[Critical Care Original Research]

CHEST

Peripheral Administration of Norepinephrine

A Prospective Observational Study

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BACKGROUND: Historically, norepinephrine has been administered through a central venous catheter (CVC) because of concerns about the risk of ischemic tissue injury if extravasation from a peripheral IV catheter (PIVC) occurs. Recently, several reports have suggested that peripheral administration of norepinephrine may be safe.

RESEARCH QUESTION: Can a protocol for peripheral norepinephrine administration safely reduce the number of days a CVC is in use and frequency of CVC placement?

STUDY DESIGN AND METHODS: This was a prospective observational cohort study conducted in the medical ICU at a quaternary care academic medical center. A protocol for peripheral norepinephrine administration was developed and implemented in the medical ICU at the study site. The protocol was recommended for use in patients who met prespecified criteria, but was used at the treating clinician's discretion. All adult patients admitted to the medical ICU receiving norepinephrine through a PIVC from February 2019 through June 2021 were included.

RESULTS: The primary outcome was the number of days of CVC use that were avoided per patient, and the secondary safety outcomes included the incidence of extravasation events. Six hundred thirty-five patients received peripherally administered norepinephrine. The median number of CVC days avoided per patient was 1 (interquartile range, 0-2 days per patient). Of the 603 patients who received norepinephrine peripherally as the first norepinephrine exposure, 311 patients (51.6%) never required CVC insertion. Extravasation of norepinephrine occurred in 35 patients (75.8 events/1,000 d of PIVC infusion [95% CI, 52.8-105.4 events/1,000 d of PIVC infusion]). Most extravasations caused no or minimal tissue injury. No patient required surgical intervention.

INTERPRETATION: This study suggests that implementing a protocol for peripheral administration of norepinephrine safely can avoid 1 CVC day in the average patient, with 51.6% of patients not requiring CVC insertion. No patient experienced significant ischemic tissue injury with the protocol used. These data support performance of a randomized, prospective, multicenter study to characterize the net benefits of peripheral norepinephrine administration compared with norepinephrine administration through a CVC.

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KEY WORDS: catheter; hypotension; infusions; norepinephrine; parenteral; shock; vasoconstrictor agents

ABBREVIATIONS: CVC = central venous catheter; IQR = interquartile range; PIVC = peripheral IV catheter

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Take-home Points

Study Question: In patients treated in the medical ICU, can a protocol for peripheral IV catheter (PIVC) norepinephrine administration safely reduce the number of days of central venous catheter (CVC) use and frequency of CVC placement?

Results: In this prospective observational cohort study, we observed a median number of days of CVC use avoided per patient of 1 day (interquartile range, 0-2 d/patient), with avoidance of CVC placement for administration of norepinephrine in 51.6% of patients. Although 5.5% of patients did experience a norepinephrine extravasation event (incidence, 75.8 events/1,000 d of PIVC administration [95% CI, 52.8-105.4 events/1,000 d]), the resulting tissue injury was minimal.

Interpretation: Our findings suggest that peripheral administration of norepinephrine can be operationalized safely for patients and can prevent approximately half of the central line insertions for norepinephrine administration.

Administration of vasoactive medications often is necessary to support BP and optimize tissue perfusion in patients with circulatory shock. Historically, the administration of many vasoactive medications has occurred via a central venous catheter (CVC) because concern exists regarding local tissue injury resulting from vasoconstriction if extravasation of these medications occurred from a peripheral IV catheter (PIVC). However, placement of CVCs can lead to vasopressor administration delays (prolonging time to restoration of effective tissue perfusion), procedural complications, and central line-associated bloodstream infections.[1] In light of this potential for CVC-associated complications, several institutions have adopted protocols for PIVC administration of vasoactive medications, with few significant adverse safety events reported.[2-6] Furthermore, the 2021 Surviving Sepsis Campaign Guidelines suggest starting vasopressors peripherally, rather than delaying initiation until central venous access is obtained.[7] However, this was a weak recommendation with very low-quality evidence because of few articles evaluating the practice having been published. In 2019, the medical ICU at our clinical site initiated a protocol for the peripheral administration of norepinephrine. This report details the implementation and outcomes of this protocol. We hypothesized that norepinephrine administration via PIVC would be associated with safe CVC avoidance.

