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Comparison of push-dose phenylephrine and epinephrine in the emergency department

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ABSTRACT

Background: There is limited evidence to support the efficacy and safety of push-dose vasopressor (PDP) use outside of the operating room (OR). Specifically, there are few head-to-head comparisons of different PDP in these settings. The purpose of this study was to compare the efficacy and safety of push-dose phenylephrine (PDP-PE) and epinephrine (PDP-E) in the Emergency Department (ED).

Methods: This retrospective, single-center study evaluated adults given PDP-PE or PDP-E in the ED from May 2017 to November 2020. The primary outcome was a change in heart rate (HR). Secondary outcomes included changes in blood pressure, adverse effects, dosing errors, fluid and vasopressor requirements, ICU and hospital lengths of stay (LOS), and in-hospital mortality.

Results: Ninety-six patients were included in the PDP-PE group and 39 patients in the PDP-E group. Median changes in HR were 0 [−7, 6] and − 2 [−15, 5] beats per minute (BPM) for PDP-PE and PDP-E, respectively ($p = 0.138$). PDP-E patients had a greater median increase in systolic blood pressure (SBP) (33 [24, 53] vs. 26 [8, 51] mmHg; $p = 0.049$). Dosing errors occurred more frequently in patients that received PDP-E (5/39 [12.8%] vs. 2/96 [2.1%]; $p = 0.021$). PDP-E patients more frequently received continuous epinephrine infusions before and after receiving PDP-E. There were no differences in adverse effects, fluid requirements, LOS, or mortality.

Conclusion: PDP-E provided a greater increase in SBP compared to PDP-PE. However, dosing errors occurred more frequently in those receiving PDP-E. Larger head-to-head studies are necessary to further evaluate the efficacy and safety of PDP-E and PDP-PE.

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1. Introduction

Hypotension is common in critically ill patients managed in the emergency department (ED) and has been associated with risk of cardiac arrest and mortality [1,2]. Due to the extreme risks of untreated hypotension, guidelines recommend that hypotension be addressed immediately with intravenous (IV) fluids and vasopressors [3]. Traditional use of vasopressors involves preparation and administration as a continuous IV infusion. However, due to potential delays in preparation and initiation of continuous vasopressors, clinicians have sought alternative methods to reduce time to administration.

Push-dose vasopressor (PDP), also known as push-, bolus-, or intermittent-dose vasopressors, use describes administration of small doses of vasopressors as an IV bolus for rapid correction of blood pressure or other hemodynamic parameters [4,5]. PDPs are frequently utilized in the perioperative setting and have been shown to normalize or prevent hemodynamic abnormalities, such as hypotension, bradycardia, and reduced cardiac output [6-13]. Push-dose phenylephrine (PDP-PE) and epinephrine (PDP-E) have emerged as the most common PDP agents used in critical care settings outside of the perioperative setting [14-16]. PDP-PE and PDP-E have attractive pharmacologic profiles, due to their rapid onset and short duration of action [4,5,17,18]. Both epinephrine and phenylephrine can increase blood pressure via alpha-1 adrenergic receptor agonism, which leads to vascular smooth muscle vasoconstriction [19,20]. Unlike phenylephrine, epinephrine also stimulates cardiac beta-1 receptors to produce positive chronotropic and inotropic responses [19,20]. Positive chronotropy and inotropy can be useful in patients with bradycardia or heart block unresponsive to atropine or cardiac pacing [19]. Despite the favorable features of PDP use, there is limited data on the efficacy and safety of this practice. Although studies have highlighted that PDP may be effective in correcting hypotension, several studies have highlighted that PDP use is associated with frequent adverse effects and human errors

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[14,16,21-23]. Additionally, there are few studies comparing the efficacy and safety of different PDP. The objective of this study was to compare the efficacy and safety of PDP-PE and PDP-E used in the ED.

