American Journal of Emergency Medicine 37 (2019) 494–498

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Brief Report

Push dose pressors: Experience in critically ill patients outside of the operating room

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ARTICLE INFO

Article history:
Received 26 August 2018
Received in revised form 25 November 2018
Accepted 1 December 2018

Keywords:
Push dose pressors
Vasopressor
Phenylephrine
Hypotension
Critical care

ABSTRACT

Purpose: Evaluate push dose vasopressor (PDP) practice patterns, efficacy, and safety in critically ill patients.
Methods: Critically ill patients receiving phenylephrine or ephedrine PDP from November 2015–March 2017 were included. Patient demographics, medication administration details, vital signs pre- and post-administration, adverse effects, and medications errors were collected. Descriptive data are presented and comparisons were made with paired samples *t*-test, Wilcoxon Rank Sum and Chi-squared analysis or Fisher's Exact Test as appropriate.
Results: A total of 146 patients (155 PDP events) were included; mean age 64.5 ± 13.3 years and 66.4% males, respiratory failure (39.8%) or sepsis (24.9%) admission diagnosis. The surgical intensive care unit (ICU) (44.5%) and medical ICU (33.6%) used PDPs most often, and during the peri-intubation period (57.3%) or for other transient hypotension (38.2%). Following PDP, mean systolic blood pressure (BP), diastolic BP, and heart rate (HR) increased 32.5% (80 to 106 mmHg), 27.2% (48 to 61 mmHg), and 6.4% (93 to 99 bpm), respectively. There were 17 (11.6%) adverse events; most often related to excessive increases in BP or HR and one incidence of dysrhythmia. Thirteen patients (11.2%) had a dose related medication error (phenylephrine dose >200 μg or ephedrine dose >25 mg), nine (6.2%) received PDP with normal/elevated hemodynamics (systolic BP > 100 mmHg or HR > 160 bpm) and 15% while on a continuous infusion vasopressor.
Conclusion: PDPs were used in a variety of patient diagnoses and for select indications. Overall, they were efficacious but associated with adverse drug events and medication errors.

1. Introduction

Peripheral push dose vasopressors ("push dose pressors", PDP) have gained widespread use in an array of medical settings and are commonly used in operating rooms (OR) for peri-intubation hypotension. Outside the OR, PDP are used less often but are becoming increasingly more frequent for peri-intubation hypotension, as a bridge to continuous infusion vasopressors and for medication related hypotension during procedural sedation and anaphylaxis despite limited studies [1-4].

In November 2015, we developed and implemented a PDP guideline with restricted use for critically ill patients with limited indications including: transient hypotension in the setting of post-intubation or procedural sedation, as a bridge to continuous vasopressor infusion, and for emergent transport in an unstable patient without time to begin a vasopressor continuous infusion. Two PDP options were made available, phenylephrine with alpha-1 receptor activity only and ephedrine with both alpha-1 receptor and beta-1 receptor activity, for provider preference. Phenylephrine bolus doses from 50 to 200 μg and ephedrine bolus doses from 5 to 25 mg administered every 2–5 min were recommended for physician administration only and pre-filled diluted phenylephrine (1000 μg/10 mL) and ephedrine (50 mg/10 mL) syringes were made available in the medical, surgical, neuromedical and burn/trauma intensive care units (ICU). Recommended doses were translated from previous OR data [5-7]. The emergency department was not included in this practice change for concern of medication errors and adverse effects with high-risk medications in a vulnerable practice setting (pre-made continuous infusion vasopressors are readily available).

The purpose of this study was to perform a medication use analysis evaluating PDP practice patterns in critically ill patients in non-OR

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https://doi.org/10.1016/j.ajem.2018.12.001
0735-6757/

settings throughout the hospital. We sought to characterize overall use, determine efficacy, and identify adverse drug events or medication-related safety concerns.

2. Materials and methods

2.1. Study design

This was a retrospective, observational analysis of hypotensive adult patients that received a PDP in a clinical area outside of the OR at an urban university tertiary care hospital. Approval for this study was obtained from the university's institutional review board.

