**Pharmacology in Emergency Medicine**

**EFFICACY OF BOLUS-DOSE PHENYLEPHRINE FOR PERI-INTUBATION HYPOTENSION**

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Abstract—Background: Intubation in hypotensive emergency department (ED) patients may increase the risk of life-threatening complications such as hypoperfusion and cardiovascular collapse. Peripherally administered, diluted “push-dose” phenylephrine has been advocated to treat peri-intubation hypotension, however, its effectiveness is unknown. Study Objective: To investigate the efficacy and usage patterns of bolus-dose phenylephrine for peri-intubation hypotension at an academic medical center. Methods: A retrospective chart review of all adult intubated, hypotensive patients (systolic blood pressure [SBP] < 90 mm Hg) over 12 months was conducted. During the peri-intubation period (30-min prior to/after intubation), the effect of phenylephrine was evaluated pre/post drug administration by comparing SBP, diastolic blood pressure (DBP), and heart rate (HR). Results: A total of 119 patients met eligibility criteria. Phenylephrine was given to 29/119 (24%) patients and 20 (17%) were treated during the peri-intubation period. Phenylephrine was given for many different conditions, and treatment timing varied greatly. Phenylephrine was given with other vasopressors 70% of the time (14/20), however, the timing of vasopressor infusion also varied greatly. When phenylephrine was given during the peri-intubation period, there were significant increases in SBP and DBP (p < 0.01) with no change in HR. Conclusion: In this academic ED, bolus-dose phenylephrine was used by practitioners without a systematic pattern. Although phenylephrine improved hemodynamics, it is possible that nonsystematic use of phenylephrine may cause inadvertent negative effects. Further studies will need to be conducted to better understand the best practices for use of phenylephrine. © 2015 Elsevier Inc.

Keywords—phenylephrine; hypotension; peri-intubation; sepsis; vasopressors; shock

INTRODUCTION

Postintubation hypotension can be a life-threatening complication and has been associated with hypoxemia and death (1,2). These patients have a higher mortality and longer time spent in intensive care units in comparison with patients without postintubation hypotension (3–5). The causes of postintubation hypotension can be multifactorial, with common causes being drug-mediated vasodilation or consequences of positive pressure ventilation (6). Despite this knowledge, it is unclear what is the best method of prevention and treatment of postintubation hypotension.

In the emergency department (ED), hypotensive patients often present requiring airway management. Management of hypotension in these patients is difficult and regularly requires the use of vasopressors. Recently, emergency physicians have utilized peripherally...
administered diluted phenylephrine ("push-dose") boluses to treat the hypotensive period. Several anesthesia studies have shown efficacy with bolus-dose phenylephrine for hypotension induced by spinal anesthesia (7–9). However, there are no data on the benefit of this therapy in the ED during the peri-intubation period. Furthermore, there is no evidence concerning emergency physician practice concerning the use of phenylephrine with peri-intubation hypotension.

This study examines the use and efficacy of bolus-dose phenylephrine for peri-intubation hypotension in an urban academic ED. Objectives include evaluating the practice pattern of phenylephrine use by emergency physicians and the efficacy of phenylephrine when used during peri-intubation hypotension.

**MATERIALS AND METHODS**

*Study Setting and Population*

This study is a retrospective chart review of hypotensive adult patients requiring intubation who presented to an urban, academic ED from February 2011 to February 2012. The study site is a Level I trauma center, a 487-bed hospital that treats approximately 75,000 emergency patients annually and has training programs in emergency medicine (postgraduate years 1–3) and combined pediatric emergency medicine (postgraduate years 1–5). The study was reviewed and granted approval by the university’s institutional review board.

*Patient Selection*

All adult patients during this time period were eligible for analysis. Inclusion criteria were hypotensive patients requiring intubation. The peri-intubation time period was defined as 30 min prior to and after intubation. Hypotension was defined as at least one systolic blood pressure (SBP) reading below 90 mm Hg.

Patients were excluded if they were <18 years old, they did not receive bolus-dose phenylephrine, or they did not have clear documentation of the timing of phenylephrine dose. Bolus-dose phenylephrine at our institution is a prepackaged 10-mL syringe at a concentration of 100 μg/mL.