2. Methods

2.1. Study design

This was a retrospective, single center, chart review of patients treated in the ED at Loma Linda University Medical Center, a 900-bed academic teaching hospital and level 1 trauma center. The 65-bed ED treats an average of 75,000 adult and pediatric patients per year. The study site has onsite ED pharmacists available daily from 0600 to 0200. Prior to April 2018, ED pharmacists were only available daily from 0900 to 1930. ED pharmacists evaluate and approve medication orders, facilitate medication preparation and delivery, provide drug information, and assist other ED practitioners with bedside care. The ED stocks premixed syringes of both phenylephrine (100 mCg/mL, 10 mL) and epinephrine (10 mCg/mL, 5 mL) in automated drug dispensing cabinets. Adults 18 years of age and older who received PDP-PE or PDP-E in the ED between May 2017 and November 2020 were included in the study. Patients were excluded if they only received one-time doses of PDP-E > 100 mCg/dose (e.g. 1 mg for cardiac arrest), PDP doses were ordered but not administered in the ED, vital signs within 30 min of PDP administration were not recorded, or if the PDPs were used for non-hemodynamic indications such as priapism or allergic reaction without hypotension. Patients were also excluded if they received both PDP-PE and PDP-E.

2.2. Outcomes

The primary outcome was change in heart rate (HR) within 30 min of PDP administration. This outcome was selected because phenylephrine does not possess direct chronotropic properties while epinephrine can directly induce tachycardia via cardiac beta-1 adrenergic receptor agonism [19,20]. Based on these pharmacodynamics differences, we hypothesized that blood pressure differences would be similar but HR differences would be greater in those given PDP-E. Secondary efficacy outcomes included acute changes (defined as changes between baseline and 30 min after PDP administration) in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and shock index (SI). SI was defined as HR divided by SBP [24]. When multiple vital signs were charted, the highest value within 30 min of PDP administration was selected. Percent change, or relative change, in hemodynamic parameter was defined as the difference between post- and pre-dose parameter divided by the pre-dose parameter. Additional secondary efficacy and safety outcomes included peak serum lactate within 24 h of PDP administration, incidence of acute kidney injury (AKI) per the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, fluid and continuous vasopressor requirements, ICU and hospital lengths of stay (LOS), in-hospital mortality, severe cardiovascular adverse effects, and PDP-related dosing errors [25]. Severe adverse cardiovascular effects included severe hypertension within 30 min of PDP administration (SBP >180 mmHg or DBP >120 mmHg), extreme tachycardia or bradycardia within 30 min of PDP administration (HR <60 or > 140 beats per minute [BPM], respectively), new onset dysrhythmias (atrial fibrillation, atrial flutter, ventricular tachycardia, or ventricular fibrillation noted in progress notes), or requirement for PDP reversal with antihypertensives (beta-blocker, calcium channel blocker, nitroglycerin, or hydralazine), negative chronotropes (beta-blocker, calcium channel blocker, digoxin, or amiodarone), or positive chronotropes (atropine or cardiac pacing). Dosing errors were defined as any PDP-PE dose >500 mCg or PDP-E dose >20 mCg. This PDP-PE dosing error cutoff was selected due to evidence that PDP-PE doses 200–500 mCg may provide greater increases in blood pressure without causing more adverse effects [26]. The PDP-E dosing error cutoff was in line with previously published dose recommendations [4,5].

Data were collected from electronic medical records by a single investigator. A second investigator randomly audited collected data. Discrepancies identified by the second investigator were reviewed and addressed by a third investigator. Investigators were not blinded to the study question. Data were collected using Microsoft Excel (Microsoft Office Professional Plus 2016; Microsoft, Redmond, WA). The Loma Linda University Health Institutional Review Board initially approved this study on September 30, 2019 and granted a data collection extension on January 6, 2021.

2.3. Statistical analysis

A sample size calculation based on the findings of Cole et al. indicated 66 patients (33 patients per group) were necessary to detect a mean difference in HR of 8 BPM between groups with an alpha of 0.05 and 90% power [22]. Cole et al. demonstrated median heart rate change

