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# Safety of bolus-dose phenylephrine for hypotensive emergency department patients☆

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ABSTRACT

*Introduction:* Bolus-dose phenylephrine (BDPE) is routinely used to treat hypotension in the operating room. BDPE's fast onset of action and ability to be administered peripherally have prompted calls for its use in the Emergency Department (ED). There are few published data on the safety of BDPE use in the ED. Primary concerns include BDPE's potential to cause dangerous hypertension or reflex bradycardia. We hypothesize that BDPE is a safe short-term vasopressor choice for hypotensive ED patients.

*Methods:* We conducted a structured chart review for all patients who received BDPE from preloaded syringes over 42 months. We defined an adverse event (AE) as sBP > 180, dBP > 110, or HR < 50 within 30 min of receiving BDPE. We defined a serious adverse event (SAE) as an AE with pharmacologic intervention to correct vital sign abnormality. We also compared mean arterial pressure (MAP), sBP, and dBP pre/post BDPE administration to assess effectiveness. We used a two-sample *t*-test to assess for differences between the mean delta MAP after low versus high-dose BDPE.

*Results:* We identified 181 cases of ED use. 147 cases had complete pre/post vital signs. We identified 5 AEs and no SAEs. Three patients developed sBP > 180 mm Hg. The patients suffered no apparent harm. No patients had dBP > 110. Two patients developed bradycardia post-drug. In both cases, MAP improved despite bradycardia.

*Conclusions:* BDPE does not appear to cause reflex bradycardia or hypertension requiring intervention among hypotensive ED patients. The apparent safety of BDPE should be confirmed in prospective trials.



## 1. Introduction

Hypotension in the Emergency Department (ED) is common, with one retrospective study estimating prevalence as high as 19% in non-trauma patients being admitted to the hospital [1]. Causes of hypotension in this setting are varied and often multifactorial; potential etiologies include septic, neurogenic, hemorrhagic, hypovolemic or cardiogenic shock. Patients may also have transient hypotension related to medications administered during procedural sedation or intubation. In one retrospective cohort study in an urban ED, approximately 23% of patients undergoing intubation developed post-intubation hypotension [2].

Large, single-center, prospective, cohort studies have shown exposure to hypotension in the ED to be an independent predictor of in-hospital mortality with odds ratios from 2.0 (95% CI, 1.3 to 2.8; n = 4790) (1) to 3.88 (95% CI, 2.62 to 5.75; n = 4388) [3]. Non-sustained hypotension in ED patients has also been associated with increased mortality in sepsis patients [4]. Moreover, the severity of hypotension and its duration in the ED has been associated with adverse hospital outcomes including acute organ failure, need for Intensive Care Unit (ICU) stay, and in-hospital mortality [5]. Post-intubation hypotension has also been shown to be a risk factor for in-hospital mortality with an OR of 2.1 (95% CI, 1.2–3.9) [2].

Several studies from the anesthesia literature support the use of peripherally administered bolus doses of diluted vasopressors, or "bolus-dose vasopressors" for hypotension that is expected to be transient. Much of this literature examines the use of phenylephrine, ephedrine, and epinephrine in the setting of spinal anesthesia [6]. These drugs are used to counteract the rapid decrease in systemic vascular resistance (SVR) that occurs as a result of spinal anesthesia. Several studies have found phenylephrine to be effective at counteracting hypotension in this clinical scenario [6-10].

There has been increased interest in the Emergency Medicine community about the use of bolus-dose vasopressors for critically ill ED patients. Bolus-dose vasopressors may be given rapidly through a peripheral line and can serve as a temporizing measure while placing a central line or preparing a vasopressor infusion. They may also be

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indicated for transient hypotension, such as during procedural sedation, post-intubation, or while crystalloid or blood product volume resuscitation is in progress.

Bolus-dose phenylephrine (BDPE) has several characteristics that make it ideal for use in the ED setting. Phenylephrine is a selective alpha-1 adrenergic agonist that acts on smooth muscle in the vasculature to cause vasoconstriction, resulting in an increase in mean arterial pressure (MAP) [11]. In contrast to epinephrine, phenylephrine has no effect on inotropy. Potential adverse effects include hypertensive crisis, reflex bradycardia, cardiac arrhythmia, ischemia, reduced cardiac output and hypersensitivity reaction [12]. When administered intravenously, onset of vasoconstriction is almost immediate and peak effect occurs in 1–5 min. Phenylephrine may be safely administered through a peripheral line [13,14]. There are no published case reports of harm related to phenylephrine extravasation in the English literature [13,14]. These qualities make phenylephrine an ideal vasopressor for bolus-dose use in the Emergency Department, particularly given that ED patients usually lack central venous access at the time of presentation.

Several studies from the anesthesia literature investigated a dose-response relationship for the drug when used for spinal anesthesia [6-10]. There is also literature describing phenylephrine infusion dosing for critically ill patients. We are not aware of any studies reporting a dose-response relationship for BDPE when used for critically ill patients. While BDPE has been used routinely in the operating room, we are aware of only two other studies describing its use in the ED. Panchal et al. conducted a retrospective chart review of 20 patients with peri-intubation hypotension who received BDPE [15]. This study found that phenylephrine was effective at increasing blood pressure in patients who were hypotensive after intubation [15]. Schwartz et al. reported that bolus-dose phenylephrine similarly increased blood pressure in their Emergency Department patient population with no significant effect on heart rate [16].

