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REVIEW

The use of peripheral vasopressors and its implications for hospital medicine

Michael Kalinoski[1]

Thomas Kalinoski[2]

Kathryn Pendleton[3]

Author details can be found at the end of this article

Correspondence to:
Michael Kalinoski
(kali0135@umn.edu)

Abstract

Vasopressor medications for circulatory shock have historically been administered through central venous catheters due to concern for extravasation injury when given peripherally. However, recent studies have demonstrated the safety of peripheral administration of vasopressor medications at lower doses and for a limited duration. Peripheral use of vasopressors is appealing to both patients and providers, as obtaining central access is an invasive procedure associated with the risk of pneumothorax, bleeding, and infection. Furthermore, waiting to initiate these medications until central access is obtained can lead to delays in care. Conversely, valid concerns remain regarding the risk of tissue extravasation associated with peripheral vasopressors, which can be life and limb threatening. We discuss the guidelines and data for optimal dose, duration, intravenous line (IV) size, IV location, and nursing IV site monitoring for peripheral vasopressors. We then explore adverse events associated with peripheral vasopressors. Finally, we describe how this practice change may impact hospital medicine providers.

Key words: Central venous catheter; Hypotension; Peripheral vasopressors; Sepsis; Septic shock; Shock; Vasoactive medications

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Introduction

Circulatory shock denotes a mismatch between oxygen delivery and oxygen consumption. It is one of the primary indications for intensive care unit (ICU) admission and is associated with high morbidity and mortality if not treated early (Kashani et al, 2022). Vasopressors mitigate the effects of shock by creating vasoconstriction for the purpose of increasing mean arterial pressure (MAP) and perfusion of organs. These medications are most often administered as a continuous titratable infusion with close monitoring of vital signs and infusion rates in an ICU setting (VanValkinburgh et al, 2023). Due to early reports of extravasation injury and skin necrosis around peripheral veins with the advent and widespread use of these agents (Humphreys et al, 1955; Lewis et al, 2017), vasopressors have historically been delivered exclusively through central venous catheters (CVCs) to minimise these risks. However, new evidence suggests these medications can be given safely through peripheral intravenous lines (IVs) at lower doses and for a limited duration (Tian et al, 2019; Pancaro et al, 2020; Owen et al, 2021). This paradigm shift has the potential to change clinical practice for both hospital medicine providers and intensivists alike.

Peripheral use of vasoactive agents is appealing for several reasons. Firstly, in the treatment of shock, there is no time to waste. Delays in achieving adequate MAP, such as those that may occur while awaiting CVC placement, are associated with increased mortality. The use of peripheral vasopressors has been shown to expedite vasopressor delivery, thereby reducing these delays (Black et al, 2020; Colon Hidalgo et al, 2020; Munroe et al, 2023). Next, CVC placement is a procedure, and procedures require time and expertise which may not always be readily available, especially in resource limited settings. Additionally, CVC placement is an invasive procedure with risks such as pneumothorax, bleeding, thrombus, and infection (Patel et al, 2019). Catheter-associated bloodstream infections (CLABSIs) are a particularly problematic complication of CVCs as they are a source of morbidity and mortality for patients and an important quality metric for hospitals (Toor et al, 2022). The potential benefits of peripheral vasopressor use are not merely theoretical though, with a

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recent study showing that a protocol guiding peripheral use of noradrenaline prevented the need for CVC placement in 51.6% of patients (Yerke et al, 2024). Thus, for patients with mild shock that quickly resolves, using peripheral vasopressors may be particularly advantageous as it mitigates these risks altogether.

Data regarding the safe utilisation of peripherally administered vasopressors is evolving rapidly. The use of peripheral vasopressors with dose and duration limits is already occurring at many institutions. However, in the absence of comprehensive international guidelines, policies vary widely between hospitals and many hospitals lack a formal policy on this topic (Teja et al, 2022; Munroe et al, 2023). This practice change will affect not only hospitalists working in an open ICU setting but also resuscitation practices and management of care transitions between the medical ward and ICU.

In this review, we describe the guidelines and data regarding recommended and optimal dose, duration, IV size, IV location, and nursing IV site monitoring for peripheral vasopressors. We then explore adverse events associated with these agents. Finally, we discuss the implications peripheral vasopressor use may have on hospital medicine providers and provide clinical vignettes to help apply this information to common clinical scenarios.