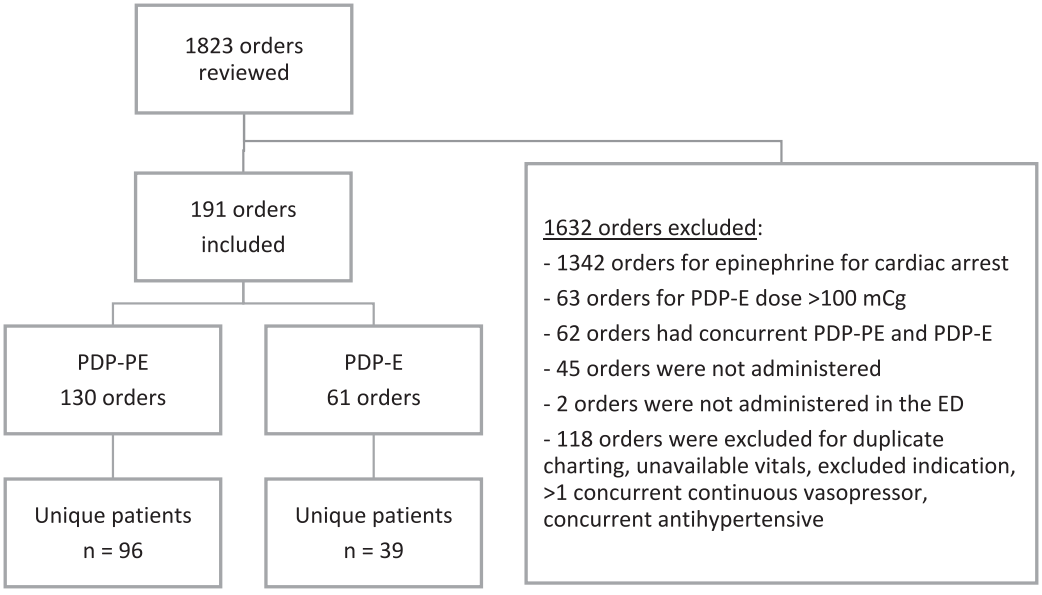

Fig. 1. Study Flow Diagram.
Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, ED- emergency department.

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was 3 BPM in patients receiving PDP-PE and 11 BPM in patients receiving PDP-E [22]. Descriptive statistics for quantitative variables are presented using the mean with standard deviation (SD) for parametric data or median with first and third quartile (interquartile range [IQR]) for nonparametric data. Categorical variables are presented as number and percentage. The two-independent samples *t*-test was used to compare quantitative variables between groups, whereas the Mann-Whitney *U* test was used when data were not normally distributed. The Fisher exact test was used to assess associations between categorical variables between groups. Statistical significance was set at a p-value of less than 0.05. Statistical analysis was performed using SPSS Statistics software (Version 25.0; IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics

Overall, 1823 orders were reviewed and 191 orders (130 PDP-PE and 61 PDP-E) met inclusion criteria (Fig. 1). After adjusting for duplicate orders for single patients, 96 patients were included for final analysis for the PDP-PE group and 39 patients for the PDP-E group (Fig. 1). Demographics were similar between both groups with two exceptions. Patients given PDP-E were more frequently treated in the ED due to cardiac arrest and were more frequently admitted to the medical intensive care unit (MICU) (Table 1).

Table 1
Patient demographics.

Characteristic	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Age (years)- Median (IQR)	64 (52.5,74.5)	71 (57,75.5)	0.219
Female- n (%)	38 (39.6)	18 (46.2)	0.564
Weight (kg)- Median (IQR)	72.9 (60.9, 94.1)	75.305 (55.5,88.7)	0.289
Comorbidities- n (%)			
Heart failure	22 (22.9)	9 (23.1)	1
Atrial fibrillation	19 (19.8)	7 (17.9)	1
Hypertension	28 (29.2)	11 (28.2)	1
Admitting diagnosis- n (%)			
Altered mental status	26 (27.1)	6 (15.4)	0.183
Cerebral vascular accident	8 (8.3)	0 (0)	0.104
Trauma	19 (19.8)	5 (12.8)	0.458
Respiratory Distress	13 (13.5)	10 (25.6)	0.128
Cardiac Arrest	10 (10.4)	12 (30.8)	0.008
Bleeding	4 (4.2)	0 (0)	0.324
Cardiac arrhythmia	10 (10.4)	3 (7.7)	0.756
Pain	4 (4.2)	1 (2.6)	1
Other	8 (8.3)	3 (7.7)	1
Admitted to ICU- n (%)			
Medical	51 (53.1)	29 (74.4)	0.033
CT Surgery	1 (1)	0 (0)	1
Surgery	17 (17.7)	4 (10.3)	0.432
Neurologic	14 (14.6)	1 (2.6)	0.066
Cardiac	4 (4.2)	3 (7.7)	0.412
Total	87 (90.6)	37 (94.9)	0.51
Admitted to non-ICU n (%)	1 (1)	0 (0)	1
Home medications with push-dose DDI- n (%)			
Beta-Blocker	25 (26)	13 (33.3)	0.405
Calcium channel blocker	12 (12.5)	5 (12.8)	1
Digoxin	0 (0)	0 (0)	1
Amiodarone	3 (3.1)	2 (5.1)	0.626
Clonidine	2 (2.1)	4 (10.3)	0.058
Other[a]	11 (11.5)	4 (10.3)	1
ED medications with push-dose DDI- n (%)			
Beta-Blocker	2	0	1
Calcium channel blocker	3	0	0.557
Digoxin	0	0	1
Amiodarone	2	1	1
Clonidine	0	0	1
Sympathomimetic	0	0	1
Cholinergic	0	0	1
Other[b]	3	0	0.557

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, IQR- interquartile range, ICU- intensive care unit, CT- cardiothoracic, DDI- drug-drug interaction, ED- emergency department.
[a] Other medications: guanfacine, midodrine, isosorbide dinitrate, and hydralazine.
[b] Other ED medications: nebulized albuterol.