Study Design and Methods

A written protocol for the administration of peripheral norepinephrine was developed by medical ICU physician, pharmacy, and nursing leadership and was approved by the local medical ICU quality committee. Briefly, this protocol included criteria for PIVC size, placement location, and ultrasound confirmation; assessment of PIVC to ensure continued blood return; and maximum PIVC norepinephrine dose and duration of infusion. Initially, we required that patients were able to report pain or discomfort at the site of infusion in an attempt to identify extravasations rapidly if they occurred. We also limited peripheral norepinephrine duration to 48 h in an attempt to limit the total number of extravasation events. However, after an initial rollout period in which we observed few extravasations and no substantial tissue injury, both requirements were removed. At the time of the removal of these requirements, a requirement to assess for extravasation every 2 h by pausing the norepinephrine infusion and performing a blood aspiration from the PIVC before resuming the norepinephrine infusion was added in an attempt to decrease time to extravasation discovery and to decrease the volume of drug extravasated. Ultrasound placement and confirmation of PIVC were performed by trained bedside nurses and consisted of visualization of the PIVC within the vessel along with the visualization of increased echo contrast within the vein after flushing of the PIVC with normal saline. Nurses also performed routine patency assessments of the PIVC that were used for norepinephrine administration by assessing for blood return every 2 h. Protocol elements were chosen based on practice standards of the Infusion Nurses Society.[8] If the maximum allowable dose (15 μg/min) or duration (48 h initially; no time limitation after protocol amendments) of peripheral norepinephrine administration was reached, it was mandatory for providers to place a CVC for continued norepinephrine administration. Patients also could undergo CVC placement if it was needed to administer other medications, if an extravasation event occurred (although this was not mandatory), or at the discretion of the treating clinician. If an extravasation event occurred and peripheral norepinephrine infusion was continued, the nurse was instructed to switch the infusion to the second eligible PIVC and to obtain an additional eligible PIVC if needed. Complete protocol details and changes to the protocol that occurred during the study period are reported in Figure 1. Before protocol initiation, in-depth education was provided to physicians, advanced practice providers, pharmacists, and nurses who would provide care in the medical ICU.

The treating provider determined the choice of vasoactive medication to administer. If norepinephrine was the vasoactive medication of choice, providers were encouraged, but not required, to administer it peripherally if patients met the criteria for the protocol. The norepinephrine product used was the standard concentration available at the institution (norepinephrine 16 mg diluted in 250 mL of dextrose 5% in water). The standard concentration was chosen, rather than a more dilute concentration, to limit the risk for dispensing errors and medication pump misprogramming and to limit the infusion volume, possibly lowering peripheral blood vessel wall stress and limiting the amount of tissue exposed to norepinephrine in the event of an extravasation. In addition, extravasation antidotes

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Initial Protocol Requirements (February 2019)	Protocol Version 2 (February 2020)	Protocol Version 3 (August 2020)
• Two available PIV which are 20 or 22 gauge • PIV must be placed above the wrist and below the antecubital fossa • PIV placement must be confirmed via ultrasonography • Assessment of PIV patency every 2 hours • Maximum norepinephrine dose of 15 mcg/min • Maximum infusion time of 48 hours • Included patients must be able to report pain or discomfort	• Addition of an automated page that is sent to a nurse supervisor at the time of peripheral norepinephrine order entry • The alerted nurse supervisor assesses the patient for protocol adherence	• Removal of the 48 hour infusion duration limit • Removal of the requirement for patients to be able to report pain or discomfort • Addition of every 2 hour PIV aspiration to assess blood return to the every 2 hour PIV patency checks • Expanded to allow 18 gauge PIV

Figure 1 – *Description of peripheral norepinephrine administration protocol. PIVC = peripheral intravenous catheter.*

(subcutaneous phentolamine and nitroglycerin paste, both to be administered at the site of extravasation) were stocked in all unit automated dispensing cabinets. An order panel was created within the study site electronic medical record that contained the appropriate norepinephrine drug file with a preselected dose range as well as orders for the appropriate norepinephrine antidotes to be used as needed in the event of an extravasation. This order panel was the only means to order peripheral norepinephrine.