2.2. Study setting and population

This study was conducted at an 850-bed university teaching hospital with 74 relevant adult intensive care unit beds. Data was collected from November 2015 through March 2017. Patients were captured from the electronic medical record through medication orders of phenylephrine 1000 μg/10 mL or ephedrine 50 mg/10 mL syringes. All patients 18 years of age and older who received at least one phenylephrine or ephedrine PDP were included. Patients receiving phenylephrine for priapism or a PDP in the post anesthesia care unit were excluded. Any patient that did not have a particular vital sign (systolic blood pressure [SBP], diastolic blood pressure [DBP], or heart rate [HR]) available before and after PDP or were determined to have a dose related medication error were excluded from the efficacy analysis.

Any patient with unclear dosing documentation (documentation in the medication administration record did not match the nursing notes) were excluded from dose description and dose related medication error evaluation, but were included in the safety evaluation.

2.3. Study protocol

Three abstractors conducted a complete medical record review using a standardized data collection tool and data dictionary. Education sessions regarding data collection to ensure that data was extracted in the same way were completed with the two of the investigators. Patients may receive PDP at different times during their hospitalization, and as such we sought to capture these as discrete events. Each PDP "event" was defined as PDP administration occurring within a 2-hour period. If a PDP was administered outside of this window then this was included as a separate event. Data collected included patient and service demographics, PDP administration details including medication, indication, dose, frequency, and total number of doses, vital signs pre- and post-administration, number of patients started on a continuous infusion vasopressor, incidence of crystalloid fluid prior to PDP administration, and adverse events and medication errors.

Systolic blood pressure and DBP from 30 min prior (using the lowest value if multiple readings) to administration and 30 min after administration (using the highest value if multiple readings) were collected. In some cases, subsequent administrations of PDPs altered the 30-minute time period and shorter pre- and post-timeframes were used.

Adverse effects including SBP > 200 mmHg or increase >100%, HR increase or decrease >30%, incidence of dysrhythmia (within 30min), ischemia (troponin elevation or myocardial infarction within 24 h), hypertension or reflex bradycardia requiring treatment were evaluated. Also, medication errors such as a single dose of phenylephrine >200 μg or ephedrine >25 mg, PDP administration to patients with a SBP > 100 mmHg or HR > 160 bpm, or PDP administration while already on a continuous infusion vasopressor were identified. Lastly, we evaluated how often PDPs were used in the peri-death period defined as <1 h before time of death to evaluate the frequency of survival versus death in these patients.

2.4. Data analysis

Descriptive statistics were used to characterize the study sample and current PDP practice. Patient demographics, medical service characteristics, and circumstances surrounding PDP administration were quantified by stratifying the sample in three groups: patients who received phenylephrine, patients who received ephedrine, and patients who received both medications. Efficacy was evaluated by describing the absolute and percent change.

Comparisons between groups were made using paired sample *t*-test, Wilcoxon rank sum, Chi-squared analysis, or Fisher's Exact Test as appropriate. Efficacy metrics for vital signs were calculated by quantifying the mean value pre- and post-PDP administration and the mean change from baseline and percent change. Frequency of adverse effects was quantified using proportions. A p-value <0.05 was considered statistically significant for all analyses.

3. Results

During the study period there were 155 PDP events in 146 patients (mean age 64 ± 13.3 years and 66.4% were males). The most common admitting diagnosis was respiratory failure (39.8%) and most frequent vasopressor used was phenylephrine (104), although many patients did receive ephedrine (33), or both phenylephrine and ephedrine [9]. There were 116 PDP events where the doses administered were clear in the documentation. Of those, the mean phenylephrine and ephedrine dose were 147 ± 68.8 μg and 14.2 ± 8.5 mg, respectively. Most patients (75%) received one dose of PDP during an event, 19.8% required two and infrequently were three or more doses required (5.2%). One patient received five doses of PDP during an event.