3.2. Hemodynamic and clinical outcomes

There were no differences in HR prior to the first PDP dose, after PDP administration, or in percent change when patients that received PDP-PE were compared to those given PDP-E (Table 2). Median change in HR was 0 BPM (−7, 6) in patients given PDP-PE and − 2 BPM (−15, 5) in patients given PDP-E (p = 0.139). Median change in SBP and percent change in SBP were greater in patients given PDP-E (Table 2). Although baseline and peak SI was similar between groups, PDP-E patients had greater reduction in SI compared to PDP-PE patients (Table 2). There were no differences in peak serum lactate, incidences of AKI, ICU and hospital LOS, and in-hospital mortality (Table 3). Peak serum lactate was similar between groups in patients that required continuous vasopressor infusion after PDP administration (3.1 mMol/L [1.7, 7] in PDP-PE vs. 2.9 mMol/L [1.75, 7.12] in PDP-E; p = 0.92) and in those that did not require continuous vasopressor infusion after PDP administration (1.5 mMol/L [1.15, 2.375] in PDP-PE vs. 2.3 mMol/L [1.45, 3.35] in PDP-E; p = 0.267).

3.3. Adverse effects

There were no differences in adverse effects between groups (Table 4). One patient that received PDP-E was noted to have global hypoxic ischemic encephalopathy. This patient presented to the ED after out of hospital cardiac arrest and received PDP-E due to hypotension after return of spontaneous circulation. Progress notes suggested

Table 2
Hemodynamic effects of push-dose vasopressor administration.

Category	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Prior to first push-dose- Median (IQR)			
SBP (mmHg)	73.5 (60.2, 92)	65 (52, 82)	0.089
DBP (mmHg)	47.5 (38, 56.8)	42 (30, 56)	0.254
MAP (mmHg)	55.83 (46.3, 68.9)	49.33 (39, 64.3)	0.131
HR (bpm)	94 (76, 118)	99 (75, 124)	0.826
SI[a]	1.26 (0.93, 1.7)	1.44 (1.11, 1.74)	0.159
Peak within 30 min of push-dose- Median (IQR)			
SBP (mmHg)	105 (90, 123)	115 (94, 136)	0.246
DBP (mmHg)	61 (51.5, 74)	65 (50, 78)	0.497
MAP (mmHg)	75.65 (68.6, 88.8)	82.33 (66, 93)	0.25
HR (bpm)	92.5 (79.2, 117)	89 (74, 113)	0.298
SI[a]	0.93 (0.7, 1.19)	0.84 (0.61, 1.05)	0.165
Post-dose and pre-dose difference - Median (IQR)			
SBP (mmHg)	26 (8, 51)	33 (24, 53)	0.049
DBP (mmHg)	14 (1.5, 28)	20 (7, 34)	0.254
MAP (mmHg)	19.33 (4.99, 35.3)	24.66 (13, 43.3)	0.116
HR (bpm)	0 (−7, 6)	−2 (−15, 5)	0.139
SI[a]	−0.31 (−0.64, −0.1)	−0.52 (−0.98, −0.27)	0.008
Percent change[b]- Median (IQR)			
SBP	33.75 (10.2, 80.1)	51.35 (27.5, 88)	0.039
DBP	24.62 (3.56, 70.7)	36.67 (12.1, 131)	0.19
	31.91 (8.46, 73)	46.1 (17.4, 98.5)	0.072
HR	0 (−6.94, 8.33)	−2.326 (−16, 4.59)	0.101
SI[a]	−25.99 (−43.7, −8.36)	−36.59 (−56.2, −24.5)	0.007

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, SD- standard deviation, IQR- interquartile range, SBP- systolic blood pressure, DBP- diastolic blood pressure, MAP- mean arterial pressure, HR- heart rate, BPM- beats per minute, SI- shock index.
[a] SI = HR / SBP.
[b] Percent change: relative change in parameter (i.e. [post-PDP parameter - pre-PDP parameter] / [pre-PDP parameter] x 100).

