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Safety of the Peripheral Administration of Vasopressor Agents

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Abstract

Vasopressors are an integral component of the management of septic shock and are traditionally given via a central venous catheter (CVC) due to the risk of tissue injury and necrosis if extravasated. However, the need for a CVC for the management of septic shock has been questioned, and the risk of extravasation and incidence of severe injury when vasopressors are given via a peripheral venous line (PVL) remains poorly defined. We performed a retrospective chart review of 202 patients who received vasopressors through a PVL. The objective was to describe the vasopressors administered peripherally, PVL size and location, the incidence of extravasation events, and the management of extravasation events. The primary vasopressors used were norepinephrine and phenylephrine. The most common PVL sites used were the forearm and antecubital fossa. The incidence of extravasation was 4%. All of the events were managed conservatively; none required an antidote or surgical management. Vasopressors were restarted at another peripheral site in 88% of the events. The incidence of extravasation was similar to prior studies. The use of a PVL for administration of vasopressors can be considered in patients with a contraindication to a CVC.

Keywords

vasopressors, septic shock, peripheral venous line, central venous catheter, extravasation, safety

Introduction

Septic shock is a leading cause of mortality in critically ill patients.[1-3] The management of septic shock often requires the administration of vasopressor agents to stabilize the patient and reverse end-organ hypoperfusion.[4] Vasopressor administration has traditionally been an indication for insertion of a central venous catheter (CVC) due to the risk of serious tissue injury if extravasation occurs through a peripheral venous line (PVL). The CVCs are associated with significant morbidity leading to a complication in approximately 15% of patients.[5-7] Following a single-center trial of Early Goal-Directed Therapy,[8] CVC insertion was thought to be an integral component of the management of septic shock; however, 3 recent randomized clinical trials have deemphasized the need for a CVC, although none of these trials reported on the incidence of peripheral vasopressor administration.[9-11]

While the risk of serious tissue injury is high if a vasopressor agent is extravasated through a PVL, few studies have sought to characterize the true incidence and severity of extravasation events. A recent systematic review captured 85 articles reporting patient-level data or aggregate patient data that described local tissue injury or extravasation when a vasopressor was administered via a PVL or a CVC.[12] The majority of the publications constituted case reports or series and were published prior to 1969. Risk factors for extravasation included longer duration of peripheral infusion ($\geq$24 hours) and more distal locations of PVL. Overall, the authors found that current reports of extravasation suffer from publication bias and may not accurately reflect current practice. Two other single-center retrospective reviews discuss their experience with peripheral administration of vasoactive medications based on an institutional protocol and reported an extravasation rate of 2% to 5%.[13,14] Although these studies provide evidence for the safety of vasopressors administered via a PVL, these results must be interpreted in the setting of the institutional protocol that was employed and the heightened awareness of the potential for extravasation events. As it is not unusual for vasopressors to

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be administered through a PVL in patients with a contraindication to a CVC at our institution, we sought to describe the use of nonprotocolized vasopressor administration through a PVL and the incidence of adverse events associated with this practice.

Material and Methods

Study Design

A single-center, retrospective chart review was conducted at New York University Langone Medical Center, a 726-bed tertiary care academic teaching hospital. Institutional review board approval was granted by our institution, and a waiver of informed consent was obtained. Electronic charts of patients admitted to the intensive care unit (ICU) between January 2015 and April 2016 who received a vasopressor agent via a PVL at our institution were reviewed.

Patients were entered into the study if the following criteria were met: ≥18 years of age and received a vasopressor agent through a PVL in the ICU. Those who had a CVC in place at the time of initiation of vasopressors or received vasopressors via a PVL for <1 hour were excluded. During this time period, our institution did not have a protocol in place to help guide clinicians with the administration of vasopressor agents through a PVL. The decision to initiate treatment with vasopressors was made by the ICU intensivists.

Data collection included patient demographics, admitting service, characteristics of the PVL, and the presence of risk factors for extravasation at the time of admission.[15] The primary etiology of shock was determined based on medical notes, and an Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated at the time of vasopressor initiation. Vasopressor infusion data included concentration, duration, dose (initial, median, and maximum rate of infusion), and time to CVC, if applicable. If the patient obtained a CVC during the infusion of a vasopressor agent (ie, the vasopressor agent administration was transitioned to a CVC), data collection for that particular patient was terminated. The data collected for extravasation events included time to extravasation, location and gauge of the PVL, any corrective measure and a grade for severity of the event were extracted from the nursing flow sheet.

