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**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 20-3826 / S\_0000

**Drug Name:** Phenylephrine Hydrochloride Injection

**Indication(s):** Increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension

**Applicant:** West-Ward Pharmaceutical Corp.

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

The clinical studies and meta-analyses identified from published literature seem to suggest that phenylephrine has an effect in increasing blood pressure, measured by SBP, DBP, MAP to treat or prevent hypotension in the acute peri-operative setting, and septic shock. Although a large body of published literature is available, the evidence for concluding the efficacy of phenylephrine does not appear to be solid, because of potential biases from published literature and the unresolved issues that hinder proper interpretation of the results of the studies. In this reviewer's opinion, the results from the identified studies and analyses are still exploratory.

### **1.2 Brief Overview of Clinical Study**

This NDA is a 505(b)(2) application that relies on published literature to support the nonclinical profile, clinical pharmacology, safety, and efficacy of Phenylephrine, Hydrochloride Injection, USP drug product. The proposed indication is the parenteral use via intravenous injection to increase blood pressure in acute hypotensive states, such as shock and in the peri-operative setting. The sponsor conducted extensive literature search covered the time period from 1937 to 2010. 54 studies were identified, including randomize/non-randomized, placebo/ active controlled, blind/open label trials, and case reports in both adults and pediatrics. The majority of the studies were conducted in patients undergoing surgery (42 studies), of which 26 studies were conducted in pregnant women during elective or emergent cesarean delivery performed under neuraxial anesthesia. Fewer studies were in septic shock (8 studies) and even fewer in pediatrics with different conditions (4 studies). A total of 2484 patients were enrolled across 50 studies, 1682 patients were treated with phenylephrine.

### **1.3 Statistical Issues and Findings**

The clinical efficacy data in this NDA come from published literatures. Therefore the data inherit biases such as publication bias, time lag bias, multiple publication bias, location bias, citation bias, language bias and outcome reporting bias.

In the clinical studies identified to support efficacy, none of them meet the standards for conducting a confirmatory trial. Statistical issues are found in all the studies, such as no pre-defined primary endpoint, no multiplicity adjustment, un-approved comparator as controls, selectively reporting study result.

## 2. INTRODUCTION

### 2.1 Overview

Phenylephrine has been used as a vasopressor, a mydriatic, and a decongestant agent, and has historically been marketed under the “Grandfather” exemption. Parenteral phenylephrine has been used in different medical settings, notably in critical care, cardiology, and anesthesia for over 75 years. The first publications on the clinical use of phenylephrine date back to 1937 and the publications have continued over decades. Several contemporary studies were published in 2010.

### 2.2 Data Sources

The sponsor’s SAS datasets were stored in the directory of [\\cdsesub1\EVSPROD\NDA203826\0000](#) of the Center’s electronic document room.

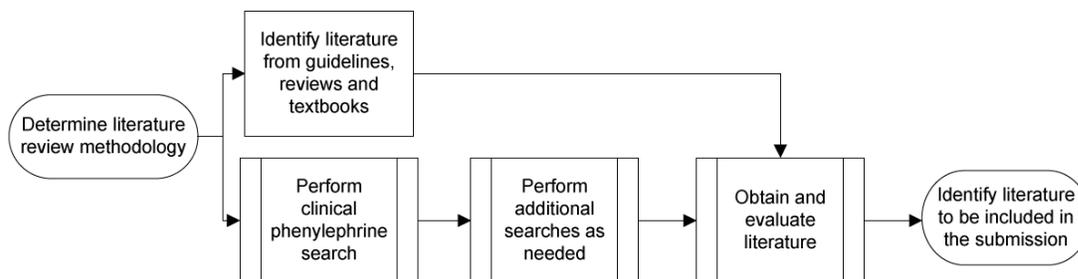
## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 THE SPONSOR’S EVALUATION

##### 3.1.1.1 Literature Search Strategy and Data Source

The sponsor conducted an extensive literature review to identify published studies that support the clinical pharmacology, clinical efficacy, and clinical safety for the intended and proposed clinical use. The literature review process consisted of the following steps:



(Source: Module 5. app-2-clin-lit-rev-meth.pdf )

Database (Table 1) of published scientific literature was searched for articles associated with the use of phenylephrine. The initial search covered the period from January 1, 1933 through October 31, 2009. Periodic updates of the bibliographic databases were made using the same search strategy as the initial search and covered the period from November 1, 2009 through December 31, 2010.