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Table 3
Clinical effects of push-dose vasopressors.

Category	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Peak serum lactate within 24 h of administration (mMol/L)- Median (IQR)	2.7 (1.5, 6)	2.9 (1.75, 6.57)	0.638
AKI Developed[a]- n (%)	16 (16.7)	4 (10.3)	0.43
ICU length of stay (days)- Median (IQR)	4.325 (2.13, 8.66)	4.82 (1.7, 7.14)	0.631
Hospital length of stay (days)- Median (IQR)	7.67 (2.83, 15.9)	7.11 (2.04, 11.5)	0.194
In-Hospital mortality- n (%)	36 (37.5)	21 (53.8)	0.088

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, IQR- interquartile range, AKI- acute kidney injury, ICU- intensive care unit.
[a] AKI per KDIGO criteria.

that ischemia was likely due to cardiac arrest and was not explicitly attributed to the use of PDP-E. Use of medications or interventions with antihypertensive, negative chronotropic, and positive chronotropic properties within 30 min of PDP use was similar between groups (Table 4).

3.4. Resuscitation characteristics

Normal saline (0.9% sodium chloride) was the most frequently administered IV fluid administered to both PDP-PE and PDP-E patients (Table 5). There were no differences in IV fluid use between groups (Table 5). Epinephrine was more frequently administered as a continuous infusion in patients treated with PDP-E; however, use of other continuous vasopressors was similar (Table 5). There were no differences in blood product administration between groups (Table 5).

3.5. PDP dosing characteristics and dosing errors

Median smallest dose was 100 mCg (100,200) and largest dose 200 mCg (100, 200) in patients given PDP-PE (Table 6). Median smallest dose was 10 mCg (10,20) and largest dose 20 mCg (10, 20) in patients given PDP-E (Table 6). The number of PDP doses required within 24 h was similar between groups (Table 6). There were two instances of dosing errors in the PDP-PE group (2.1%) and five dosing errors in the PDP-E group (12.8%) (p = 0.021). PDP-PE dose errors ranged from 700 to 900 mCg per dose while PDP-E dose errors ranged from 30 to 50 mCg per dose. No adverse effects due to these errors were noted in medical records.

4. Discussion

To our knowledge, this is one of the first studies to compare both efficacy and safety outcomes of PDP-PE and PDP-E in the ED. We observed that PDP-E use was associated with greater increases in SBP, without parallel increases in HR, and larger reductions in SI. Epinephrine has high affinity for both alpha- and beta-adrenergic receptors present in cardiac and vascular smooth muscle [4,19,20]. Phenylephrine has minimal affinity for beta-adrenergic receptors and would not be expected to induce tachycardia; instead, reflexive bradycardia can develop [4,19,20]. Surprisingly, we did not observe differences in HR when comparing PDP-PE and PDP-E. Both absolute and relative changes in heart rate were similar between groups. In a comparative study of PDP-PE and PDP-E in the ED, Cole et al. observed that changes in HR were numerically greater in those that received PDP-E [22]. Rates of extreme

Table 4
Serious adverse effects within 30 minutes of last push-dose vasopressor dose.

Adverse effect	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Dosing error[a]- n (%)	2 (2.1)	5 (12.8)	0.021
SBP > 180 or DBP > 120 mmHg- n (%)	3 (3.1)	0 (0)	0.555
HR < 60 bpm- n (%)	4 (4.2)	5 (12.8)	0.12
HR > 140 bpm- n (%)	7 (7.3)	5 (12.8)	0.327
New-onset dysrhythmia- n (%)			
Atrial fibrillation	0 (0)	0 (0)	1
Atrial flutter	0 (0)	0 (0)	1
Ventricular tachycardia	0 (0)	0 (0)	1
Ventricular fibrillation	0 (0)	0 (0)	1
Myocardial infarction within 24 h of push-dose administration- n (%)	0 (0)	0 (0)	1
Stroke within 24 h of last push-dose administration- n (%)	0 (0)	0 (0)	1
Other tissue ischemia within 24 h of last push-dose administration- n (%)	0 (0)	1 (2.6)[b]	0.289
Reversal of push-dose required- n (%)			
Anti-hypertensive[c]	3 (3.1)	1 (2.6)	1
Negative chronotrope[d]	3 (3.1)	1 (2.6)	1
Positive chronotrope[e]	6 (6.3)	3 (7.7)	0.717
Total Patients	10 (10.4)	4 (10.3)	1