Most patients received PDP in the peri-intubation period (57.3%) and the surgical ICU was the most common user of PDP followed by the medical ICU, contributing to 78% of use outside of the OR. Lastly, only 26.7% of patients received fluid administration in response to decreased blood pressure at the time of PDP. Complete demographics are available in Table 1. Fig. 1 describes the number of patients included in each efficacy and safety analysis.

3.1. Efficacy

We were able to assess efficacy based on pre- and post-PDP vital signs in almost 80 patients in each vital sign category (Table 2). The mean change in SBP was 26 mmHg (32.5% change from baseline), DBP was 13 mmHg (27.2% change from baseline), and HR was 6 beats per minute (6.4% change from baseline). Interestingly, mean HR increased more in the phenylephrine group (6.3%) than in the ephedrine group (3.5%). Overall 41 patients (28%) were started on a continuous infusion vasopressor after PDP (most often norepinephrine) and no patient died within an hour after PDP.

3.2. Safety

Table 3 describes all adverse events and medication errors. A total of 17/146 (11.6%) patients had an adverse event associated with PDP administration. Thirteen of 116 patients (11.2%, 116 had clear dose information, Fig. 1) had a dose related medication error (phenylephrine dose >200 μg or ephedrine dose >25 mg), nine (6.2%) received PDP with normal/elevated hemodynamics (systolic BP > 100 mmHg or HR > 160 bpm) and 15% while on a continuous infusion vasopressor.

4. Discussion

To our knowledge there are limited studies evaluating PDP usage patterns, efficacy, and safety outside of the OR [1-3]. Other reports and commentaries have been focused on medication safety and errors [4,8,9]. We sought to characterize PDP use in our critically ill population

Table 1
Demographics (n = 146).

Push dose pressor	Phenylephrine (n = 104) No. (%)	Ephedrine (n = 33) No. (%)	Both (n = 9) No. (%)	Total (n = 146) No. (%)
Gender				
Male	68 (65.4)	23 (69.7)	6 (66.7)	97 (66.4)
Female	36 (34.6)	10 (30.3)	3 (33.3)	49 (33.6)
Admitting Diagnosis				
Respiratory failure	64 (61.5)	14 (42.4)	2 (22.2)	80 (39.8)
Other[a]	38 (36.5)	10 (30.3)	2 (22.2)	50 (24.9)
Sepsis	24 (23.1)	10 (30.3)	3 (33.3)	37 (18.4)
Altered mental status	13 (12.5)	3 (9.1)	1 (11.1)	17 (8.5)
ICH, stroke, or TBI	10 (9.6)	2 (6.1)	–	12 (6.0)
Trauma	1 (1.0)	1 (3.0)	1 (11.1)	3 (1.5)
Cardiac	2 (1.9)	–	–	2 (1.0)
Treatment Team				
SICU[#]	32 (30.7)	26 (78.8)	7 (77.8)	65 (44.5)
MICU	44 (43.2)	3 (9.1)	2 (22.2)	49 (33.6)
NMICU	24 (23.1)	2 (6.1)	–	26 (17.8)
BTICU	4 (3.9)	1 (3.0)	–	5 (3.4)
CVICU	–	1 (3.0)	–	1 (0.7)
Treatment Indication				
Peri-intubation	62 (59.6)	23 (69.7)	5 (55.6)	90 (61.6)
Transient hypotension	45 (43.3)	11 (33.3)	4 (44.4)	60 (41.0)
Fluid administration at the time of PDP	29 (27.9)	10 (30.3)	–	39 (26.7)

ICH = intracranial hemorrhage, TBI = traumatic brain injury, SICU = surgical intensive care unit, MICU = medical intensive care unit, NMICU = neuromedical intensive care unit, BTICU = burn trauma intensive care unit, CVICU = cardiovascular intensive care unit.
[a] Include: cirrhosis, subdural hematoma, upper gastrointestinal bleeds, seizures/status epilepticus, and acute abdominal aneurysms.
[#] More patients in the SICU received ephedrine ($p < 0.0001$), no other statistical differences.