**Table 1 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

(Source: Module 5. app-2-clin-lit-rev-meth.pdf )

### 3.1.1.2 Clinical Efficacy Studies

The primary published literature comprised peer-reviewed journal articles of 52 clinical studies and 2 case reports. The efficacy of IV phenylephrine in increasing or maintaining blood pressure was supported by number of studies conducted in varied populations: 42 studies were conducted in adults undergoing surgery under neuraxial and general anesthesia; 8 studies in septic shock; and 4 studies in children of age from 7 days to 17 years with varied conditions (Table 2).

**Table 2 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

(Source: Module 5. rpt-post-mark-exp.pdf)

### 3.1.1.2.1 Efficacy of Phenylephrine in the Setting of Acute Perioperative Hypotension

Acute perioperative hypotension, defined as hypotension occurring before, during, and after surgery, is a frequent effect after induction of neuraxial (spinal or epidural) anesthesia and also may occur after general anesthesia, particularly in the setting of cardiopulmonary bypass. 42 studies are identified and described in Table 3.

**Table 3 Clinical Studies for Acute Perioperative Hypotension**

No. of Studies (N=42)		Procedure	No. of Patients Treated with PE (N=1527)
Randomized	Non-randomized		
<b>Neuraxial Anesthesia</b>			
26		Cesarean Delivery	1153
2	1	Nonobstetric	83
<b>General Anesthesia</b>			
4	6	Cardiac	216
2	1	Non-cardiac	75

(Source: Module 5. rpt-post-mark-exp.pdf)

Summary and conclusions:

- Data from the published literature support the use of phenylephrine to treat or prevent hypotension associated with cesarean delivery under neuraxial anesthesia, other nonobstetric surgeries (urologic, gynecologic, orthopedic, and abdominal) under neuraxial anesthesia, and in cardiac and other vascular surgeries under general anesthesia.
- Efficacy of the perioperative use of phenylephrine for the treatment of hypotension has been demonstrated in published clinical studies of adult patients across a range of ages, including those > 65 years.
- Phenylephrine efficacy has been demonstrated in published studies following IV continuous infusion or IV bolus infusion.

### 3.1.1.2.2 Efficacy of Phenylephrine in the Setting of Acute Hypotension Due to Shock

Phenylephrine is one of the vasoactive drugs used to correct cardiovascular imbalances in shock. 8 studies are described in Table 4.

**Table 4 Studies for Septic Shock**

No. of Studies (N=8)			Patient Population	No. of Patients Treated with PE (N=144)
Randomized	Non-random	Case Report		
2	3	1	Hypotension	127
	2		Normotensive	17

(Source: Module 5. rpt-post-mark-exp.pdf)

Summary and conclusions:

- Data from the published literature support the efficacy of phenylephrine in the treatment of hypotension due to septic shock.
- Efficacy of phenylephrine for the treatment of hypotension due to septic shock has been demonstrated in published clinical studies of adult patients across a range of ages, including those > 65 years.
- In the septic shock setting, phenylephrine is effective when administered by IV continuous infusion, with the dose titrated to effect.

### 3.1.1.2.3 Efficacy of Phenylephrine in Pediatric Patients

Four clinical studies were identified in children with varied conditions (Table 5).

**Table 5 Studies in Pediatric Patients**

No. of Studies (N=4)		Patient Population	No. of Patients Treated with PE ( N=103)
Non-randomized	Case Report		
1		Tetralogy of Fallot	4
1		Neurocardiogenic Syncope	16
1		Traumatic Brain Injury	82
	1	Kidney Transplant	1

(Source: Module 5. rpt-post-mark-exp.pdf)

Summary and conclusions:

- The available published data suggest that phenylephrine is active and effective for increasing blood pressure in children with hypotension due to several etiologies (neurocardiogenic syncope, brain trauma, and renal disease) and recommend that this vasopressor be maintained as an option for treatment of children with hypotension due to shock of different etiologies.

### 3.1.2 STATISTICAL REVIEWER'S EVALUATION

#### 3.1.2.1 Review Strategy

The NDA includes a large body of published literature on phenylephrine use in varied populations. The review team decided to focus on prospective, randomized, double-blinded, placebo/active controlled studies that demonstrated superior efficacy. The meta-analyses identified in the literature were also reviewed.