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, SBP- systolic blood pressure, DBP- diastolic blood pressure, HR- heart rate, BPM- beats per minute.
[a] Dosing error considered any one-time phenylephrine dose >500 mCg or epinephrine dose >20 mCg.
[b] Global hypoxic ischemic encephalopathy.
[c] Anti-hypertensive includes beta-blocker, calcium channel blocker, nitroglycerin, or hydralazine.
[d] Negative chronotrope includes beta-blocker, calcium channel blocker, digoxin, or amiodarone.
[e] Positive chronotrope includes atropine or cardiac pacing.

Table 5
Resuscitation characteristics within 24 hours of push-dose vasopressor administration.

Agent	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Fluid administered- n (%)			
NS	47 (49)	18 (46.2)	0.85
LR	35 (36.5)	17 (43.6)	0.443
D5W	0 (0)	1 (2.6)	0.289
Other crystalloid[a]	1 (1)	2 (5.1)	0.2
Albumin	4 (4.2)	1 (2.6)	1
None	12 (12.5)	4 (10.3)	1
Continuous infusion vasopressor before push-dose- n (%)			
Phenylephrine	4 (4.2)	1 (2.6)	1
Epinephrine	2 (2.1)	5 (12.8)	0.021
Norepinephrine	26 (27.1)	9 (23.1)	0.672
Vasopressin	2 (2.1)	1 (2.6)	1
None	64 (66.7)	26 (66.7)	1
Continuous Infusion Vasopressor after push-dose- n (%)			
Phenylephrine	5 (5.2)	3 (7.7)	0.69
Epinephrine	9 (9.4)	16 (41)	<0.001
Norepinephrine	69 (71.9)	25 (64.1)	0.412
Vasopressin	21 (21.9)	12 (30.8)	0.279
Angiotensin II	1 (1)	1 (2.6)	0.496
None	19 (19.8)	6 (15.4)	0.632
Blood Products Administered- n (%)			
PRBC	8 (8.3)	3 (7.7)	1
FFP	4 (4.2)	2 (5.1)	1
Platelets	4 (4.2)	1 (2.6)	1
Cryoprecipitate	0 (0)	1 (2.6)	0.289
None	86 (89.6)	36 (92.3)	0.756

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, NS- 0.9% sodium chloride, LR- lactated ringer's, D5W- dextrose 5%, PRBC- packed red blood cells, FFP- fresh frozen plasma.
[a] Other crystalloid includes dextrose 10%–0.45% sodium chloride, dextrose 10%-NS, and Isolyte.

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Table 6
Push-dose vasopressor dosing characteristics.

Category	PDP-PE (n = 96)	PDP-E (n = 39)	p-Value
Smallest dose (mCg)- Median (IQR)	100 (100, 200)	10 (10, 20)	–
Largest dose (mCg)- Median (IQR)	200 (100, 200)	10 (10, 20)	–
Total dose within 24 h (mCg)- Median (IQR)	200 (100,300)	20 (10, 35)	–
One-time dose >500 mCg- n (%)	2 (2.1)	–	–
One-time dose >20 mCg- n (%)	–	5 (12.8)	
Push-doses required within 24 h- Median (IQR)	1 (1,2)	1 (1, 2)	0.379

Abbreviations: PDP-PE- push-dose phenylephrine, PDP-E- push-dose epinephrine, mCg- micrograms, IQR- interquartile range.

tachycardia (HR > 140) were similar between groups [22]. PDP-E median dosing ranged from 1 to 100 mCg in Cole et al. versus 10–20 mCg in our study [22]. These findings suggest that smaller epinephrine doses given as IV pushes may not generate increases in HR expected based on the drug's mechanism of action [22].

