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Safety of peripheral administration of phenylephrine in a neurologic intensive care unit: A pilot study

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ABSTRACT

Integral to the management of the neurocritically injured patient are the prevention and treatment of hypotension, maintenance of cerebral perfusion pressure, and occasionally blood pressure augmentation. When adequate volume resuscitation fails to meet perfusion needs, vasopressors are often used to restore end-organ perfusion. This has historically necessitated central venous access given well-documented incidence of extravasation injuries associated with peripheral administration of vasopressors. In this pilot study, we report our 6-month experience with peripheral administration of low-concentration phenylephrine (40 μg/mL) in our neurocritical care unit. We were able to administer peripheral phenylephrine, up to a dose of 2 μg/(kg min), for an average of 14.29 hours (1-54.3) in 20 patients with only 1 possible minor complication and no major complications. This was achieved by adding additional safety measures in our computerized physician order entry system and additional nurse-driven safety protocols. Thus, with careful monitoring and safety precautions, peripheral administration of phenylephrine at an optimized concentration appears to have an acceptable safety profile for use in the neurocritical care unit up to a mean infusion time of 14 hours.

1. Introduction

Fluid resuscitation and hemodynamic support are two of the major tenets of critical care [1]. When fluid administration fails to restore adequate arterial pressure and organ perfusion, vasopressors are recommended [2]. Given their potent and immediate hemodynamic effects, vasopressors may also be transiently required to maintain perfusion in the face of life-threatening hypotension when adequate filling pressures have not been attained or verified [2]. The choice of vasopressor is largely based on physician preference [1,3]. The decision to initiate vasopressor therapy has historically necessitated the insertion of a central venous catheter (CVC). This practice is based on a significant volume of reports in the literature describing skin damage, sloughing, necrosis, and gangrene associated with extravasation during peripheral infusion of vasopressors [4–9]. Central venous catheter placement and maintenance, however, are not devoid of risk. Complication rates of 15% have been reported, which include the following: mechanical complications (arterial puncture, pneumothorax, hemothorax, mediastinal hematoma, misplacement of the catheter tip, soft-tissue hematoma, or air embolism), catheter-related infections (bloodstream or insertion site infection), and catheter-related thrombosis [10]. Some of these complications may lead to significant morbidity and mortality, which makes the clinical decision to initiate vasopressor therapy through a CVC critical to patient outcomes [11–13]. Distinct from existing literature on other vasopressors (epinephrine, norepinephrine, dopamine, and vasopressin), to our knowledge, there is no literature reporting extravasation injury associated with peripheral administration of phenylephrine.

Phenylephrine is a direct-acting α-adrenergic agonist which produces immediate systemic arterial vasoconstriction and is associated with an increase in systemic vascular resistance in a dose-dependent manner [14]. With a short half-life of 5 minutes and a duration of action of only 15 to 20 minutes, phenylephrine is an ideal agent in the intensive care unit (ICU) setting [14]. Given phenylephrine's absence of β_1 (chronotropic and inotropic) activity, unlike its counterparts (norepinephrine, epinephrine, and dopamine) [15,16], phenylephrine can accomplish its therapeutic end point without an increased risk of tachydysrhythmias [17]. By increasing systemic vascular resistance, the use of phenylephrine may present a potential disadvantage by decreasing stroke volume and thus cardiac output. However, most studies report that cardiac output is either maintained or increased in patients exposed to phenylephrine who are without preexisting cardiac dysfunction [18,19].

In the critically ill neurologic patient, vasopressors are a particularly attractive and common adjunct to patient management to ensure ideal cerebral and spinal perfusion. Induced hypertension is recommended as a primary therapy for cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage [20] and has demonstrated encouraging results in management of certain carefully selected subtypes of acute

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ischemic cerebral infarction [21–25]. Vasopressors are also recommended to maintain spinal perfusion pressure in the hyperacute period after spinal cord injury [26,27]. In addition, vasopressors are frequently used to maintain cerebral perfusion pressure in the setting of severe traumatic brain injury and cerebral hypoperfusion due to elevations in intracranial pressure [28–30]. With the advent of invasive cerebral perfusion monitoring, augmentation of cerebral perfusion pressure has become key to preventing secondary brain damage after initial injury.

Based on the aforementioned therapeutic needs for administration of phenylephrine, we obtained conditional approval by our institution's Pharmacy and Therapeutics committee for use of peripheral phenylephrine in patients without central venous access. A protocol to peripherally infuse phenylephrine at a concentration of 40 μg/mL was developed and implemented. This concentration is in contrast to our institutional standard 160-μg/mL concentration administered via CVC. In this retrospective case series, we sought to ascertain the safety and feasibility of peripherally administered phenylephrine in patients admitted to our neurologic intensive care unit.