No formal statistical analysis was conducted, studies were critiqued and results were summarized and integrated.

## 3.1.2.2. Review of Clinical Studies

## 3.1.2.2.1 Placebo Controlled Studies

The sponsor identified four prospective, randomized, double-blinded, placebo controlled studies that demonstrated superior efficacy. The studies are discussed individually as follows (Tables 6-9):

**Table 6 Allen et al study (*Anesth Analg* 2010;111:1221-9)**

Sample Size	101
Population	SPA for elective c-section
Treatment group and dose	Placebo (n=20) Phenylephrine: 25(n=20), 50(n=20), 75(n=19), 100 (n=22) µg/min
Administration Route	iv bolus
Primary Endpoint(s)	# of physician interventions needed to maintain SBP within 20% of baseline, and to treat bradycardia
Other Endpoint(s)	a. # of pts experienced any episode of hypotension, reactive hypertension b. # of hypotension or hypertension episodes per patient
Definition of Hypotension	SBP decreases 20% of baseline
Statistical Method	a. Kruskal-Wallis rank test for numeric variables b. $\chi^2$ test for categorical variables c. step-down permutation method controlling for multiplicity
Results	1. Fail on the primary endpoint 2. Win on other endpoints: a. Incidence of predelivery hypotension: PE50 vs. placebo, p=0.001; PE 75 & 100 vs. placebo, p<.001 b. Incidence of predelivery hypertension: PE75 & 100 vs. placebo, p<.001
Comments	The statistical analyses seem to be appropriate, especially multiplicity was adjusted for pair-wise comparisons. However the study failed on the primary endpoint. It may be confounded by the higher rate of hypertensive episodes in the phenylephrine 75 and 100 µg/min dose groups.

**Table 7 Langesaeter et al study (*Anesthesiology* 2008;109:856-63)**

Sample Size	80
Population	SPA for elective c-section
Treatment group and dose	Bupivacaine 7mg+placebo (n=20) Bupivacaine 7mg+PE 0.25 ug/kg/min (n=20) Bupivacaine 10mg+placebo (n=20) Bupivacaine 10mg+PE 0.25 ug/kg/min (n=20)
Administration Route	iv
Primary Endpoint(s)	SBP, CO
Other Endpoint(s)	SVR, mean arterial pressure, DBP, stroke volume, HR
Definition of Hypotension	SBP<90 mmHg
Statistical Method	Linear mixed model with treatment and time as factors, and baseline as covariate
Results	1. Statistically significant differences were found in both primary endpoints: p=0.033 for CO, p=0.049 for SBP.  2. Pair-wise comparisons: - B7 + PE vs. B10 + placebo: p=0.005 for CO, p=0.012 for SBP  - B10+B7+PE vs. B10+B7+placebo: p=0.009 for CO, p=0.004 for HR
Comments	- Though an overall treatment effect was statistically significant for CO and SBP, the comparison between B7+PE and B10+placebo is not relevant. The comparison between B7+PE vs. B7 + placebo or B10+PE vs. B10 +placebo should be done. - Multiplicity wasn't controlled

**Table 8 Ngan Kee et al study (*Anesth Analg* 2004;98:815-21)**

Sample Size	50
Population	SPA for elective c-section
Treatment group and dose	PE 100 ug/min iv (n=26) PE100 ug iv bolus (n=24)
Administration Route	
Primary Endpoint(s)	Umbilical arterial (UA) cord blood pH
Other Endpoint(s)	Incidence, frequency & magnitude of hypotension; systolic arterial blood pressure (SAP)
Definition of Hypotension	SAP< 80% baseline
Statistical Method	1. $\chi^2$ test and Fisher's exact test for nominal data 2. ANOVA repeated measures for continuous data
Results	a. Umbilical cord blood gases were similar between groups (UA pH: p=0.4; UV pH: p=1.0) b. Incidence, frequency & magnitude of hypotension was lower in infusion group (p<0.05)
Comments	It wasn't a placebo controlled study. It compared the PE effect by different administration routes