Guidelines for use

There are no consensus guidelines on the use of peripheral vasopressors. The Surviving Sepsis Campaign (SSc) provides some guidance on peripheral vasopressor use. The SSc suggests initiating vasopressors peripherally rather than delaying initiation until central access is obtained, advising limiting peripheral vasopressors to 6 hours and administrating via central access as soon as feasible. For IV location, the SSc recommends using an upper extremity vein in or proximal to the antecubital fossa. Limits on the vasopressor type and dose for peripheral use are not mentioned, nor is a specific IV size or IV site monitoring protocol (Evans et al, 2021). While formal guidance on the use of peripheral vasopressors varies widely, a secondary analysis of the CLOVERS trial found that initiation and continuation of peripheral vasopressors beyond 6 hours is common in practice, occurring in 84.2% and 57.2% of patients, respectively (Munroe et al, 2023).

According to a 2022 survey conducted by Munroe et al (2022), hospitals that use vasopressors peripherally are reliant on individualised institutional policies and, as previously mentioned, the content of these policies varies considerably. Generally, these policies include direction on vasopressor type, dose, and duration allowed peripherally. Recommended peripheral IV size, location, and nursing parameters for IV site monitoring are also occasionally included. This study found vasopressin to be the most commonly prohibited vasopressor, followed by adrenaline. 45% of hospitals had limits on vasopressor dose, although exact doses weren't specified. Duration limits for peripheral vasopressors ranged from only allowing use while obtaining central access to a maximum of 48 hours. 47% had no minimum IV size requirements, and a 20-gauge IV was the most recommended minimum size in policies that specified. Leg, hand, and wrist were the most commonly prohibited locations for peripheral use. Nursing IV site monitoring was required in 63% of policies.

Safest dose and duration of peripheral vasopressors

Finding the safest dose and duration of vasopressors is complex, as studies differ in their quality, patient population, reporting of dose (mcg/kg/min vs mcg/min), and safety protocols. Almost all studies available are single-centre designs, which limits their generalizability. Furthermore, it is unclear if all vasoactive medications have an equal risk profile when given peripherally. A recent systematic review noted noradrenaline (80.4%), dopamine (9.3%), and vasopressin (6.9%) were most commonly administered in instances of local tissue complications (Loubani and Green, 2015), however, a meta-analysis on the topic found no significant difference in adverse events based on vasopressor type or duration (Owen et al, 2021). We report what is currently known on the safest dose and duration of each individual vasopressor medication in Table 1 (Cardenas-Garcia et al, 2015; Lewis et al, 2017; Putland et al, 2006).

Table 1. Safest studied dose and duration of individual vasopressors

Vasopressor	Maximum dose	Maximum duration (hours)	Study	Study type	Patients
Noradrenaline	0.7 ± 0.23 mcg/kg/min	49 ± 22 (mean)	Cardenas-Garcia et al (2015)	Prospective	506
Vasopressin	0.04 units/mn	12.5 (median)	Lewis et al (2017)	Prospective	4
Dopamine	12.7 mcg/kg/mn	49 ± 22 (mean)	Cardenas-Garcia et al (2015)	Prospective	101
Phenylephrine	3.25 mcg/kg/mn	49 ± 22 (mean)	Cardenas-Garcia et al (2015)	Prospective	176
Adrenaline	1.5 mcg/mn	19.5 (median)	Putland et al (2006)	Retrospective	220

Noradrenaline is the first-line vasopressor for septic shock and is a reasonable option for other types of shock as well (Evans et al, 2021). The highest peripheral dose studied with a robust patient population was 0.7 ± 0.23 mcg/kg/min in a study of 506 patients and 16 reported extravasations (all reported to be mild without tissue injury). The longest duration of peripheral noradrenaline was reported in the same study, which was 49 ± 22 hours (Cardenas-Garcia et al, 2015). This study is an outlier compared to other studies that cite doses of 0.04–0.2 mcg/kg/min and duration of <24 hours for the majority of patients (Loubani and Green, 2015; Lewis et al, 2017; Cape et al, 2020). Practically speaking, a second vasopressor is typically added well before reaching noradrenaline doses of 0.7 mcg/kg/min, and thus a CVC would likely be placed in these patients regardless.