Study Outcomes

The primary outcome of this study was the incidence of extravasation events related to the peripheral administration of a vasopressor. For the purpose of this article, *extravasation* is defined as "the extravenous administration of a medication or solution that has the potential for severe tissue or cellular damage into the surrounding tissue."[16] The Infiltration Scale is used to grade extravasation events hospital wide according to nursing standards based on the most severe presenting indicator (Table 1).[16] Extravasation events were defined as *confirmed* or *possible* due to the inability to attribute an extravasation event to a vasopressor agent based on the nursing flow sheet documentation alone. A *confirmed* extravasation event was identified by specific documentation in the medical notes detailing the event, whereas *possible* extravasation events were events that were documented in the nursing flow sheet during the time a vasopressor was administered via a PVL but without additional documentation in the medical notes. Secondary outcomes included describing the dose, concentration, and duration of peripheral vasopressor use; the location and gauge of PVLs used for vasopressor administration; and the frequency and time until CVC insertion.

Table 1. Society of Infusion Nurses Infiltration Scale.

Grade	Clinical Criteria
0	No symptoms
1	Skin blanched Edema <1 inch in any direction Cool to touch With or without pain
2	Skin blanched Edema 1-6 inches in any direction Cool to touch With or without pain
3	Skin blanched, translucent Gross edema >6 inches in any direction Cool to touch Mild–moderate pain Possible numbness
4	Skin blanched, translucent Skin tight, leaking Skin discolored, bruised, swollen gross edema >6 inches in any direction Deep pitting tissue edema Circulatory impairment Moderate–severe pain Infiltration of any amount of blood product, irritant, or vesicant

[a]Adapted from Society of Infusion Nursing.[16]

Risk factors for extravasation were defined utilizing patient- and procedural-related factors. Factors related to patients include gender, obesity, hypertension, coronary artery disease, cerebrovascular accident, lymphedema, peripheral neuropathy, connective tissue disease, and peripheral vascular disease. Procedural-related factors include anatomical location and gauge of peripheral venous catheter. The dose of vasopressor at the time of extravasation was converted to norepinephrine equivalents using the following formula: norepinephrine equivalents = (norepinephrine [μg/min]) + (dopamine [μg/kg/min]/2) + (epinephrine [μg/min]) + (phenylephrine [μg/min]/10) + (vasopressin [units/h] × 8.33).[17]

Statistical Analysis

The SPSS statistical software package (Chicago, IL, software for Windows; version 23.0) was used for data processing. For our descriptive analysis, variables were expressed as median values and interquartile ranges (25% and 75%).

Table 2. Baseline Characteristics.[a]

Characteristic	All Patients (N = 202)
Female gender	95 (47)
Age, median (IQR)	75 (64-83)
BMI, median (IQR)	25 (21-29)
Service	
Medical ICU	90 (45)
Medical stepdown unit	84 (42)
Comorbidities	
Hypertension	123 (61)
Coronary artery disease	55 (27)
Stroke/cerebrovascular accident	38 (19)
Peripheral vascular disease	17 (8)
Diabetes mellitus	63 (31)
Connective tissue disease	9 (4)
Lymphedema	3 (1)
Peripheral neuropathy	7 (3)
APACHE II, median (IQR)	21 (17-25)
Indication for vasopressors	
Septic shock	147 (73)
Cardiogenic shock	28 (14)
Stroke/neurological disorder	15 (7)
Other	12 (6)

Abbreviations: APCHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit.
[a] All values reported as number (%), unless otherwise specified

Results

In total, we reviewed 485 patients who received a vasopressor from January 1, 2015, to April 30, 2016. The primary reason for exclusion was that the patient had a CVC in place at the time of initiation of vasopressors, which was present in 283 patients. A total of 202 patients were evaluated for the incidence of extravasation events related to the peripheral administration of a vasopressor.

Baseline characteristics are presented in Table 2. These 202 patients had a median age of 75 years with a body mass index of 25 kg/m^2 and an APACHE II score of 21. The majority of patients (87%) were admitted to either the medical ICU or the medical stepdown unit. The most common indication for a vasopressor agent was septic shock (73%) followed by cardiogenic shock (14%). Documented risk factors for extravasation mainly included a history of hypertension (61%) and female gender (47%). Two or more risk factors for extravasation were encountered in 48% of the total population.