2. Methods

A retrospective medical record review was conducted of all patients admitted to the neurocritical care unit between August 2013 and February 2014 who received peripheral administration of phenylephrine according to our protocol. Peripheral phenylephrine was administered to patients who met prespecified criteria for hemodynamic support or blood pressure augmentation:

1. Necessity for augmentation of cerebral or spinal perfusion pressure as determined by the neurointensivist.
2. As a temporizing measure in the setting of an emergent drop in blood pressure in patients who cannot receive a CVC.
3. As a temporizing measure in the setting of an emergent drop in blood pressure while central venous access is obtained.
4. During a procedure risking clinically significant acute hypotension due to a temporary insult.

Administration of peripheral phenylephrine was only implemented in the neurocritical care unit with a 2:1 patient-to-nurse ratio in a concentration of 40 μg/mL and at an infusion rate not to exceed 2 μg/(kg min). Infusions were administered via an 18-gauge or larger peripheral intravenous (IV) which was in the upper extremity, proximal to the wrist. The ICU nurses administering peripheral phenylephrine had to review our institution's extravasation guideline at the start of each shift.

The primary objective of this medical record review was to assess infusion characteristics and adherence to guidelines, determine safety and feasibility, and identify complications. Complications of peripheral infusion of a vasopressor or toxic agent were reviewed in the published literature and classified as major or minor. *Major complications* were defined as IV line infiltration, drug extravasation, thrombophlebitis, skin necrosis, and gangrene. *Minor complications* were defined as IV line site pain, swelling, erythema, and/or a need to replace the IV.

A Powervision report was performed to identify dispenses of phenylephrine based on PharmNet data from August 16, 2013, to February 16, 2014. For each dispense, medical record review was performed in PowerChart to identify demographic data such as age, sex, weight, length of stay, ethnicity, primary admit diagnosis, and clinical indication for use. PowerChart was also reviewed to assess for the presence of an appropriate peripheral IV line (18 gauge or larger), total time of infusion, average dose, peak dose, and complications associated with infusion or during the subsequent 4 hours. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Utah. REDCap (Research Electronic Data Capture) is a secure, Web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources [31].

3. Results

Twenty patients were identified during the study period as having received peripheral phenylephrine during their admission to the neurocritical care unit from August 2013 through February 2014 (Table 1). The average age of patients receiving peripheral phenylephrine was 62 years (range, 14-90) with a mean duration of hospitalization of 11 days (range, 1-29). The mean duration of peripheral infusion was 14.29 hours (range, 1-54.3) with a mean dose of 0.53 μg/(kg min) (Table 2). No patients received phenylephrine infusions exceeding the dose limit of 2 μg/(kg min). Ninety-five percent of patients had appropriate IV access during the time of infusion, and there was 1 deviation from protocol where a patient had two 20-gauge IV line sites documented during the infusion. There were no reported complications related to this. There were no documented major complications related to peripheral phenylephrine infusion in the entire sample and only 1 minor complication reported as pain, erythema, and swelling around an 18-gauge antecubital infusion site. The IV line was removed and replaced at a new site, and the patient continued to receive therapy with peripheral phenylephrine without any further events.

4. Discussion

All patients admitted to an ICU require some form of intravenous cannulation [32]. Initiation of vasopressor support has traditionally necessitated insertion of a CVC to mitigate the risks of extravasation injury secondary to peripheral administration of vasoactive agents (epinephrine, norepinephrine, dopamine, and vasopressin) [4–9]. In the United States alone, greater than 5 million CVCs are inserted per year, with reported complication rates exceeding 15% [10,13]. This represents a significant clinical hindrance in the management of critically ill patients where the use of vasopressors is limited by the necessity of a CVC and its inherent risks and complications.

Arterial blood pressure is a dynamic parameter that can fluctuate significantly with serious adverse consequences. Hypotension is known to be exceptionally deleterious in the neurologically injured patient. In the severe traumatic brain injury population, both prehospital hypotension and in-hospital hypotension (systolic blood pressure <90 mm Hg) have proven themselves to be strong independent predictors of morbidity and mortality, with a single episode conferring a 150% increase in mortality in 1 study [33]. The avoidance of hypotension (systolic blood pressure <90 mm Hg) is clearly recommended in the 2007 iteration of the Brain Trauma Foundation guidelines on the management of severe traumatic brain injury, and vasopressors are frequently

Table 1
Characteristics of patients receiving peripheral phenylephrine

Demographics	All (N = 20)	Complication(s) (n = 1)
Age (y)	62 (14-90)	49
Sex ratio (male-female)	1.22	1 Female
Ethnicity		
Asian	2	–
White	14	1
Hispanic	1	–
Unknown/not reported	3	–
Length of stay in days (range)	11 (1–29)	5
Primary admit diagnosis		
Brain tumor/elective postop	1	–
Elective neurointerventional	2	–
Neuroinfection/neuroinflammatory	2	–
Encephalitis	1	–
Ischemic stroke	5	1
Subarachnoid hemorrhage	5	–
Spinal cord injury	2	–
Traumatic brain injury	2	0