**Table 9 Cheng et al study *Anesth Analg* 1999;88:1322-6 )**

Sample Size	80
Population	Epidural anesthesia for inguinal herniorrhaphy
Treatment group and dose	Placebo (n=20) PE 50, 100, 200 ug (n=20, per dose group)
Administration Route	iv
Primary Endpoint(s)	BP, HR
Other Endpoint(s)	Incidence of hypotension
Definition of Hypotension	MAP<80% baseline
Statistical Method	a. Repeated measures ANOVA for MAP and HR b. Spearman rank correlations to test association between PE doses and the presence of hypotension or ephedrine use. Fisher's exact test was used for pair-wise comparisons c. Bonferroni correction for multiple comparisons
Results	a. The overall treatment effect wasn't statistically significant for both MAP and HR. The interaction of "dose by time" wasn't statistically significant for MAP, but was statistically significant for HR (p=0.0148). Statistically significant differences in HR were found for some doses groups at some time points. b. Hypotension and ephedrine use were found to be negatively correlated with PHE dose (hypotension: r=-0.25, p=0.023; ephedrine use: r=-0.28, p=0.013) c. The incidence of hypotension was statistically significant lower in the PE 200 group compared to placebo (p<0.05)
Comments	a. The endpoint of MAP fails b. Some of the statistical analyses were not clearly described, and therefore whether the analysis is appropriate cannot be assessed. For example, were all pair-wise comparisons done by Fisher's exact test, including continuous and categorical variables ?

**Summary:**

- 3 out of 4 studies were conducted in pregnant women undergoing elective cesarean section delivery under SPA, one study was conducted in patients for inguinal herniorrhaphy procedure. IV administration was a common route. The studies seem to suggest that phenylephrine reduces the incidence of hypotension or increases BP (measured by MAP SBP, DBP).
- There are many statistical issues. Primary endpoint is not pre-specified, and measurement of BP is not always the primary endpoint; different definition/criteria for hypotension; multiplicity in multiple endpoints is never controlled, and multiple comparison is not always adjusted; the statistically significant results are more likely to be reported.

## 3.1.2.2.2 Active Controlled Study

Nine active controlled studies that demonstrated superior efficacy over the control arm were identified (Table 10). The studies were summarized as follows:

**Table 10 Active Controlled Studies**

Study	Sample Size	Patient Population	Comparator	Endpoints	Results
Gunda CP et al <i>Arch Med Sci</i> 2010;6:257-63	100	Elective cesarean delivery	Ephedrine	SBP, DBP, and MAP	Vasopressor therapy, and changes in SBP, DBP and MAP are similar between groups
Moran DH et al <i>J Clin Anesth</i> 1991;3:301-5.	60	Elective cesarean delivery	Ephedrine	SBP	Both groups preserved maternal SBP
Ngan Kee WD et al <i>Anaesthesia</i> 2008;63:1319-26.	204	Nonelective cesarean delivery	Ephedrine	Doses of vasopressor required	The number of doses of vasopressor required are similar between groups
Prakash S et al <i>Int J Obstet Anesth</i> 2010;19:24-30	60	Elective cesarean delivery	Ephedrine	Doses of vasopressor required	The number of doses of vasopressor required are similar between groups
Thomas DG et al <i>Br J Anaesth</i> 1996;76:61-5.	38	Elective cesarean delivery	Ephedrine	SBP, SAP	Both vasopressors increase SBP
Brooker RF et al <i>Anesthesiology</i> 1997;86:797-805	13	Elective surgery under spinal anesthesia	Ephedrine	SBP, DBP, MAP	Both vasopressors restore SBP
Goertz AW et al <i>Ancsthsio, V</i> 78, No 5, May 1993	38	CABG	Ephedrine	MAP	Both vasopressors increase MAP
Jain G et al <i>Indian J Crit Care Med</i> 2010;14:29-34.	54	Septic shock	Ephedrine	Response Rate	Response rates are similar in both groups
Morelli A et al <i>Crit Care</i> 2008;12:R143.	32	Septic shock	Ephedrine	MAP, SVRI	Both drugs increase MAP and SVRI

(Source: Module 5.3.6.4. rpt-post-mark-exp.pdf)