A total of 340 peripheral venous catheters were available for the assessment of peripheral vasopressor infusion (Table 3). The location of the peripheral venous catheter was primarily placed in the forearm (74%) followed by antecubital (54%) and metacarpal (40%) veins. Eighty-four percent of all lines were 20 gauge or smaller. Of the 202 patients receiving peripheral vasopressor infusions, a total of 46% of patients were transitioned to a CVC. The major indication for a CVC was continuation of vasopressor therapy. The median time until CVC insertion was 6 hours.

Table 3. Characteristics of PVLs Used.[a]

Characteristic	All Patients (N = 202)
Location	
Forearm	145 (72)
Antecubital fossa	109 (54)
Hand	81 (40)
Other	5 (2)
Gauge	
20	149 (74)
22	103 (51)
18	46 (23)
Other	6 (3)
CVC inserted	93 (46)
Time till insertion, hour, median (IQR)	6 (3-23)

Abbreviations: CVC, central venous catheter; PVL, peripheral venous line.
[a]All values reported as number (%), unless otherwise specified.

Vasopressor Agents

The characteristics of peripheral vasopressor infusions are displayed in Table 4. The total median duration of peripheral vasopressor administration was 11.5 hours. In patients who were not transitioned to a CVC, the median duration of peripheral vasopressor administration was 19 hours. Norepinephrine was the most common vasopressor administered via a PVL (72%), with a median duration of 7.5 hours. From the 3 concentrations of norepinephrine solution available at our institution, 16 μg/mL was the most commonly infused (54%); however, 16% of the patients received a 64 μg/mL concentration. The median dose of norepinephrine was 0.08 μg/kg/min, with a median initial and maximum dose of 0.04 μg/kg/min and 0.13 μg/kg/min, respectively. Phenylephrine was the second most common vasopressor administered peripherally (36%); the median duration infused was twice as long as norepinephrine (15 hours). The only concentration of phenylephrine available at our institution is 400 μg/mL, but 2 patients had phenylephrine solutions compounded at a concentration of 20 μg/mL. The initial dose of phenylephrine was 50 μg/min, with a median initial and maximum dose of 25 μg/min and 95 μg/min, respectively. Only 4% of patients received peripherally administered epinephrine, vasopressin, or dopamine.

Twenty-four (12%) patients received 2 or more vasopressors via a PVL during their admission. Of these 24 patients, 5 patients received 2 or more vasopressor agents simultaneously. The 2 most common agents infused concomitantly were norepinephrine and phenylephrine. The median duration of concomitant peripheral infusion was 13.5 hours.

Extravasation Events

The primary outcome of extravasation occurred in 8 (4%) patients during the time that a vasopressor was administered via a PVL: 3 of these were confirmed to be due to a vasopressor by detailed notes in the patient's chart and 5 were only possible based on the time of extravasation overlapping with the period

Table 4. Vasopressor Agents Used.[a]

	Norepinephrine	Phenylephrine[b]	Vasopressin[c]	Epinephrine	Dopamine
Number (%)	146 (72)	73 (36)	4 (2)	2 (1)	2 (1)
Duration, hour, median (IQR)	7.5 (3-23)	15 (6-38)	12.5 (4-23)	4.5	23.5
Conc., μg/mL	16: 79 (54) 32: 43 (30) 64: 24 (16)	20: 2 (3) 400: 71 (97)	0.16 units/mL: 4 (100)	16: 2 (100)	800: 2 (100)
Initial dose, median (IQR)[d]	0.04 (0.01-0.1)	25 (11-69)	0.04	0.03	7.5
Max dose, median (IQR)[d]	0.13 (0.08-0.3)	95 (50-150)	0.04 (0.04-0.06)	0.06	9
Total median dose (IQR)[d]	0.08 (0.05-0.17)	50 (25-100)	0.04	0.05	8

Abbreviation: IQR, interquartile range.
[a]All values reported as number (%), unless otherwise specified.
[b]Doses reported in μg/min.
[c]Doses reported in units/min.
[d]All doses reported in μg/kg/min, unless otherwise specified.