Vasopressin is used as a second-line agent for septic shock and is recommended to be started if MAP is inadequate despite low-to-moderate doses of noradrenaline (Evans et al, 2021). Safety data is sparse. The highest dose studied for shock has been 0.04 units/min in a study of 4 patients and 0 reported extravasations, with a median duration of 12.5 hours (Lewis et al, 2017). Loubani and Green (2015) described vasopressin as having a comparatively high rate of local tissue complications, however, it appears this data was from case reports only. We suspect the use of this agent peripherally will be limited clinically as vasopressin is usually used in addition to other agents, and thus central access would be highly preferred.

Dopamine has historically been used for cardiogenic shock and unstable bradyarrhythmias (VanValkinburgh et al, 2023). The highest peripheral dose of dopamine studied has been 12.7 mcg/kg/min in a study of 101 patients with 3 reported extravasations (all reported to be mild without tissue injury). The longest duration was from the same study, which was 49 ± 22 hours (Cardenas-Garcia et al, 2015).

Phenylephrine is usually used only in conjunction with other agents for indications such as spinal shock due to its potential to cause reflex bradycardia. An exception to this is the wide use of phenylephrine to counteract the vasodilatory effects of anaesthesia (VanValkinburgh et al, 2023). The same Cardenas-Garcia study reported the highest dose and longest duration for phenylephrine, which were 3.25 mcg/kg/min and 49 ± 22 hours, respectively, in a study of 176 patients and 0 reported extravasations (Cardenas-Garcia et al, 2015).

Adrenaline is used in anaphylactic shock, unstable bradyarrhythmias, and as a third-line agent for septic shock (VanValkinburgh et al, 2023). The highest dose and longest duration of adrenaline studied in a robust patient population was 1.5 mcg/min (0.019 mcg/kg/min in an 80 kg patient) for a median of 19.5 hours in a study of 220 patients with 11 reported extravasations (all reported to be mild without tissue injury) (Putland et al, 2006).

Safest intravenous line (IV) size, location, and site monitoring for peripheral vasopressors

The only robust study investigating the safest IV size for peripheral vasopressor use is from a meta-analysis by Owen et al (2021) described previously. In their subgroup analysis, they found no statistical difference in adverse events associated with peripheral IV size. Data regarding the safest peripheral IV location is mixed. A 2015 systematic review by Loubani

and Green found that 85% of reported extravasations occurred in a peripheral catheter placed distal to the antecubital fossa. However, Owen et al (2021) found no significant difference in adverse events based on anatomical infusion site.

There are no studies comparing nursing protocols for peripheral IV site monitoring when administering peripheral vasopressors. However, a monitoring protocol is included in most hospital policies and should be considered when using vasopressors peripherally (Araiza et al, 2022; Munroe et al, 2022). Protocols should include routine monitoring of areas proximal and distal to the infusion site for fluid leakage, oedema, skin injury or discolouration, and vesicle formation (Gorski et al, 2021).

Adverse events with peripheral vasopressors

Vasopressors started to see widespread use in the 1950s, and reports of tissue extravasation injuries soon followed. These reports detailed skin and soft tissue necrosis when vasopressors were delivered peripherally. Most of the reports of these adverse events were published before the 1960s, during a time period when peripheral access techniques utilised tied-in metal needles or catheters (Humphreys et al, 1955; Lewis et al, 2017). Central venous access soon became routine to avoid the extravasation risks detailed in these case reports.