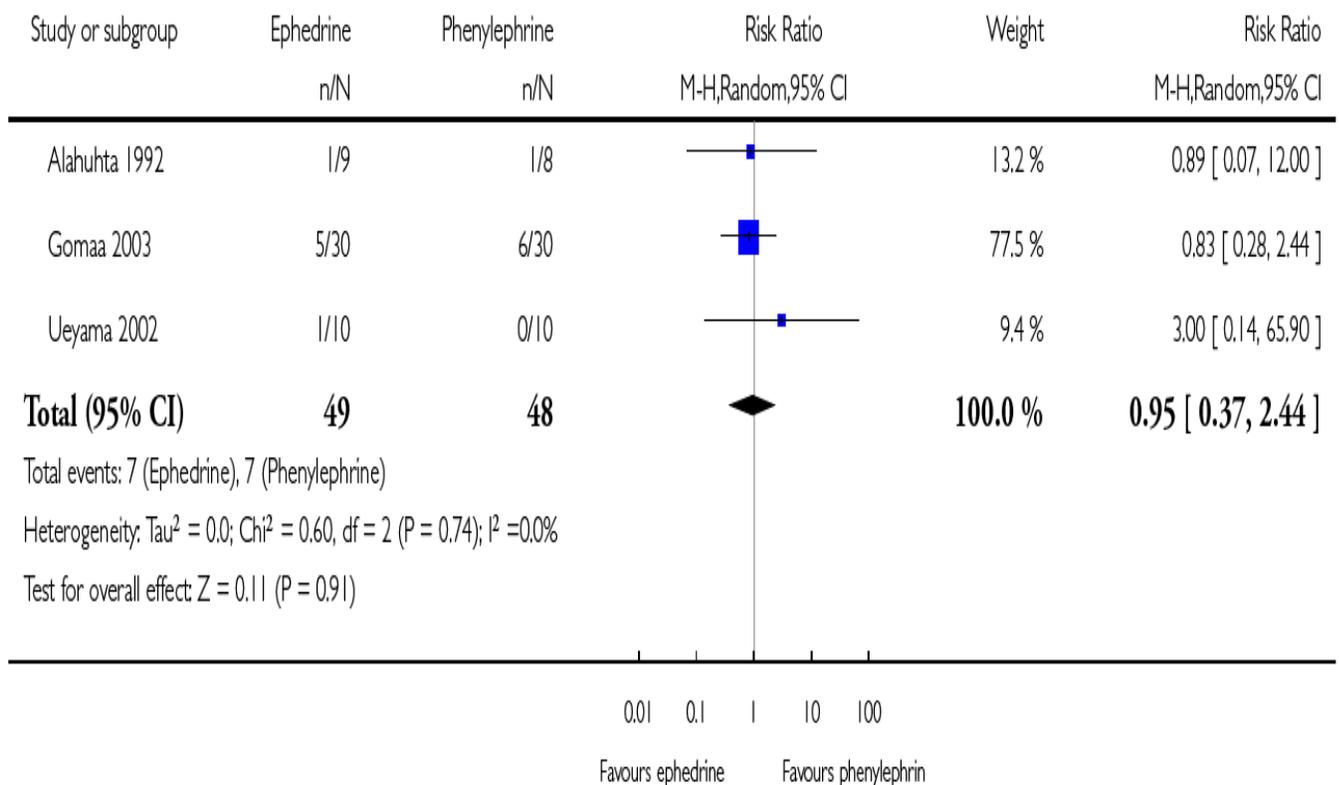
**Summary:**

- Ephedrine is the common active control agent used in the active controlled studies. Similar efficacy —PE is as good as ephedrine, was found for the treatment or prevention of hypotension in patients undergoing elective/nonelective cesarean delivery, general surgery or CABG procedure, and patients with septic shock. However, IV ephedrine has not been approved by FDA, and therefore it is not a good comparator.
- The margin needs to be defined if these studies were considered as a non-inferiority study.