*Data Collection*

The final patient population evaluated included hypotensive adult patients requiring intubation. Key data points were collected to define the population’s demographics and hemodynamics. Two authors extracted data independently, and a correlation was done on primary outcome variables to confirm that data extraction was consistent. Specific demographic data points collected include: age, gender, reason for intubation, intubation method, sedation/paralytic used, traumatic presentation and type (blunt vs. penetrating), admission diagnosis, phenylephrine given, phenylephrine dosage and time, and additional vaspressors given and times. Hemodynamic data were collected 60 min pre- and postintubation, including SBP, diastolic blood pressure (DBP), and heart rate.

*Data Analysis*

The efficacy of peripherally administered bolus-dose phenylephrine for peri-intubation hypotension was examined in patients treated during the peri-intubation time period. Demographic data were compared using chi-squared, Fisher’s exact, and the t-test where appropriate. The quantitative hemodynamic effects were compared pre- and postadministration of phenylephrine using the Wilcoxon signed rank test to determine statistical significance in differences for SBP, DBP, and heart rate (HR) prior to and after first phenylephrine dose administration.

**RESULTS**

During the study period, 444 patients were intubated in the ED; 325 patients were excluded from the analysis because 56 patients were <18 years old and 269 patients were not hypotensive. The remaining 119 patients were eligible for inclusion (Figure 1). Only a small portion of these patients (29/119, 24%) were treated with bolus-dose phenylephrine for their hypotension. Of these,
20/119 (17%) were treated during the peri-intubation period.

Data extraction was completed independently by two of the study authors, and a correlation was done to confirm that data extraction was consistent. For the primary variables of whether phenylephrine was given, presence of sepsis, and admission diagnosis, the correlation coefficient was >0.9. For intubation time and phenylephrine dose time, the correlation coefficient was >0.85. All hemodynamic data (i.e., SBP, DBP, and HR) had a correlation coefficient of >0.9.

Table 1 shows the demographic data for intubated patients treated with phenylephrine for hypotension. Patients were intubated primarily for medical causes of hypotension (15/20), with only a small percentage intubated for trauma (5/20). Five of 20 did not receive sedation or a paralytic for intubation. Half of the patients were male, with a mean age of 64 ± 16 years. Primary admission diagnoses are noted in Table 1, with unspecified respiratory failure and pneumonia as the most common.

The practice pattern for the use of phenylephrine is noted in Table 2. Of the total population (119 patients), 29 patients (24%) were treated with phenylephrine and only 20 patients (17%) received phenylephrine during the peri-intubation period. Providers treated 13/20 with multiple doses of phenylephrine (65%). The timing of when phenylephrine was given ranged widely (18 min prior to intubation to 29 minutes post intubation), with a mean time of phenylephrine administration after intubation of 4 ± 13 min.

Seventy percent (14/20) of patients receiving bolus-dose phenylephrine were also treated with continuous intravenous infusion of vasopressors (Table 2). Five patients were treated with vasopressors prior to phenylephrine, whereas 9/20 were started on vasopressor infusions after phenylephrine administration. The most commonly utilized vasopressor was norepinephrine (10/20; 50%). Additional vasopressors were administered within a wide range of time in relation to the first phenylephrine dose, from 30 min prior to phenylephrine treatment to 108 min after phenylephrine administration.

Table 3 describes the hemodynamic effects of peri-intubation phenylephrine. Bolus-dose phenylephrine
successfully raised SBP from 73 mm Hg (95% confidence interval [CI] 67–78) to 93 mm Hg (95% CI 80–105). DBP increased similarly from 42 mm Hg (95% CI 35–48) to 52 mm Hg (95% CI 44–58). There was no change in HR post-administration of phenylephrine (prephenylephrine 114 [95% CI 99–130]; postphenylephrine 115 [95% CI 101–130]).