Although our study did not observe differences in clinical outcomes, other studies have highlighted that PDP may have a negative impact on mortality. In an observational study of patients administered PDP-E or PDP-PE for circulatory shock due to drug overdose, Clifford et al. observed that PDP-PE reduced the odds of in-hospital mortality while PDP-E increased the odds of in-hospital mortality [27]. These results were similar after unadjusted analysis and after adjusting for sex, diabetes, suicidality, number of drug exposures, and study site [27]. Drug class exposures varied but most were due to opioids (25 of 55 patients) [27]. PDP dosing was similar to dosing used in other studies (i.e. PDP-E 10 mCg per dose, PDP-PE 100 mCg per dose) [14,21,23,26,27]. In our study, we did not observe any differences in ICU length of stay, hospital length of stay, or in-hospital mortality between PDP-PE and PDP-E groups. Overall in-hospital mortality was similar in our study (42%) and in the study performed by Clifford et al. (42%) [27]. Contrary to the study performed by Clifford et al., our study included more patients (135 versus 55 patients), patients with a wide variety of admitting diagnoses, and patients that were admitted to several different ICU settings [27]. Median ICU length of stay was higher in our study (PDP-E 4.82 days, PDP-PE 4.33 days) compared to Clifford et al. (PDP-E 2.15 days, PDP-PE 1.78 days) [27]. These differences in demographics and ICU length of stay suggest the association of PDP-E with higher mortality in patients with shock due to drug overdose may not be applicable to patients with different shock types and etiologies.

In a retrospective, multicenter study of patients with septic shock requiring continuous norepinephrine infusion, Hawn et al. observed that use of PDP-PE prior to norepinephrine infusion was associated with higher incidence of hemodynamic stability within three hours compared to patients that did not receive PDP-PE [28]. However, PDP-PE receipt was associated with higher ICU mortality both before and after multivariate adjustment, which led the authors to recommend that PDP-PE be used cautiously in patients receiving norepinephrine for septic shock [28]. Although this study had a large sample size (141 patients that received PDP-PE and 282 patients that did not receive PDP-PE), it only included patients treated in the ICU [28]. Therefore, extrapolation to other settings (e.g. ED) and patients with other shock types may not be appropriate. In a retrospective, case-cohort study of critical care transport patients with hypotension (SBP < 70 mmHg), Guyette et al. observed that PDP-E was associated with increased post-treatment SBP compared to patients not given PDP-E [29]. However, PDP-E use was associated with lower 24 h and 30-day survival both before and after adjustment for differences in baseline characteristics [29]. Although this study had a large sample size (3302 total patients) and robust patient matching process (nearest neighbor matching on multiple parameters), the authors noted that selection bias was probable and patients given PDP-E were likely more severely ill even after matching [29]. The findings of Hawn et al., Clifford et al., and Guyette et al. highlight that randomized trials are needed to confirm the risks and benefits of PDP use in the ED and ICU settings.

Our study adds to a body of literature that suggests PDP use carries notable risk of adverse effects and dosing errors. Several studies have reported adverse effects incidence ranging from 1.1% to 45% and dosing errors in 11.2% to 20% of patients [14,21-23,26,30]. In our study, the most frequent adverse effects were extreme tachycardia (7.3% of PDP-PE and 12.8% of PDP-E patients) and bradycardia (4.2% of PDP-PE and 12.8% of PDP-E patients); however, these events did not appear to influence incidence of atrial or ventricular dysrhythmias, ischemic events, LOS or mortality. Dosing errors occurred in 2.1% of those given PDP-PE and 12.8% of those given PDP-E. Our study institution utilizes prefilled syringes of both PDP-PE and PDP-E. Prefilled syringes generally reduce the risk of dosing errors and adverse effects related to dosing errors because they ensure standardized labeling, concentrations, syringe sizes, and dosing [4,5]. PDP use that requires clinicians to dilute, label, and select appropriate doses at the bedside of patients that are critically ill is a high-risk for medication errors [4,5]. Even though our institution has prefilled syringes, dosing errors still occurred frequently in those given PDP-E. This is likely due to the variety of epinephrine products available and differences in dosing and route of administration for different indications. For example, epinephrine can be administered as a continuous IV infusion for hypotension, intramuscular injection for anaphylaxis, and IV injection for cardiac arrest [31,32]. Dosing is notably different for each indication [31,32]. The study institution's electronic medical record does not require providers to list who administered PDP, so we were unable to identify if these errors were due to specific providers (e.g. physicians vs. nurses). In contrast, phenylephrine is used for fewer indications and only available as a vial for preparation as a continuous infusion or syringe for PDP-PE use [31]. This limited selection likely explains why dosing errors were less frequent when using PDP-PE. Institutions that utilize PDP-E should ensure education, naming, ordering, storage, preparation, and administration are standardized to promote safer use [4].