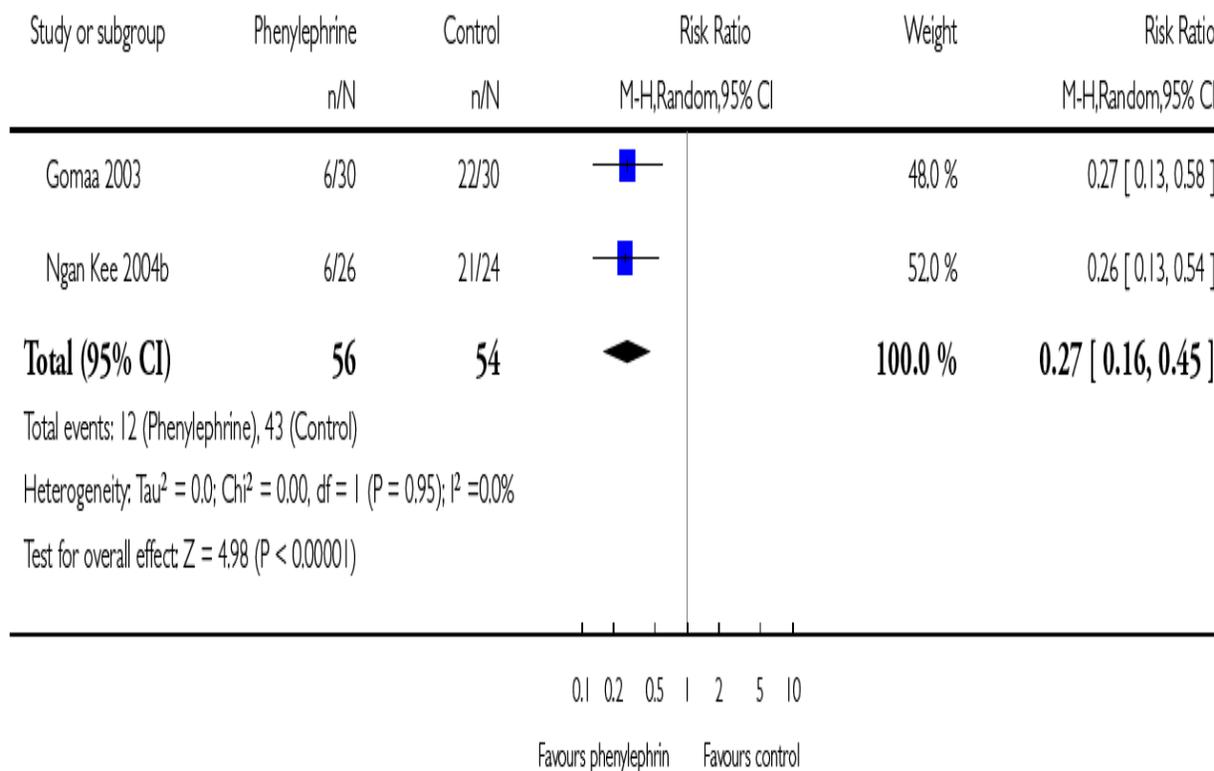
3.1.2.2.3 Meta-analysis

1. Two meta-analyses (by Cyna et al) were identified by the sponsor. The analyses showed that Phenylephrine is similar to ephedrine in the intervention of hypotension; and Phenylephrine is better in the intervention of hypotension compared to controls (Tables 11, 12).

**Table 11 Meta-Analysis: Phenylephrine vs. Ephedrine**



(Source: Module 5.3.6.4. rpt-post-mark-exp.pdf)

**Table 12 Meta-Analysis: Phenylephrine vs. Controls**

(Source: Module 5.3.6.4. rpt-post-mark-exp.pdf)

2. A newly published review article (M. Veaser et al, *Acta Anaesthesiol Scand* 2012; 56:810-816) published a meta-analysis result. The meta-analysis included 20 trials with 1069 patients who were undergoing cesarean section under spinal anesthesia. Ephedrine was the comparator. The analysis showed that no differences were observed between PE and ephedrine in hypotension and hypertension.

**Summary:**

- The meta-analyses seem to confirm the finding from other studies in the literature. However, the two analyses were based on very few studies.
- Ephedrine is not a good comparator.

### 3.1.3 CONCLUSION

The identified prospective, randomized, double-blinded, placebo/active controlled studies and meta-analyses seem to suggest that phenylephrine has an effect in increasing blood pressure in varied population. Data from most of the studies seem to suggest that

phenylephrine has efficacy in pregnant women undergoing cesarean section delivery under SPA.

### **3.2 Conclusions and Recommendations**

The clinical studies and meta-analyses identified from published literature seem to suggest that phenylephrine has an effect in increasing blood pressure, measured by SBP, DBP, MAP to treat or prevent hypotension in the acute peri-operative setting, and septic shock. Although a large body of published literature is available, the evidence for concluding the efficacy of phenylephrine does not appear to be solid, because of potential biases from published literature and the unresolved issues that hinder proper interpretation of the results of the studies. In this reviewer's opinion, the results from the identified studies and analyses are still exploratory.

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