This was a prospective observational cohort study conducted from February 2019 through June 2021. The study was approved by the institutional review board of the study site (Identifier: 19-116) with an exemption from informed consent. Patients were included if they were admitted to the medical ICU at the Cleveland Clinic main campus and received peripheral norepinephrine during the study period. No other vasoactive medications that typically require a CVC for administration were allowed to be given peripherally in the study ICU. Study data were collected and managed using Research Electronic Data Capture tools hosted at Cleveland Clinic.[9,10] The manuscript was prepared according to Standards for Quality Improvement Reporting Excellence version 2.0 guidelines.[11]

Data were collected to describe the duration and maximum dose of norepinephrine administered peripherally. The primary outcome was the number of central line days avoided per patient, which was calculated according to guidelines set forth by the National Healthcare Safety Network.[12] This was calculated as the number of calendar days in which peripheral norepinephrine was infused; if a central line was placed on a day in which norepinephrine also was infused through a PIVC, that day was not counted as a central line day avoided. Secondary outcomes included the incidence of extravasation events, the number of CVC placements avoided, and the degree of tissue injury caused by each extravasation event. For the purposes of calculating the incidence of extravasation, a PIVC infusion day was considered to be a full 24-h period of norepinephrine infusion through a PIVC. This was chosen rather than calendar days because it was believed to provide the most clear description of the extravasation incidence that can be expected if this protocol were implemented at another site.

A post hoc analysis was performed to compare the rate and incidence of extravasation events in patients receiving peripheral norepinephrine for ≤ 24 h with those receiving peripheral norepinephrine for > 24 h. This analysis was performed to evaluate the safety of use for longer durations, because most previous studies of this topic described a mean infusion time of < 24 h, and PIVC dwell time of > 24 h is a known risk factor for extravasation.[6,8] An additional exploratory analysis was performed comparing patients who experienced extravasation events with those who did not in an attempt to identify factors that may put patients at risk of extravasation.

Statistical analysis was performed using STATA version 16.1 software (StataCorp, LLC) and R version 4.2.3 software (R Foundation for Statistical Computing). The primary analysis used descriptive statistics only. The post hoc and exploratory analyses compared categorical outcomes by calculating the between-group absolute percentage difference with the 95% CI. Continuous outcome variables were not normally distributed; therefore, they are expressed as median (interquartile range [IQR]), and between-group mean differences with 95% CIs were calculated with the bootstrap procedure with 1,000 replications. Extravasation incidence was compared using the incidence rate ratio with 95% CI.

Results

Six hundred thirty-five patients received peripheral norepinephrine from February 2019 through June 2021. Six hundred three of these patients received norepinephrine via PIVC as the first norepinephrine exposure and 32 patients transitioned from receiving norepinephrine via a CVC to receiving it via a PIVC to allow CVC removal. Table 1 highlights the baseline characteristics of included patients. The median maximum peripherally administered norepinephrine dose was 10 μg/min (IQR, 6-15 μg/min). Ninety-three patients (14.6%) received a norepinephrine dose of > 15 μg/min during peripheral administration. One hundred thirty patients (20.5%) received peripheral norepinephrine for ≥ 24 h. Peripheral norepinephrine was administered for a total of 11,084 h (median duration, 5.8 h [IQR, 2.0-19.7 h]; mean ± SD duration, 17.5 ± 33.0 h). Three hundred fifty patients (55.1%) failed to meet at least one line-related component of the protocol at some point during PIVC norepinephrine

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TABLE 1] Baseline and Infusion Characteristics[18]

Characteristic	Received Norepinephrine via Peripheral Administration Protocol (N = 635)
Age, y	63 (55-71)
Weight, kg	82.7 (68.9-99.3)
BMI, kg/m^2	28.2 (23.7-33.6)
Maximum dose, μg/min	10 (6-15)
Infusion duration, h	5.8 (2.0-19.7)
Required CVC	292/603 (48.4)
Extravasation events	35 (5.5)
Highest infiltration grade[a]	
0	5 (14.3)
1	16 (45.7)
2	13 (37.1)
3	0 (0)
4	1 (2.9)[b]
Protocol criteria met at time of norepinephrine initiation	
Catheter size criteria	529 (83.3)
Catheter placement location criteria	422 (66.5)
Catheter ultrasound confirmation criteria	316 (49.8)
Appropriate norepinephrine dose	535 (84.3)

Data are presented as No. (%), No./total No. (%), or median (interquartile range). CVC = central venous catheter.

[a]Infiltration grades: grade 0, no symptoms; grade 1, edema < 1 inch in any direction, cool to touch, with or without pain; grade 2, skin blanched and translucent, edema 1-6 inches in any direction, Cool to touch, with or without pain; grade 3, skin blanched and translucent, gross edema > 6 inches in any direction, mild to moderate pain, possible numbness; grade 4, skin blanched and translucent, gross edema > 6 inches in any direction, deep pitting edema, circulatory impairment, moderate to severe pain.

