febrile and anuric. Hemodynamic parameters were consistent with septic shock. Two doses of IV phenylephrine 100 µg were administered at 5-minute intervals; MAP improved to 70-80 mm Hg within 1 minute of each phenylephrine dose. Phenylephrine was then given as a continuous infusion at 40 µg/min and titrated to maintain MAP > 65 mm Hg; the maximum phenylephrine dose was 320 µg/min . Because of continued low urine output, dopamine was added 5 hours after the initiation of phenylephrine therapy. Serial calculations of oxygen transport indicated an improvement in oxygen delivery; urine output increased. The patient remained on a phenylephrine infusion for a total of 88.5 hours, after which he was gradually weaned from pressors, extubated and transferred out of the SICU.

9.1.6. Studies in the pediatric population.

9.1.6.1. Shaddy (1989)

This was a 4-patient (7 days to 3.5 years) open-label study of phenylephrine in patients with Tetralogy of Fallot and severe hypoxemic spells refractory to knee-chest position, oxygen, and intravenous morphine. Patients received 5 µg/kg phenylephrine followed by continuous phenylephrine infusions. One patient developed hypotension and hypoxemia during preparation for surgical repair and was “successfully managed with continuous intravenous phenylephrine.” *However, the paper contains no specific blood pressure or heart rate data.*

9.1.6.2. Strieper (1993)

In an open-label study, 16 patients (mean age 13.1 years) with recurrent syncope and positive baseline head-up tilt response were studied; after the positive baseline tilt response, phenylephrine was infused at an average rate of 1.74 µg/kg/min (range 0.6 to 3 µg/kg/min) and repeat tilt was performed for 30 minutes or until the test result was positive. In 15 patients, the infusion completely blocked the symptoms; one patient developed a blunted mixed response, becoming pre-syncopal at 22 minutes. During baseline tilt testing, baseline supine mean BP decreased immediately on tilt and declined significantly at endpoint; repeat tilt during phenylephrine infusion showed slight reduction in mean BP with no further decrease during the tilt.

9.1.6.3. DiGennaro (2010)

This was a retrospective cohort study of children (0-17 years-old) admitted to a level 1 trauma center (2002-2007) with moderate-to-severe traumatic brain injury who received a vasopressor to increase blood pressure. A total of 82 patients contributed data to the entire dataset. Patients receiving phenylephrine and norepinephrine tended to be older than those receiving dopamine and epinephrine. Thirteen of the patients received a second vasopressor during the first 3 hours of treatment and were not included in the regression analyses; these patients received more fluid resuscitation and exhibited higher in-hospital mortality.
In one analysis, patients who received phenylephrine showed a median increase in MAP of 10 mm Hg (IQR 4, 16) and a median decrease in HR of 4 bpm (IQR -16, 1).

9.1.6.4. Kim (2006):

This was a case report of a 2 year-old male with chronic renal failure who underwent renal transplantation. SBP remained in the range of 80 mm Hg despite treatment with dopamine, adding phenylephrine increased SBP to 95 to 110 mm Hg once the infusion rate reached 15 µg/kg/min.

9.1.7. ASA (American Society of Anesthesiologists): classification system:

ASA Physical Status 1 - A normal healthy patient

ASA Physical Status 2 - A patient with mild systemic disease

ASA Physical Status 3 - A patient with severe systemic disease

ASA Physical Status 4 - A patient with severe systemic disease that is a constant threat to life

ASA Physical Status 5 - A moribund patient who is not expected to survive without the operation

ASA Physical Status 6 - A declared brain-dead patient whose organs are being removed for donor purposes

9.2 Labeling Recommendations

Labeling recommendations will follow separately.

9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled for September 13, 2012.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARI L TARGUM
08/11/2012