DISCUSSION

Patients presenting to the ED with hypotension requiring airway management are at higher risk of significant morbidity and mortality (3,6,10). Recommendations have been presented on the use of peripherally administered phenylephrine as a method to treat peri-intubation hypotension. Significant data exist on the utilization and benefit of phenylephrine for hypotension induced by spinal anesthesia and neurologic emergencies, however, no clear data exist demonstrating improved outcomes through the treatment with phenylephrine in critically ill patients with hypotension (7,8,11). Further, no data exist on emergency physician practice patterns in regards to the use of bolus-dose phenylephrine.

This study evaluated the practice patterns of emergency physician use of bolus-dose phenylephrine for peri-intubation hypotension at an urban academic ED. During the study period, 24% of intubated patients with hypotension were treated with bolus-dose phenylephrine, with 66% of these receiving multiple doses. The time of administration of phenylephrine varied greatly, with 70% of patient’s receiving treatment during the peri-intubation period. Furthermore, emergency physicians utilized phenylephrine to treat general hypotension without focused interventions on specific disease processes, with 70% of these patients being subsequently treated with intravenous vasopressor infusions. Lastly, hemodynamic evaluation of bolus-dose phenylephrine during peri-intubation hypotension demonstrates an increase by 20% in both SBP and DBP from pretreatment levels, with no effect on heart rate (Table 3).

This is the first evaluation of the use of bolus-dose phenylephrine for hypotension in the ED. There are no data concerning the use of phenylephrine by emergency physicians and whether this practice has increased in our population. In this system, phenylephrine was used in 24% of intubated patients with hypotension. The pattern of practice is variable, with no consistency for the use of phenylephrine, though in this population it was used primarily as a bridge to an intravenous vasopressor, with 66% of patients receiving subsequent infusions. Treatment with phenylephrine occurred in trauma patients (25%) as well as patients with septic shock (55%). The admission diagnoses of patients treated with phenylephrine demonstrated the wide variability of conditions treated (Table 1).

In this critically ill ED population, hypotension has a 10-fold increased risk of sudden death in the hospital, not limited to those presenting with cardiovascular diagnoses (3,4). Treating patients early on before severe tissue or organ hypoxia has beneficial outcomes in preventing death (12,13). To treat hypotension, administration of intravenous fluids combined with use of vasopressors is a standard method of supportive care (14). Vasopressor therapy is important for hypotensive patients who need adequate perfusion pressure, sometimes despite and in addition to volume resuscitation (12,13).

In the ED, phenylephrine is being used as a peripheral bolus bridge to centrally given vasopressors in the peri-intubation period. Phenylephrine specifically agonizes the alpha-1 adrenergic receptor, which can aid in increasing systemic vascular resistance through vasoconstriction of large arterioles, with little impact on constriction of terminal arterioles (7). Further, being purely an alpha agonist, it does not have any intrinsic inotropic effect. When used to treat hypotension from spinal anesthesia, phenylephrine can maintain normal arterial pressure within 20% of baseline values (7,9). Furthermore, with phenylephrine’s fast rate of action (mean onset 60 s), it is an attractive option as a vasopressor given as a bolus (9). Our data support the literature with an increase in SBP and DBP by 20% with no effect on heart rate (Table 3). This agent may be particularly beneficial for patients with significant tachycardia where increased inotropy may increase myocardial oxygen demand and cause demand ischemia. However, there is the potential for harm with phenylephrine when used inappropriately. The pure vasoconstriction induced by phenylephrine may lead to worsened shock despite improved blood pressure in the setting of further depressed myocardial function due to increases in afterload.

In this study, though many different etiologies were treated with bolus-dosed administration of phenylephrine, phenylephrine was primarily used as a bridge to vasopressors or aggressive volume resuscitation. Of all patients treated with phenylephrine, 70% of patients were converted to continuous vasopressor infusions, with norepinephrine and epinephrine being the primary vasopressors chosen (Table 2). No patient was placed on a phenylephrine intravenous infusion after bolus dose (Table 2). Those not treated with a vasopressor after phenylephrine were no longer hypotensive in this dataset.