[b]One patient was graded as showing infiltration grade 4 by the bedside nurse, but was transitioned to comfort care measures and died before being evaluated by the study team. Study site policy suggests marking all vasopressor extravasations as infiltration grade 4 in the electronic medical record initially regardless of degree of tissue injury, so it is unclear whether this truly constituted significant tissue damage.

administration. Additional details on protocol violations can be found in Table 1.

Of the 603 patients who received norepinephrine via PIVC as the first norepinephrine exposure, 311 patients (51.6%) never required placement of a CVC. The median time from initial PIVC norepinephrine administration to placement of a CVC was 3.6 h (IQR, 1.5-12.5 h) in those who required CVC placement. Of the 32 patients who transitioned to receiving norepinephrine via PIVC from via a CVC to allow for CVC removal, eight patients (25%) required the replacement of a CVC at some point in the treatment course. The median number of CVC days avoided per patient was 1 (IQR, 0-2 days per patient; total of 807 CVC days avoided for the study period). Extravasation of norepinephrine occurred in 35 patients (5.5%; incidence, 75.8 events/1,000 d of PIVC administration [95% CI, 52.8-105.4 events/1,000 d]). All extravasation events were graded according to the Infusion Nurses Society Infiltration Scale.[12] No patient demonstrated tissue injury that required surgical intervention, with 21 of 35 patients (60%) who experienced extravasation having either no tissue injury (infiltration grade, 0) or skin blanching with edema of < 1 inch in any direction (infiltration grade, 1) (Table 1). Of the 35 patients who experienced an extravasation event, 17 patients (48.6%) required CVC insertion. Norepinephrine infusion via an alternative PIVC frequently was continued in patients who experienced extravasation events (mean duration after extravasation, 7.5 h; median duration after extravasation, 3 h [IQR, 0.19-12.5 h]).

Table 2 summarizes characteristics of norepinephrine administration and extravasation in patients receiving ≤ 24 h of peripherally administered norepinephrine vs those receiving > 24 h of peripherally administered norepinephrine. Although the percentage of patients experiencing an extravasation event was higher in those receiving peripheral norepinephrine for > 24 h vs those receiving norepinephrine for ≤ 24 h (8.7% vs 4.7%, respectively; difference, 3.9% [95% CI, –0.4% to 10.3%]), the extravasation incidence was lower in those receiving norepinephrine via PIVC for > 24 h (33.8 events/1,000 d of PIVC administration vs 176.4 events/1,000 d of PIVC administration, respectively; incidence rate ratio, 0.19 [95% CI, 0.09-0.39] for PIVC for > 24 h). No difference was detected in the highest infiltration grade of patients experiencing extravasation events when comparing these groups.

Table 3 reports an exploratory comparison of characteristics of patients who experienced an extravasation event vs patients who did not experience an extravasation event. Patients experiencing extravasation seemed to be older (mean difference, 4.0 years; 95% CI, –0.5 to 8.0 years) and to have undergone a longer duration of peripheral norepinephrine administration (mean difference, 6.8 h; 95% CI, –3.1 to 19.3 h). Notably, overall protocol adherence and adherence to individual protocol elements were not lower in patients experiencing extravasation. A Kaplan-

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TABLE 2] Post Hoc Comparison of Outcomes Stratified by Duration of Peripheral Norepinephrine Infusion

Variable	≤ 24 h (n = 508)	> 24 h (n = 127)	Effect Estimate (95% CI)
Infusion duration, h	3.8 (1.5-9.7)	42.4 (32.4-66.1)	[a]
Maximum dose, μg/min	10 (5-15)	10 (7-15)	−1.2 (−2.9 to 0.6)[b]
Extravasation events	24 (4.7)	11 (8.7)	3.9 (−0.4 to 10.3)[c]
Extravasation incidence, per 1,000 d of peripheral infusion (95% CI)	176.4 (113.1-262.5)	33.8 (16.9-60.4)	0.19 (0.09-0.39)[d]
Highest infiltration grade[e]			8.0 (−23.3 to 39.1)[f]
0	5 (20.8)	0 (0)	
1	10 (41.7)	6 (54.5)	
2	8 (33.3)	5 (45.5)	
3	0 (0)	0 (0)	
4	1 (4.2)	0 (0)	