Since the 1950s, there have been considerable improvements in peripheral venous access techniques as well as the initiation of nurse-driven safety protocols to prevent extravasation. Recent studies report extravasation injuries to be quite low. The CLOVERS trial included 500 patients who received vasopressors via peripheral administration and noted only 3 occurrences of extravasation; all of which resolved without intervention or clinical consequence (Shapiro et al, 2023). A 2019 meta-analysis of 7 studies that included a total of 1382 pooled patients by Tian et al (2019) found extravasation occurred in 3.4% of patients. All events were reported as mild and there were no episodes of tissue necrosis or limb ischaemia. Extravasation events were successfully managed conservatively or with vasodilatory medications such as phentolamine or nitroglycerine paste. Vasopressors represented in this meta-analysis included noradrenaline (most frequently administered), adrenaline, vasopressin, phenylephrine, dopamine, and metaraminol. A 2021 meta-analysis of 11 studies that included a total of 16,055 pooled patients by Owen et al (2021) found that adverse events (defined as extravasation, infiltration, pain, oedema, blanching, or necrosis) occurred in 1.8% of patients. Most adverse events were mild. Serious adverse events included thrombophlebitis (one case) and ischaemia with skin necrosis (one case). Again, all events were successfully managed conservatively or with vasodilatory medications. Vasopressors represented in this meta-analysis included noradrenaline (most frequently administered), adrenaline, vasopressin, phenylephrine, and dopamine. Table 2 (Owen et al, 2021; Tian et al, 2019) summarises these findings. Most research included in both meta-analyses were retrospective studies, which limits data interpretation. Also, many studies had rigorous safety protocols that included vigilant nursing monitoring of IV sites. The safety of peripheral vasopressors in the context of routine care is less clear.

Table 2. Adverse events from meta-analysis data (Owen et al, 2021; Tian et al, 2019)

Vasopressor	Extravasations (%)	Limb ischaemia or necrosis	Thrombophlebitis	Surgical intervention needed
Noradrenaline	1.4–4%	1	1	0
Vasopressin	0–4.5%	0	0	0
Dopamine	0–3%	0	0	0
Phenylephrine	2–5.5%	0	0	0
Adrenaline	0	0	0	0

Hospital medicine implications

Adoption of peripheral vasopressors is increasing. A recent international survey of ICU pharmacists from 132 institutions found that 86% of respondents were using peripheral vasopressors in their ICUs (Abu Sardaneh et al, 2023). It is imperative that hospital medicine providers are familiar with peripheral vasopressor use, particularly as it may relate to practice changes before and after ICU transfer. We discuss these practice changes below, and Table 3 (Evans et al, 2021) provides clinical vignettes.

The first potential practice change is the use of peripheral vasopressors as a bridge to central administration while awaiting ICU transfer. Initiation of vasopressors through peripheral IVs of appropriate size and location with close monitoring by an experienced nurse can prevent periods of prolonged hypotension or unnecessary fluid loading in patients awaiting ICU transfer. As noted earlier, resuscitation delays lead to increased mortality, and peripheral vasopressor use is associated with faster time to vasopressor delivery (Black et al, 2020; Colon Hidalgo et al, 2020; Munroe et al, 2023).

Utilisation of peripheral vasopressors also has the potential to change resuscitation practices among hospital medicine providers. A recent study by Shapiro et al (2023) compared a restrictive fluid strategy (prioritising vasopressors and lower IV fluid volumes) to a liberal fluid strategy (prioritising higher volumes of IV fluids before vasopressor use) in patients with sepsis-induced hypotension following initial resuscitation. They found similar mortality outcomes with both strategies, but the restrictive fluid strategy led to statistically fewer cases of volume overload. Consequently, arguments have been made for less aggressive fluid resuscitation upfront and earlier initiation of vasopressors (Carlos Sanchez et al, 2023). Use of peripheral vasopressors may help to make this an easier practice change for physicians as CVC placement has traditionally been a major barrier to vasopressor initiation. This is especially important in patients who are sensitive to volume loading, such as those with heart failure or those who have already received the 30 millilitres per kilogram of body weight fluid resuscitation suggested by the SSc guidelines (Arfaras-Melainis et al, 2020; Evans et al, 2021).