and also evaluate efficacy and safety. Overall, we found that phenylephrine is often used in the peri-intubation period, which is similar to previous reports of PDP use outside of the OR [1,2]. Selection of phenylephrine or ephedrine varied, but our surgical ICU had the highest percentage of ephedrine use likely due to comfort of anesthesia/critical care providers and familiarity with use compared to other critical care areas. Another interesting finding was that patients receiving phenylephrine required additional doses more often than ephedrine, which may be related to the shorter half-life.

As expected, PDP improved BP and HR, however it was surprising that phenylephrine, only having alpha-1 receptor activity had a greater HR increase than ephedrine. In our study, only 28% of patients were started on a continuous infusion vasopressor after PDP compared to 70% and 59% in other reports [1,2]. One explanation may be attributed to patient population differences; ICU compared to emergency department (ED). Specifically, it seems that PDP were being used to bridge to continuous infusion vasopressors in the ED studies, but this was not the intent of PDP use in the majority of our patients (temporary

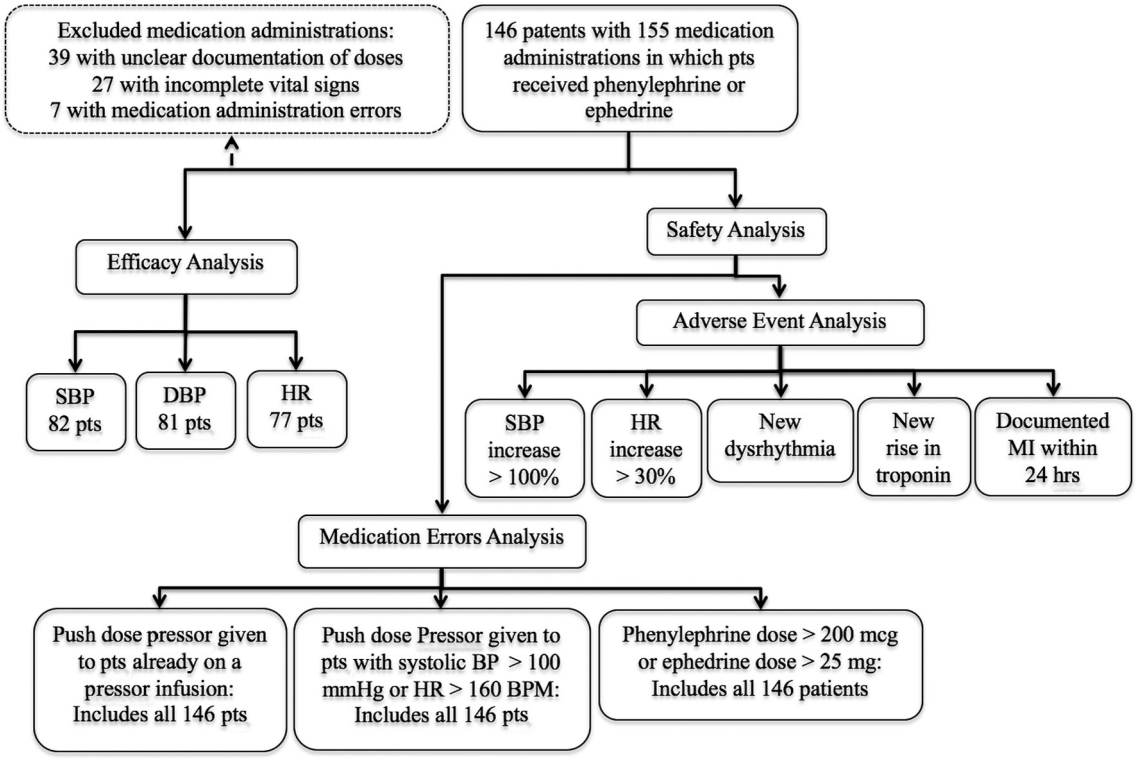

Fig. 1. Study population.