Data are presented as No. (%) or median (interquartile range), unless otherwise indicated. Effect estimates with 95% CIs compare the effect in the group of patients receiving peripheral norepinephrine for > 24 h with the effect in the group of patients receiving peripheral norepinephrine for ≤ 24 h.
[a]Only descriptive statistics for the groups without an effect estimate are reported because of the expected between-group difference resulting from how the cohorts were generated.
[b]Mean difference.
[c]Absolute percentage difference.
[d]Incidence rate ratio.
[e]Evaluated only in the 35 patients experiencing an extravasation event (n = 24 and n = 11, respectively). One patient was graded as showing infiltration grade 4 by the bedside nurse, but was transitioned to comfort care measures and died before being evaluated by the study team. Study site policy suggests marking all vasopressor extravasations as infiltration grade 4 in the electronic medical record initially regardless of degree of tissue injury, so it is unclear whether this truly constituted significant tissue damage.
[f]Absolute percentage difference for highest infiltration grade ≥ 2.

Meier curve displaying time to extravasation in those experiencing an extravasation event can be found in Figure 2.

Discussion

Our study assessing the implementation of a protocol for administration of norepinephrine through a PIVC observed a median number of CVC days avoided per patient of 1 d/patient (IQR, 0-2 d/patient), with avoidance of CVC placement for administration of norepinephrine in 51.6% of patients. Although the incidence of extravasation was 75.8 events/1,000 d of PIVC administration, harm resulting from these events was minimal. These findings suggest that the administration of norepinephrine via PIVC is logistically feasible and can reduce frequency of CVC insertions and number of days of CVC use substantially without

TABLE 3] Exploratory Analysis of Patient Characteristics in Those Experiencing vs Not Experiencing an Extravasation Event

Variable	No Extravasation (n = 600)	Extravasation (n = 35)	Effect Estimate (95% CI)
Age, y	63 (55 to 71)	67 (61 to 74)	4.0 (−0.5 to 8.0)[a]
BMI, kg/m^2	28.3 (23.9-33.5)	27.0 (20.8 to 35.9)	−0.7 (−3.6 to 2.6)[a]
All catheter criteria met	266 (44.3)	19 (54.3)	10.0 (−6.6 to 25.7)[b]
Met catheter size criteria	495 (82.5)	33 (94.3)	11.8 (−1.4 to 17.0)[b]
Met catheter placement location criteria	394 (65.7)	27 (77.1)	11.5 (−5.1 to 23.0)[b]
Met catheter ultrasound confirmation criteria	294 (49.0)	22 (62.9)	13.9 (−3.1 to 28.4)[b]
Infusion duration, h	5.5 (1.9-18.9)	13.8 (4.0 to 29.5)	6.8 (−3.1 to 19.3)[a]
Infusion duration > 24 h	116 (19.3)	11 (31.4)	12.1 (−1.2 to 28.9)[b]
Maximum dose	10 (5-15)	13 (7-15)	0.6 (−2.1 to 3.8)[a]

Data are presented as No. (%) or median (interquartile range), unless otherwise indicated. Effect estimates with 95% CIs compare the effect in the group of patients experiencing extravasation with the effect in the group of patients not experiencing extravasation.
[a]Mean difference.
[b]Absolute percentage difference.

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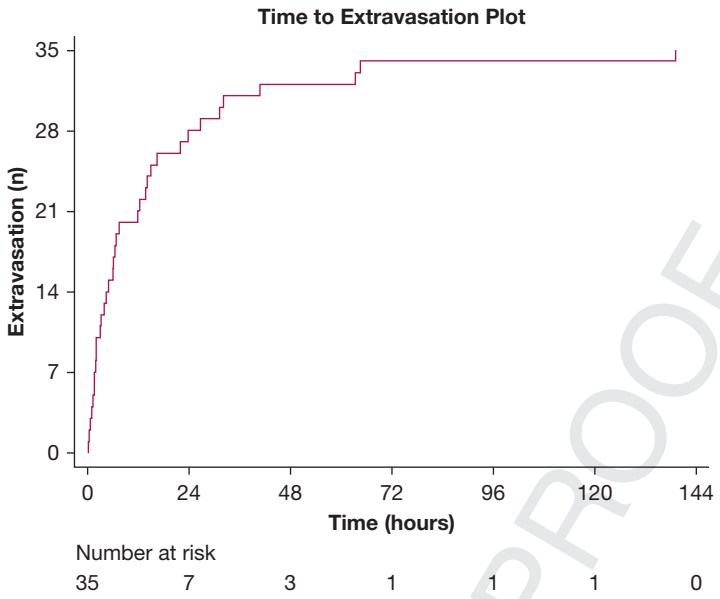