Table 5. Extravasation Events.[a]

Characteristic	All Patients (N = 202)
Extravasations	8 (4)
Vasopressor	
Norepinephrine	4 (50)
Phenylephrine	4 (50)
Time till extravasation, hour, median (IQR)	21 (12-30)
Median dose at time of extravasation[b]	0.11
Location	
Hand	2 (25)
Antecubital fossa	2 (25)
Other	4 (50)
Gauge	
<20	2 (25)
≥20	6 (75)
Injury grade	
1	2 (25)
2	6 (75)
Injury	
Blanching	8 (100)
Edema	3 (38)
Ulceration/necrosis	0
Management	
Conservative	8 (100)
Restarted vasopressors peripherally	7 (88)

Abbreviation: IQR, interquartile range.
[a]All values reported as number (%), unless otherwise specified.
[b]Dose reported in norepinephrine equivalents in μg/kg/min.

of peripheral vasopressor administration (Table 5). Three of these patients had 2 or more risk factors for extravasation. The indication for vasopressors was septic shock in 6 of the cases and stroke or neurological disease in the other 2. The median time until extravasation event was 21 hours. Four patients received norepinephrine and 4 patients received phenylephrine at the time of extravasation. Although 2 of these patients received two concomitant vasopressors peripherally, all the events occurred when only 1 agent was infusing via a PVL. The median dose of vasopressor in norepinephrine equivalents at the time of extravasation was 0.11 μg/kg/min (8 μg/min). The concentration of the vasopressor solutions was highly variable; there was also variable sites of PVL placement. All lines except for 1 were inserted in sites at or distal to the antecubital fossa. In one instance, an extravasation was documented in an external jugular line. The PVL gauge ranged from 18 to 22. Six of the events were grade 1 and 2 events were grade 2. All 8 events were assessed as exhibiting blanching, whereas 3 events were also documented as having edema around the catheter site. Only conservative management was required in all cases. This entailed removal of the PVL and insertion of a new catheter at an alternative site. There was no documentation of administration of an antidote or more invasive management. Seven of the 8 patients had the vasopressor restarted after the event. One patient had a CVC inserted, 1 patient had an upper arm line inserted, and the remainder of patients had vasopressors restarted at or distal to the antecubital fossa without further events.

Discussion

Vasopressors are an integral component of the management of septic shock.[4] The early initiation of vasopressors helps to restore end-organ perfusion and reverse the systemic shock state. A retrospective analysis of patients with septic shock enrolled in a large, international database found that every hour delay in vasopressor initiation was associated with a 7% increase in mortality (odds ratio 1.07 per hour, confidence interval 1.06-1.08).[18] A separate retrospective study confirmed the association of early administration of norepinephrine with survival in septic shock.[19] In our study, peripheral administration facilitated earlier initiation of vasopressors, especially in patients who were awaiting CVC insertion. Approximately 50% of the patients we reviewed ultimately had a CVC inserted for vasopressor therapy, and these patients received a median of 7 hours of vasopressors administered via a PVL prior to CVC insertion. In addition to expediting appropriate management, the administration of peripheral vasopressors may obviate the need for CVCs, which are known to have complications of their own.[6,7] In many patients, a CVC may not be aligned with their goals of care as was the case with some of the patients in our review, but they still may benefit from the

Table 6. Risk Factors for Extravasation.

Category	Risk Factors
Patient-related	Hypertension
	Atherosclerosis
	Peripheral vascular disease
	Diabetes mellitus
	Raynaud disease
	Connective tissue disease
	Lymphedema
	Thrombophlebitis
	Extremes in age
	Altered mental status, delirium, dementia
	Peripheral neuropathy
Infusion related	Duration of infusion
	Concentration of infusate
	Infusion rate
	PVL location and size
Institution related	Skill inserting PVL
	Skill in assessing PVL access sites
	Frequency of monitoring of high-risk medications
	Standardized grading of extravasations
	Protocol for management of extravasation

Abbreviation: PVL, peripheral venous line.
[a]Adapted from Reynolds et al.[15]

administration of vasopressors peripherally if the complication rate is low.[20]