Table 2
Efficacy of push dose pressors[a].

	Pre	Post	Mean change from baseline (%)	95% confidence interval	*p* value
SBP (n = 82), mean mmHg (SD)	80 (15.4)	106 (24.8)	+25.6 (32.5)	−31.1 to −20.2	<0.001
DBP (n = 81), mean mmHg (SD)	48 (12.1)	61 (19.1)	+13.4 (27.2)	−17.1 to −9.7	<0.001
HR (n = 77), mean bpm (SD)	93 (24.1)	99 (23.2)	−5.8 (6.4)	−10.4 to −1.3	0.013

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SD = standard deviation, bpm = beats per minute.
[a] Sample size for each group differs based on available dose and vital sign data pre- and post-push dose pressor administration.

vasopressor support during transient hypotension). Also, continuous infusion vasopressors are pre-made and readily available at our institution in medication dispensing cabinets in high-use areas making this indication of bridging to infusion unnecessary. Furthermore, many of our patients that received PDP for transient hypotension were undergoing a procedure (e.g. bronchoscopy) where hemodynamic instability is expected to resolve after completion and therefore not require continuous infusion vasopressors. In no encounters were PDP used in the peri-death period. We cannot make any conclusions regarding the efficacy in improving patient condition, clinical outcome, or preventing death, but it seems that providers are not using PDP towards the end of resuscitative efforts.

It is important to highlight that there were adverse events and medication errors associated with PDP use in our study including one case of dysrhythmia. Most often these were significant changes or elevations in SBP or HR or inappropriate PDP doses administered. We did find over 10% of patients with a medication error related to high phenylephrine or ephedrine doses; >200 μg and >25 mg, respectively. We chose these dose thresholds based on previous OR data recommending bolus doses of phenylephrine of 100–150 μg or 1–2 μg/kg [5-7]. Swenson et al. described phenylephrine bolus doses ranging from 10 to 500 μg/dose for the first dose and correlated a greater mean arterial pressure (MAP) change in the 200–500 μg dose range compared to <200 μg; +12 vs. +4–5.6 mmHg, respectively [2]. As stated in the limitations of this study, much of the documentation was from handwritten resuscitation notes and subject to recording errors. From our experience, it is difficult to assume that, for example, 500 μg was administered as a single dose or as smaller, quickly titrated, doses and then the total dose documented, which could confound the interpretation of the MAP measurement results. Also, in this study, cases were excluded for incomplete pre- and post-blood pressure measurements but it does not seem any cases were excluded for dose documentation discrepancies between the nursing notes and medication administration record like we did in our study. When comparing our mean SBP and DBP, this would correlate to a calculated higher MAP difference than Swenson and colleagues showing potentially greater efficacy as far as hemodynamic changes at lower individual doses. Although we defined these dose thresholds from our institution guidelines and previous OR literature, these may not define the upper dosing limits at all institutions.

In our evaluation there were several cases of PDP administration during normal BP or elevated HR, administrations while a continuous infusion vasopressor was already infusing, and only a small amount of patients received crystalloid fluids around the time of PDP administration. Although we did not have any patients with a relative increase in troponin level from baseline following PDP, we did have several patients receive PDP with a pre-existing elevated troponin level, but no associated adverse effects were seen. It is difficult to determine the negative clinical effects or impact on outcome of these incidents since our overall patient sample was small.

Our overall rate of adverse events was 11.6% compared to 2.7% in previous studies, but this difference is likely due to our expanded definitions for adverse events which included a percent SBP, DBP, HR change, administration of PDP with normal vital signs, and administration during vasopressor continuous infusion [2]. Our guideline restricts administration to physicians which was an attempt to reduce overall inappropriate use, create familiarity with the multi-dose syringe, and minimize medication errors. It is difficult to infer if this approach had any effect on our adverse effects and medication errors rates as we do not have a comparator group.