Table 3. Clinical vignettes

	Clinical vignette	Vasopressor administration
Case 1	A 90-year-old female with acute cystitis has a mean arterial pressure (MAP) of 55 despite 30 cc/kg intravenous line (IV) fluids. Started on 0.04 mcg/kg/min of noradrenaline, which was titrated off by morning	Data would suggest this patient would be an appropriate candidate for peripheral administration of vasopressors
Case 2	A 60-year-old male presents with shortness of breath and is found to have pneumonia. MAP of 40 despite 30 cc/kg IV fluids. Both noradrenaline and Vasopressin are needed to maintain adequate MAPs	There is limited data supporting the use of vasopressin peripherally and no data to support the use of multiple vasopressors peripherally. Central Venous Catheter (CVC) insertion should be considered
Case 3	A 45-year-old male with pyelonephritis develops hypotension in the medical ward. He already received 5 litres of IV fluids and is showing signs of volume overload. There will be an hour delay before an intensive care unit (ICU) bed is ready and a central line can be placed	Vasopressors should be administered peripherally rather than delaying initiation until CVC is obtained as recommended by the Surviving Sepsis Campaign (Evans et al, 2021)
Case 4	A 72-year-old female presents with redness and swelling of her right foot and is found to have cellulitis. MAP of 50 despite 30 cc/kg IV fluids. Started on 0.08 of noradrenaline, which was titrated off three days later	Peripheral vasopressors may have been appropriate initially, however, CVC placement should be considered after 24 –48 hours of ongoing vasopressor use

Finally, the ability to administer vasopressors peripherally could be practice changing for hospital medicine providers working in an open ICU setting. A time-limited trial of peripheral vasopressors for patients requiring minimal hemodynamic support may allow some patients to avoid needing a CVC altogether. In fact, a recent study by Yerke et al (2024) found that 51.6% of patients who were started on peripheral vasopressors avoided needing CVC placement during their ICU stay. This has important implications for patients, providers, and the healthcare system. Independent of procedural associated complications, CVCs place patients at risk of infection and thrombus formation, which can have significant impacts on healthcare costs and hospital length of stay (Patel et al, 2019; Chovanec et al, 2021). A recent study suggests that the rate of CLABSIs has been increasing in recent years, and with a mortality rate of 12–15%, they are among the most important preventable healthcare complications (Toor et al, 2022). In addition to CLABSIs prevention, healthcare systems may find peripheral vasopressor use to be beneficial in hospitals with gaps in intensivist coverage or limited resources for CVC or Peripherally Inserted Central Catheter placement capabilities. Weighing the demonstrated safety of short-term peripheral vasopressor administration with the risks that accompany CVC insertion and management, a time-limited trial of peripheral vasopressor administration paired with vigilant monitoring for signs of extravasation is often a reasonable choice.

Future study directions

Most data on the use of peripheral vasopressors is from observational studies. A randomised controlled trial looking at the effect of peripheral vs central administration of vasopressors on patient-centred outcomes is lacking and would help to clarify and confirm the results of observational studies. Further research is needed to thoroughly study optimal dose, duration, IV size, IV location, and nursing IV site monitoring protocols for various peripheral vasopressors. This is especially true for lesser-studied vasopressors, such as adrenaline and vasopressin. It is also unclear if a CVC is ever needed for low-dose vasopressors, or if the infusion can simply be moved to new peripheral IV sites on a time-based protocol.

Conclusion

A growing body of literature suggests that peripheral administration of vasopressors is safe and feasible. Advantages include faster time to vasopressor initiation and possible avoidance of CVC placement altogether in select patients. Hospitalists should be familiar with this practice as they are likely to encounter it with increasing frequency in ICUs. Outside the ICU, familiarity with these protocols can empower hospitalists to promptly initiate vasopressors for patients in shock, avoiding delays associated with CVC placement. Presently, there are no consensus guidelines on this topic and hospitalists should refer to any available institutional policies for guidance. Further research is needed to determine the maximum safe dose and duration of peripheral vasopressors to aid in the creation of consensus guidelines.

Key points

- Vasopressors have traditionally been administered through CVCs due to concern for extravasation injury when given peripherally.
- Recent studies have demonstrated the safety of peripheral vasopressors at lower doses and for a limited duration.
- The maximum safe dose and duration for peripheral use are still unclear but should likely be individualised for each medication.
- Peripheral vasopressor administration should be combined with a standardised protocol for extravasation monitoring and prevention.

Author details

[1]Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

[2]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

[3]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

Availability of data and materials

All the data of this study is included in this article.

Author contributions

MK, TK and KP were responsible for the design of the work as well as drafting and revision of content. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have contributed sufficiently to the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

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Conflicts of interest

We do not have any conflicts of interest to report.

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