Data comparing outcomes based on the type of venous access in critically ill patients is limited. A prospective, unblinded, observational study compared the initial use of PVL and CVC in critically ill patients who required infusion of certain medications known to be "venotoxic," including norepinephrine and epinephrine at doses up to 33 μg/min. The authors found that the incidence of complications associated with PVLs was significantly higher than for CVCs (133 events vs 87 events, $P = .02$); however, the 2 complications that constituted the majority of this composite outcome were difficulty with insertion (56 events vs 16 events) and erythema at insertion site (20 events vs 8 events). Similar to our study, 50% of their patients initially managed with PVLs eventually had a CVC inserted to continue vasoactive therapy.[21] An earlier study comparing complications of PVLs and CVCs when used in critically ill patients also found a higher incidence of phlebitis among patients with PVLs; however, the major complication rate was greater among those with a CVC.[22] Combined with the results of these 2 studies, our results confirm that, while complications are common with PVLs, they are usually mild and the catheter can be easily removed and a new catheter inserted at a separate site.

The results of our study parallel the low complication rate of the peripheral administration of vasopressors reported by other authors.[13,14] The individual risk for an extravasation event is the sum of many complex, unrelated factors. Well-known risk factors for extravasation are those related to the patient and the administration of the medication. Patient-specific risk factors include those that impair blood flow or weaken blood vessels and those that decrease the patient's ability to sense or report an extravasation event (Table 6). Vasopressor-related risk factors include the concentration of drug, infusion rate, and duration of infusion.[15] Less appreciated are institution-related risk factors, as outlined in Table 6. To minimize the risk of extravasation, it is important to have skilled nurses and physicians inserting PVLs; hospital-wide education regarding assessing PVL access sites for extravasation; procedures for the frequency of monitoring and standardized grading of extravasation events; and a protocol for the management of extravasation injuries. In this regard, the patients in our study were at high risk of extravasation injuries compared to other published reports: Nearly half of our patients had 2 or more comorbidities that increased their risk of extravasation; there was highly variable use of vasopressor concentrations and dosing; PVLs were frequently placed in high-risk locations; monitoring of PVLs occurred every 4 hours; and there was no protocol in place for the management of extravasation events. This is in stark contrast to the 2 prior reports of peripheral vasopressor administration. Cardenas-Garcia et al had an extensive protocol for the safe peripheral administration of vasopressors that included ultrasound-guided insertion of PVLs in a vein >4 mm, assessment of PVL access site every 2 hours, maximum of 72 hours duration of infusion per PVL site, and a protocol for the rapid administration of antidotes in the event of an extravasation.[13] Similarly, Delgado et al described their protocol which mandated 18-gauge PVLs proximal to the wrist, maximum vasopressor concentration and infusion rate, and nursing education of the institution's extravasation protocol. Despite the large discrepancy in risk between our population and theirs, we found an incidence of extravasation events that was comparable. Cardenas-Garcia et al reported an extravasation event rate of 2%, all of which were managed with local phentolamine injection, and led to no major complications.[13] Similarly, Delgado et al reported a minor complication in 1 (5%) patient who did not require further intervention.[14] This suggests that the baseline risk for extravasation injury is low and can be further reduced by implementation of a strict protocol for the use of peripheral vasopressors.

The 8 extravasation events documented during peripheral vasopressor administration in our report were highly variable in regard to PVL size and location, vasopressor and dose, and nursing documentation. Seven of the 8 events occurred at a location or through a PVL gauge that would not be presently allowed based on our recently implemented protocol (see Appendix A). The median duration of infusion prior to extravasation was 21 hours (range 8-43 hours), which is much shorter than that reported in the systematic review by Loubani and Green (55.9 hours, range 0.08-528 hours); however, the wide range limits the validity of this value.[12] Neither of the 2 observational studies of peripheral vasopressor use reported a median duration until extravasation.[13,14] Limited data regarding the association between duration of infusion and extravasation events make it difficult to give a firm recommendation on the maximal duration vasopressors can be safely infused peripherally. Future studies should aim to better describe this important component to patient safety. Three of our patients

had detailed nursing notes describing the extravasation event. The most serious reports described cool, dusky extremities with poor capillary refill. The application of warm compresses reversed this effect immediately. None of these cases required a surgical consult, and in all but one the physician felt comfortable restarting vasopressors through an alternate PVL.