There were several notable limitations for this study. This was a retrospective study with small sample size and thus our ability to control confounding factors was limited. Push dose pressor use is often during high-stress or fast-paced situations and as a result documentation was often incomplete or unclear for PDP administrations. We did attempt to clarify medication administration record documentation with nursing notes and excluded patients from certain analyses if documentation was unclear. As a result, however, this decreased our sample size, made it more difficult to identify medication errors, or correlate

Table 3
Adverse events and medication errors.

Push dose pressor	Phenylephrine (n = 104) No. (%)	Ephedrine (n = 33) No. (%)	Both (n = 9) No. (%)	Total (n = 146) No. (%)
Adverse event[a] (n = 146)	13 (12.5)	2 (6.1)	2 (22.2)	17 (11.6)
SBP increase>100%	6 (5.8)	–	1 (11.1)	7 (4.8)
HR increase>30%	6 (5.8)	2 (6.1)	1 (11.1)	9 (6.2)
Dysrhythmia	1 (1.0)	–	–	1 (0.7)
Medication errors[c] (n = 116)				13 (11.2)
Phenylephrine dose >200 μg	12[b] (10.3)	–	–	12 (10.3)
Ephedrine dose >25 mg	–	1 (8.6)	–	1 (8.6)

SBP = systolic blood pressure, HR = heart rate, bpm = beats per minute.
[a] There were no instances of myocardial infarction or new elevations in troponin within 24 h of administration, or reflex bradycardia requiring treatment. Lack of fluid administration at the time of push dose pressor or receiving a push dose pressor during continuous infusion vasopressor administration was not associated with any adverse effects.
[b] One patient received phenylephrine 1000 μg that was associated with SBP > 300 mmHg requiring antihypertensive treatment (previously reported) [2].
[c] Of all patients that received a push dose pressors (n = 146), 8 were administered when SBP was >100 mmHg and one when HR was >160 bpm. There were 22 patients (15%) that received a PDP when they were already receiving a continuous infusion vasopressor.

medication errors to negative effects or identify if treatment was administered in relation to an unwanted PDP effect or error. Real-time, individual bolus dose documentation with subsequent hemodynamic measurements between each dose would be beneficial to evaluate the efficacy of this approach. Use of the narrator function and technology integration for direct vital sign input into the electronic medical record without nursing transcription may improve documentation.

Most of the PDP use in our study was in the peri-intubation period, but we did not collect induction agent information. Medications used for induction may independently cause hypo- or hypertension which could have confounded our efficacy analysis. Study definitions for adverse events may have been too simplistic and there is the possibility that, for instance, a SBP increase by >100% may have been the goal for therapy even though our intent was to identify severe, unintended, derangements. Although we did not find an association with the lack of fluid administration, receiving a PDP while on a continuous infusion vasopressor, or PDP administration in a patient with an already elevated troponin and any adverse effects, this should be interpreted with caution as our sample size is small and there is the possibility of type II error. Lastly, there were no evaluations of clinical outcome, achievement of goal hemodynamics or a continuous infusion comparitor group. It is still unclear if there are any differences in outcomes with PDP administration compared to traditional continuous infusion vasopressor use. Also, long-term outcomes were not evaluated so it remains unclear if PDP have any influence on morbidity and mortality; however, this study provides needed data on use patterns, efficacy, and safety in the immediate post-administration period.

5. Conclusions

The study found that PDP were used in critically ill patients with a variety of diagnoses but experiencing similar and select clinical indications. Push dose pressors were shown to be efficacious regarding vital sign changes, but were also associated with adverse drug events and frequent medication errors. Additional studies need to be performed to evaluate the long-term clinical impact of PDP as well as to further examine adverse events and medication errors to better understand their overall impact on patient outcomes.

Acknowledgements

Frank Latucca, Pharm.D.
Matthew O'Connell, Pharm.D.
Christopher Nyiri, Pharm.D.
University of Rochester Medical Center, Department of Pharmacy.

Source of support

None.

Prior presentations

None.

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