Figure 2 – *Graph showing time to extravasation in those experiencing an extravasation event.*

significant extravasation-related harms. Several factors may have contributed to these outcomes. First, a multidisciplinary team of physicians, nurses, and pharmacists developed a protocol for line placement and norepinephrine administration using best practices from published experiences.[2-6,8] Before protocol implementation, and with each revision, education was performed with the nursing staff and licensed independent practitioners. We believe that this step was key to our success. Although a high rate of protocol deviations occurred, most were short-term nonadherence to the PIVC criteria while additional PIVCs were being placed. Second, key protocol components likely limited extravasation incidence and minimized tissue damage when extravasation did occur. In particular, we used ultrasonography to ensure appropriate PIVC placement, and routine line assessment ensured comprehensive and timely identification of extravasation events (and thus, timely antidote administration). Finally, a robust auditing process allowed for identification of all extravasations in nearly real time and consistent assessment of adherence to all protocol requirements. This allowed for the rapid identification of trends and iterative continuous improvement processes.

Implementing a PIVC norepinephrine infusion protocol substantially reduced the number of CVC placements. Although it is impossible to evaluate the absolute effectiveness of this protocol in reducing complications of CVC placement and maintenance, it seems likely that a reduced CVC burden would lead to a reduction in these negative outcomes. Although the median CVC days avoided per patient was minimal (1 day [IQR, 0-2 days]; 807 days total of CVC use avoided for the study period), this likely is an underestimation of the true number of days of central line use avoided because this was calculated using the assumption that the CVC would be removed the same calendar day that norepinephrine administration ceased. Our study identified a higher proportion of patients who experienced extravasation (5.5%; incidence, 75.8 events/1,000 d of PIVC administration) than many previously published reports.[4,5,14-16] In particular, this is higher than the 0.6% rate of extravasation reported in the 500 patients treated with peripheral vasopressors in the recently completed CLOVERS trial.[17] However, it should be noted that CLOVERS did not use a protocolized approach to assess for extravasation, which may explain the difference in rate. It is notable that 60% of patients who experienced extravasation experienced no or minimal tissue injury (infiltration grade, 0-1). Additionally, no patient required surgical intervention after extravasation. We hypothesize that both of these findings are explained by routine assessment of line patency every 2 h. By using PIVC aspiration to assess blood return, we likely identified additional minor extravasations that otherwise would not have been noted and identified extravasations before large volumes of norepinephrine were infused outside the vasculature. This early identification also allowed early antidote administration, which minimized the

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development of complications. Additionally, we hypothesize that limiting the dose of norepinephrine infused peripherally to a maximum of 15 μg/min helped to limit the amount of drug present to cause tissue damage in cases of extravasation. To our knowledge, this is the largest reported solely prospective cohort of patients to have received peripheral norepinephrine. This distinction of prospective vs retrospective observation is important given the known difficulties associated with identifying extravasation events retrospectively.[18] As such, this study may provide the best point estimate of peripheral norepinephrine extravasation incidence currently available and represents what may be observed in day-to-day care of critically ill patients.

Our study has several limitations. First, it was a prospective observational trial conducted at a single study site. This single-center nature limits the generalization of our results to all practice settings. In addition, because no comparator group was included, it is impossible to elucidate fully all possible benefits and harms of administering norepinephrine via a PIVC compared with a CVC. Because use of this protocol was not mandatory for all patients, it is possible that selection bias could have resulted in the incidence of complications being lower than if protocol use was mandatory. Further, because this study reports a real-world clinical experience with evolving protocol requirements, it is difficult to determine whether identical results would be obtained using any one protocol version. However, it is encouraging that these results could be observed outside the ideal clinical trial setting in day-to-day clinical practice. Additionally, because continuous process improvement should be a routine part of clinical practice, our results illustrate the implementation and improvement of a protocol in a pragmatic way that likely would mimic the process of protocol implementation at other sites. Finally, although we suspect that certain protocol components contributed significantly to our safety findings, we cannot say definitively which components were most important because the protocol was implemented as a bundle.

Interpretation

Our findings suggest that peripheral administration of norepinephrine can be operationalized safely for patients and can prevent approximately half of the central line insertions for norepinephrine administration. Although our extravasation rates were somewhat higher than reported previously, tissue injury rates were low, with no patient requiring substantial intervention. Future studies should consider the randomization of patients to PIVC vs CVC norepinephrine administration to characterize better the overall balance of benefits and harms between the two administration techniques.

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