Although we defined dosing errors as one-time PDP-PE doses >500 mCg or PDP-E doses >20 mCg, the optimal dose for PDP (i.e. the dose that clearly differentiates benefit from harm) is poorly established. Suggested doses for PDP-PE generally range from 50 to 200 mCg and PDP-E 5–20 mCg [4,5]. In a retrospective study of PDP-PE use in hypotensive ED patients, Swenson et al. reported that PDP-PE doses between 200 and 500 mCg provided greater increases in MAP and greater reductions in HR compared to doses <200 mCg [26]. Adverse effects occurred in 3% of patients; however, association with dose was not reported [26]. In contrast, Kurish et al. compared ICU patients given PDP-PE >100 mCg (median 200 mCg) or ≤ 100 mCg (median 100 mCg) per dose and observed no differences in hemodynamic changes or adverse events between groups [30]. Cole et al. reported median PDP-PE dose was 100 mCg (IQR 100, 100) and PDP-E 20 mCg (IQR 10–100) in their comparative study of PDP use in the ED [22]. Adverse hemodynamic events occurred more frequently in patients treated with PDP-E (36% vs. 17%); however, statistical comparison was not reported [22]. In our study, median largest dose of PDP-PE was 200 (IQR 100, 200) mCg and PDP-E 20 (IQR 10, 20) mCg with no differences in hemodynamic, ischemic, or other adverse effects requiring PDP reversal. These conflicting findings emphasize that future comparative studies should seek to evaluate optimal dosing of PDP-PE and PDP-E.

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5. Limitations

There were several limitations to this study. First, the sample size was small with only 96 patients in the PDP-PE group and 39 patients in the PDP-E group. Although our sample size calculation indicated that 33 patients per group were needed to meet power, this calculation was based on the findings from one study [22]. Based on our findings, change in HR after PDP-PE or PDP-E administration may be smaller than previously reported, and our study may have been underpowered to detect a difference in this outcome. Additionally, larger studies are needed to confirm our finding that PDP-E produces larger increases in SBP. Second, there were several differences in demographics between groups. Patients in the PDP-E group more frequently presented to the ED for cardiac arrest and were more frequently admitted to the MICU. However, baseline SI was similar between groups, which suggests shock severity was similar. These factors could have had unmeasured influence on efficacy- or safety-related outcomes. Although not statistically different between groups, home use of medications with negative chronotropic properties (e.g. beta-blockers) was common in both groups. Use of beta-blockers could have reduced the positive chronotropic effects of PDP-E. However, data regarding when these medications were last taken was not collected, so it is unclear if they had any impact on HR or other hemodynamic outcomes. Third, there were differences in continuous vasopressor use between groups. Patients given PDP-E more often received continuous epinephrine infusion; however, it is unclear if this difference could explain any differences in outcomes. Fourth, this was a retrospective chart review. Differences in efficacy or safety-related outcomes could have been due to measured or unmeasured confounders rather than treatment with PDP-PE or PDP-E. For example, we did not evaluate influence of ED pharmacists on PDP selection and utilization. This influence could have affected decisions to use PDP-PE or PDP-E, dosing of those agents, or study outcomes, including dosing errors. Missing or inaccurate documentation in patient charts was possible. Therefore, larger, prospective studies are needed before statements regarding PDP superiority or inferiority can be made. Fifth, authors collecting data were not blinded to the study question. This could have led to erroneous data collection. However, random data audits by one author should have reduced this risk of bias. Sixth, HR was selected as the primary outcome instead of SBP or MAP. This was due to a prior comparative study of PDP-PE and PDP-E that illustrated SBP changes were similar after administration of either drug [22]. Therefore, we expected similar changes in blood pressure between groups. Due to the differences in mechanism of action between drugs, we expected HR to be the only hemodynamic difference after administration. We acknowledge that with the exception of patients with symptomatic bradycardia, changes in HR may be less important to clinical stability compared to changes in SBP or MAP, and that changes in blood pressure would have been a more important primary outcome. However, changes in SBP, DBP, and MAP between groups were reported and suggest that PDP-E may provide greater increases in SBP compared to PDP-PE. Future studies comparing PDP should consider selecting SBP or MAP as a primary hemodynamic outcome.

6. Conclusions

We observed that PDP-E provided a greater increase in SBP compared to PDP-PE. However, dosing errors were more common in patients that received PDP-E. Although larger studies are needed to confirm the findings of this study, emergency medicine providers should consider utilizing PDP-E in patients with more severe hypotension or shock at baseline.

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Declaration of Competing Interest

We have no relevant conflicts of interest to disclose.

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