Limitations

There are several limitations to our study, primarily related to the retrospective study design, which warrant discussion. The ability to definitively identify vasopressor-related extravasation events was subject to reporting and documentation bias from the nursing flow sheet and electronic medical record, as all patients had more than 1 PVL. Similarly, we were limited in the details provided for each extravasation event. Our institution does use the extravasation grading scale provided by the Infusion Nurses Society,[16] but specific details of the local tissue injury were only reported in 3 cases. Additionally, the sample size may be a limitation. We collected over 200 patients and did not see any major extravasation events requiring surgical intervention. However, without knowledge of the baseline incidence of severe extravasation events from peripheral vasopressors, our sample size may not be large enough to capture a severe extravasation event. Currently, there is no established threshold for tolerance of an extravasation event requiring surgical intervention on an institutional level. Although the complication rate we saw was low, without a control group, we cannot definitively say that administering vasopressors through a PVL is safer than a CVC. Finally, the majority of our patients were elderly with multiple comorbidities, and an event rate of 4% with no events graded as more severe than grade 2 may not be unexpected with routine PVL insertion and infusion of non-vasopressor medications.

Conclusion

We found an overall incidence of extravasation events of 4% in patients receiving vasopressors through a PVL that were not managed under a strict safety protocol. None of these events were severe enough to require the use of an antidote or surgical intervention, and in 7 of the 8 cases vasopressors were resumed at a separate peripheral site. There are many reasons to decide against the use of a CVC which includes patient preference, fear of complications, or anticipated short duration of use. Moreover, the administration requirement of vasopressor therapy once thought to be an absolute indication for a CVC may be more of a relative indication. However, the results of our review and others should be interpreted cautiously. While the extravasation event rate associated with peripheral administration of vasopressors appears to be low based on current data, the incidence of severe events requiring surgical debridement or amputation remains undefined. Future research should seek to define this incidence, as it will help to inform institutions, providers, and patients about the risk of the peripheral administration of vasopressors. A protocol should be in place if vasopressors are to be used peripherally to standardize PVL location and size; vasopressor concentrations and dosing; and monitoring, documentation, and management of extravasation events.

Appendix A

Our Institution's Adult Guidelines for Peripheral Administration of Vasopressor Therapy and the Management of Extravasation Events

Goal. Provide guidelines for providing care to adult patients who are receiving intravenous vasopressors through a peripheral venous line (PVL)

Emphasize, accurate assessment and interventions based on the available evidence to manage a vasopressor induced extravasation event

Introduction

- The decision to use a PVL for vasopressors infusion must be assessed and approved by an attending physician trained in emergency medicine or critical care (or surrogate LMP in an emergent situation)
- Vasopressor infusion through a PVL may be utilized in the following areas
  - Any location in the hospital is acceptable in an emergency setting
  - Upon stabilization, they must be monitored in the ICUs, Step down unit, or PACU
  - Other allowable areas include the Emergency department or "vent-pressor" floor bed
- Peripheral venous access may be used for only one vasopressor
- Two working PVLs must be present
  - If access is lost and new access will be delayed, placement of an intra-osseous (IO) line emergently by the LIP is suggested
- The maximum duration recommended for peripheral vasopressor use is 24 hours
  - Durations greater than 24 hours, must have attending approval and reasoning must be documented in the patient's medical chart

Physician Responsibility

- Make the bedside nurse and medical team aware of the following:
  - Provide the hospital protocol for peripheral vasopressor administration and extravasation management
  - Review the steps needed in case of an extravasation event
- Choose the vasopressor and dosage of the infusion and ensure the appropriate order is entered in EPIC (see below)
  - In the medication order, "peripheral administration" must be placed in the order comments section.

Table A1. Vasopressors for Peripheral Administration

Vasopressor	Concentration	Indication	Starting Dose	Max Peripheral Dose[a]
Norepinephrine	4 mg/250 mL (16 μg/mL) NS	Septic shock	0.05-0.1 μg/kg/min	25 μg/min
Epinephrine	4 mg/250 mL (16 μg/mL) NS	Anaphylaxis	0.05-0.1 μg/kg/min	25 μg/min
Dopamine	200 mg/250 mL (800 μg/mL) D5W	Symptomatic bradycardia	2 μg/kg/min	10 μg/kg/min
Phenylephrine	100 mg/250 mL (400 μg/mL) NS	Second-line agent for septic shock	50 μg/min	250 μg/min

[a]Consider placing a central line if vasopressor dose exceeds 25 μg/min of norepinephrine equivalents.