Our institution began stocking preloaded, pre-diluted syringes of phenylephrine in our resuscitation bays in 2009 in an effort to increase quick and convenient access to the drug for bolus-dose use while minimizing potential drug preparation errors. This study seeks to describe the use of BDPE in the ED setting, quantify rate of potentially dangerous hypertension and reflex bradycardia and examine circumstances of such cases, and examine its dose-response in the critically ill ED patient population.

## 2. Materials and methods

The study was conducted at an urban, academic trauma center. Preloaded, pre-diluted syringes containing 1000 mcg/10 mL BDPE were stocked in the resuscitation bay automated medication-dispensing cabinets. We conducted a structured retrospective chart review for all patients who received BDPE from preloaded syringes over 42 months.

After Institutional Review Board approval, patient encounters in which phenylephrine was pulled from any automated dispensing cabinet were retrospectively identified. Study subjects included all adult patients who received BDPE during the study period. No formal training curriculum or standard dose of phenylephrine was recommended. The decision to use BDPE was at the discretion of the treating physician.

The primary investigator and a second author (an experienced ED pharmacist) used an internally developed, standardized data collection tool to manually extract data from the Cerner electronic records of all patients meeting inclusion criteria. For 12% of charts, each author independently extracted key variables (vital signs pre and post phenylephrine) to determine inter-rater reliability and ensure consistent data extraction.

The demographic data recorded included age, gender, reason for visit, primary diagnosis and context of phenylephrine administration. Safety data recorded included pre and post BDPE systolic (SBP), diastolic blood pressures (DBP), mean arterial pressure (MAP), and heart rate (HR). We also recorded the highest SBP and DBP and lowest HR within 30 min of BDPE administration. Other resuscitative medications and fluids administered, including induction agents, paralytics, vasopressors, blood products and intravenous fluids, were also documented.

Our primary safety outcomes in this study were potentially dangerous vital sign abnormalities attributable to BDPE, including marked elevation in blood pressure or decreases in heart rate. We defined an adverse event as SBP > 180 or DBP > 110 or HR < 50 within 30 min of receiving BDPE. In cases of multiple doses of BDPE, all instances in which the drug was given were examined for the above vital sign abnormalities. The blood pressure thresholds were chosen based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [17]. This report characterizes patients whose blood pressure exceeds these thresholds as being at risk for hypertensive crisis. We defined a serious adverse event (SAE) as an adverse event with subsequent treatment to correct abnormal vital signs with an antihypertensive (in cases of hypertension) or atropine (in cases of bradycardia). All cases meeting criteria for an adverse event were reviewed to assess circumstances of abnormal vital signs and likelihood they were related to BDPE administration, detect any evidence of harm related to hypertension or bradycardia, and to identify any intervention taken to treat hypertension or bradycardia.

As secondary outcomes, we compared HR, MAP, SBP, and DBP pre and post BDPE administration to assess effectiveness in cases in which complete pre and post drug vital signs were available. In cases of multiple doses of BDPE, we included only the first instance in which BDPE was given. We performed a two-sample *t*-test to assess for difference between the mean changes in MAP after low versus high dose BDPE. We also compared HR pre and post BDPE administration.

## 3. Results

181 cases were retrospectively identified and included in the study. Inter-rater reliability for key vital sign data points was 96%. Table 1 describes patient characteristics and context of BDPE use. 106 patients were male (58.6%) and 75 were female (41.4%). The mean age of patients was 53.6 years and the median age was 56 years. There were 144 medical resuscitation patients and 37 trauma resuscitation patients. Of the medical resuscitations, 81 were general medical resuscitations, 62 were cases in which BDPE was given in the peri-rapid sequence intubation period, and in one case BDPE was given during procedural sedation. Two authors extracted the data. For the key variables of vital signs pre and post-phenylephrine, inter-rater reliability was 95.6%. In most cases, disagreement was due to one author incorrectly reporting a value as missing. In two cases, disagreement was due to one author reporting an incorrect value.

Table 2 describes the primary diagnoses of medical resuscitation patients who received BDPE. Among the medical resuscitation cases, we

**Table 1**
Patient characteristics and context of bolus dose phenylephrine use.

| | n | |
|---|---|---|
| Age | | |
| Mean age | | 53.6 years |
| Median age | | 56.0 years |
| Gender | | |
| Male | 106 | 59% |
| Female | 75 | 41% |
| Context of BPE use | | |
| Medical resuscitation | 144 | 79.5% |
| General medical resuscitation | 81 | 56.3% |
| Rapid sequence intubation | 62 | 43% |
| Procedural sedation | 1 | 0.7% |
| Trauma resuscitation | 37 | 20.5% |
| General trauma resuscitation | 15 | 40.5% |
| Rapid sequence intubation | 22 | 59.5% |
| Total | 181 | |

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