It is unclear what the long-term effect of bolus-dose phenylephrine administration would have in all etiologies of hypotension. A specific concern for phenylephrine’s use is that although it increases blood pressure and systemic vascular resistance, it may decrease cardiac output (9,13,15,16). Due to this concern, in septic patients, the
Surviving Sepsis Campaign Guidelines recommends norepinephrine as the first-choice vasopressor, with epinephrine and vasopressin denoted as additional agents (Grade 1C) (13). Phenylephrine intravenous infusion was noted to be used only in specific situations where cardiac output was high and blood pressure low, and patients have a significant risk of dysrhythmias (Grade 1C) (13). However, data from Morelli et al. noted that phenylephrine intravenous infusion may be equivalent to norepinephrine for septic shock in a randomized controlled trial (17). Additionally, studies that observed phenylephrine use in septic, nonhypotensive patients did not note a change in cardiac index (18). In contrast, in the setting of neurologically mediated hypotension, phenylephrine has been recommended when patients are tachycardic (11). Lastly, it is suggested that the use of phenylephrine infusion may have deleterious effects in states where volume depletion is the primary issue (e.g., blunt or penetrating trauma, gastrointestinal bleed) (15,16). There are no data on the effect of phenylephrine bolus administration as a bridge to other vasopressors or volume resuscitation. These data suggest that care must be used in the determination of phenylephrine use for hypotension.

There are also no data on the use of phenylephrine as a bolus for hypotensive patients during the peri-intubation period. The improvement in peri-intubation hypotension demonstrated here by bolus phenylephrine administration is particularly notable. Of the patients included in this study, 90% received rapid sequence intubation as their intubation method, which tends to be associated with postintubation hypotension and may possibly be related to the types of sedatives received for the procedure (2). Further analysis of these associations, in addition to patients’ predisposing conditions, can elucidate more on the efficacy of phenylephrine in particular. Thus, the presence of hypotension during and even after intubation should be viewed holistically and systematically.

Limitations

This study also had certain limitations. Due to many confounding variables in this study, we could not evaluate a relationship for phenylephrine use with specific outcome values, including total fluids, decreased vasopressor use, and patient survival. In addition, this study was limited to patients who presented over a 1-year period at an urban hospital, which may alter the more global implications. Additionally, we addressed patients who did not have specific predisposing factors, but looked at adult hypotensive patients holistically. This can have a serious impact on the types of drugs that can be administered to specific age groups who have certain conditions already. Lastly, it is not clear if all physicians who administered phenylephrine in the peri-intubation period or all physicians in this facility received the same information on the procedures, implications, and consequences of phenylephrine use. Overall, it is evident that there was not a clear systematic practice pattern concerning the use of phenylephrine in the peri-intubation period, though evaluation of the practice does suggest that its use was limited to bolus-dose administration to bridge to other vasopressors.

CONCLUSIONS

In this urban academic ED, the use of peripheral bolus-dose phenylephrine demonstrated improved hemodynamics during the peri-intubation period. Though use was broad and inconsistent, phenylephrine is mostly used as a bridge to vasopressor infusion or aggressive fluid resuscitation. It is possible that nonsystematic use of phenylephrine may cause inadvertent negative effects. Further studies will need to be conducted to better understand the best practices for use of phenylephrine.

REFERENCES

ARTICLE SUMMARY

1. Why is this topic important?
Peri-intubation hypotension has significant effects on the morbidity and mortality of critically ill patients. Early management of hypotension can lead to improved patient outcomes. The use and efficacy of bolus-dose phenylephrine for peri-intubation hypotension is unknown.

2. What does this study attempt to show?
The objective of this study was to evaluate the efficacy and usage of bolus-dose phenylephrine for peri-intubation hypotension.

3. What are the key findings?
In this academic emergency department, bolus-dose phenylephrine was used by practitioners without a clear systematic pattern. During peri-intubation hypotension, phenylephrine treatment improved systolic blood pressure and diastolic blood pressure, and had no effect on heart rate. It is possible that nonsystematic use of phenylephrine may cause inadvertent negative effects. Further studies will need to be conducted to better understand the best practices for use of phenylephrine.

4. How is patient care impacted?
The use of bolus-dose peripherally administered phenylephrine may play a role in prevention and treatment of peri-intubation hypotension. Further studies will need to be conducted to better understand the best practices for use of phenylephrine.