Pharmacist Responsibility

- Verify the following parameters upon dispensing a vasopressor for peripheral administration (Table A1)
  - The lowest concentration of the vasopressor is being used
  - That the initial max dose for peripheral administration is not exceeded
  - The duration of the vasopressor does not exceed 24 hours
    - If the duration is greater than 24 hours, verify the reason for continuance
- Maintain the extravasation kit and ensure that it will be readily accessible for use

Registered Nurse Responsibility

- Establish a peripheral access site for vasopressor administration
- The preferred PVL for vasopressor infusion must be placed in the forearm, or upper arm
  - The antecubital fossa and veins next to joints, tendons, nerves, or arteries should be avoided as well as any IV sites requiring more than 1 venipuncture
- Clearly label the dedicated PVL at the site of the connection, indicating peripheral vasopressor
- The IV catheter must be 20 gauge or larger and must always be visible
  - There must be blood return from the IV catheter prior to vasopressor administration in order to confirm placement
  - Administer 5 to 10 mL 0.9% normal saline and withdraw a small amount of blood to test venous integrity and flow.
  - This will be performed twice during the nursing shift
- Continue to monitor/assess the IV site every 1 hour for signs and symptoms of extravasation (Table A2) along with grade of injury according to Table A3 and document these findings in the nursing flow sheet:

Management of Extravasation

- On suspecting extravasation, the infusion must be stopped immediately
- The ED attending or intensivist (or surrogate) must be contacted immediately in order to assess the site and initiate treatment
- Leave the catheter in place
  - Slowly aspirate as much drug as possible.
  - Do not apply pressure to the area
- The physician will initiate and administer *both reversal agents* in the following order:

  A) Terbutaline:
    - 1 mg diluted in 10 mL of 0.9% NaCl
    - Inject 5 mL through the indwelling catheter at the IV site
    - Inject the remaining, 5 mL subcutaneously with a 27 gauge needle into the affected area around the leading edge of the extravasation site
      - Blanching should reverse immediately
      - Additional doses may be required if blanching returns

  B) **PLUS** Topical Nitroglycerin 2%:
    - Apply 1 inch strip to the site of ischemia
    - May re-dose every 8 hours as needed
- Remove the catheter
- Establish a new peripheral access site for vasopressor administration and consider a central line
- Elevate the affected limb to minimize swelling
- Apply warm compresses for 20 minutes every 6 to 8 hours for the first 24 to 48 hours after extravasation occurs
- Advise patient to resume activity with affected limb as tolerated
- Depending on the extent of injury, debridement and excision of necrotic tissue should be considered if pain continues and surgery should be consulted

Table A2. Parameters to Monitor for Peripheral Vasopressor Use (Based on Charts Below):

Signs	Symptoms
Swelling	Tightness
Redness or blanching	Burning
Blister formation	Pain or aching tingling sensation
Unexplained reduced IV flow rate	Itchiness
Necrosis (2-4 days later)	
Lack of blood return	
Ulceration	

Table A3. Grading of Extravasation Injury Severity

Grade	Clinical Severity
0	• No symptoms
1	• Blanched skin or cool to touch • Edema <1 inch in any direction • With or without pain
2	• Blanched skin or cool to touch • Edema 1-6 inches in any direction • With or without pain
3	• Blanched skin, translucent skin • Gross edema >6 inches in any direction • Mild to moderate pain • Possible numbness
4	• Blanched skin, tight leaking skin • Gross edema >6 inches in any direction • Deep pitting edema • Moderate to severe pain

Note: This protocol was developed when phentolamine was not available. Phentolamine is the preferred antidote for vasopressor extravasation when available.

Author's Contributions

TL made substantial contributions to conception and design. He has performed data collection and participated in data analysis and interpretation. He was the main author involved in drafting and finalizing the manuscript. CM made substantial contributions to conception and design. He was involved in data analysis and interpretation. He was involved in drafting the manuscript and revising it critically for important intellectual content. He has given final approval of the version to be published. DA made substantial contributions to conception and design. She was involved in data analysis and interpretation. She was involved in drafting the manuscript and revising it critically for important intellectual content. She has given final approval of the version to be published. JP was involved in data analysis and interpretation. He was involved in drafting the manuscript and revising it critically for important intellectual content. He has given final approval of the version to be published.

Declaration of Conflicting Interests

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