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A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters☆,☆☆

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ABSTRACT

Purpose: The aim of this study was to collect and describe all published reports of local tissue injury or extravasation from vasopressor administration via either peripheral intravenous (IV) or central venous catheter.
Methods: A systematic search of Medline, Embase, and Cochrane databases was performed from inception through January 2014 for reports of adults who received vasopressor intravenously via peripheral IV or central venous catheter for a therapeutic purpose. We included primary studies or case reports of vasopressor administration that resulted in local tissue injury or extravasation of vasopressor solution.
Results: Eighty-five articles with 270 patients met all inclusion criteria. A total of 325 separate local tissue injury and extravasation events were identified, with 318 events resulting from peripheral vasopressor administration and 7 events resulting from central administration. There were 204 local tissue injury events from peripheral administration of vasopressors, with an average duration of infusion of 55.9 hours (±68.1), median time of 24 hours, and range of 0.08 to 528 hours. In most of these events (174/204, 85.3%), the infusion site was located distal to the antecubital or popliteal fossae.
Conclusions: Published data on tissue injury or extravasation from vasopressor administration via peripheral IVs are derived mainly from case reports. Further study is warranted to clarify the safety of vasopressor administration via peripheral IVs.

1. Introduction

1.1. Background

Vasopressor medications are commonly administered in the emergency department and intensive care unit to treat hemodynamic instability in critically ill patients. Administration of vasopressors via catheters located in large central veins has become the preferred route due to concerns about adverse events resulting from peripheral intravenous (IV) use [1,2]—especially local tissue ischemia secondary to the vasoconstrictive properties possessed by this class of medications [2].

Despite these concerns, using a peripheral IV to administer vasopressor may allow the medication to reach the patient sooner and reduce the time required to achieve hemodynamic stability and its concomitant clinical benefits. Although peripheral IV access is readily obtained in most patients, peripheral vasopressor administration is often avoided to minimize the risk of potential local tissue ischemia.

1.2. Importance

In some critically ill patients, the requirement for a central venous catheter (CVC) may delay administration of vasopressors while the catheter is placed (usually by a physician). This delay may have unintended negative consequences because patients must remain in a hemodynamically unstable condition while the CVC is inserted. In addition, CVC insertion during emergency circumstances may increase the risk of adverse events compared with CVC insertion for an elective procedure [3].

1.3. Goals of this investigation

The evidence cited for avoiding peripheral administration of vasopressors is a sparse collection of case studies and expert opinion [4]. We sought to describe the literature for the current practice of avoiding peripheral administration of vasopressors due to concerns of local tissue ischemia. We performed a systematic review to describe published reports on local tissue injury or extravasation during the administration of vasopressor medications using a peripheral IV or a CVC, and the

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type of vasopressor medication infused, the site of administration, and/or the duration of infusion in these events.

2. Materials and methods

2.1. Study design and database search

A systematic search was performed on January 17, 2014, using Medline, Embase, and the Cochrane Library databases. A review protocol was not registered or published. The search strategy was formulated with the aid of an experienced research librarian. Although no date restrictions were placed on our search, the dates of coverage at the time of the search were 1946 to 2014 for Medline, 1947 to 2014 for Embase, and 1992 to 2014 for the Cochrane Library. To minimize publication bias, we also did not have any language restrictions. Specific terms were selected for each of 3 categories (ie, vasopressors of interest, IV administration, and outcome complications) and combined using Boolean functions. Although we limited our search to "human" subjects, we also included papers where indexing information about "human" or "animal" was not available since many older publications did not include this information. The full Medline search strategy is presented in Web Appendix 1 and was adapted for searching Embase and the Cochrane Library.

2.2. Selection of studies for inclusion

XWe included studies that satisfied the following criteria: (*a*) design—any primary study (case reports, case series, observational cohorts, randomized controlled trials) involving human subjects; (*b*) population—adults (≥18 years of age) who received IV vasopressors as part of their intended medical care (ie, not accidentally), except in cases of cardiac arrest; (*c*) intervention—administration of vasopressors most commonly used in intensive care units and emergency departments (ie, dopamine, epinephrine, norepinephrine, vasopressin, terlipressin, phenylephrine, or ephedrine) via either peripheral IVs (ie, catheter not within internal jugular, subclavian, or femoral veins) or CVCs (ie, catheter in the internal jugular, subclavian, or femoral veins); (*d*) outcomes—adverse events that were attributed to vasopressor administration, including extravasation of vasopressor and local tissue injury (tissue necrosis, skin necrosis, gangrene, limb ischemia caused by extravasation of vasopressor, blister, ulcer, and amputation of limb or digit). These complications were chosen because they were felt to represent the most common and clinically relevant local complications of vasopressor administration. If a publication contained a specific statement that a given event had occurred, it was also accepted for consideration in this review, even in the absence of a description of the event.

An initial screening of papers based on title and abstract was performed by OL using predetermined criteria (Web Appendix 2). The reference sections of papers identified through the title and abstract review were also screened by OL using criteria listed in Web Appendix 2. The full text of articles identified through the title and abstract review process and meeting eligibility requirements were obtained and reviewed for final inclusion. Research associates fluent in both languages performed translation of foreign language papers into English. OL and RG independently reviewed full papers for study quality and final inclusion using predetermined criteria (Web Appendix 3). Identifying relevant information from the reviewed papers was not blinded at any stage. Agreement between OL and RG was measured using the κ statistic. Disagreements between OL and RG were resolved by consensus.

2.3. Data collection and analysis

Data were collected by OL using a standardized data abstraction form created with Microsoft Excel 2010 (Microsoft Corporation, Redmond, Wash). Only explicitly reported variables were abstracted; no data were imputed. Data were coded as present or absent. When data were present, it was encoded numerically based on the variable present. Where individual data were presented, it was collected as such. In cases where only aggregate data were available, it was collected and combined with individual data for analysis whenever possible. The full lists of data items collected from articles that presented individual

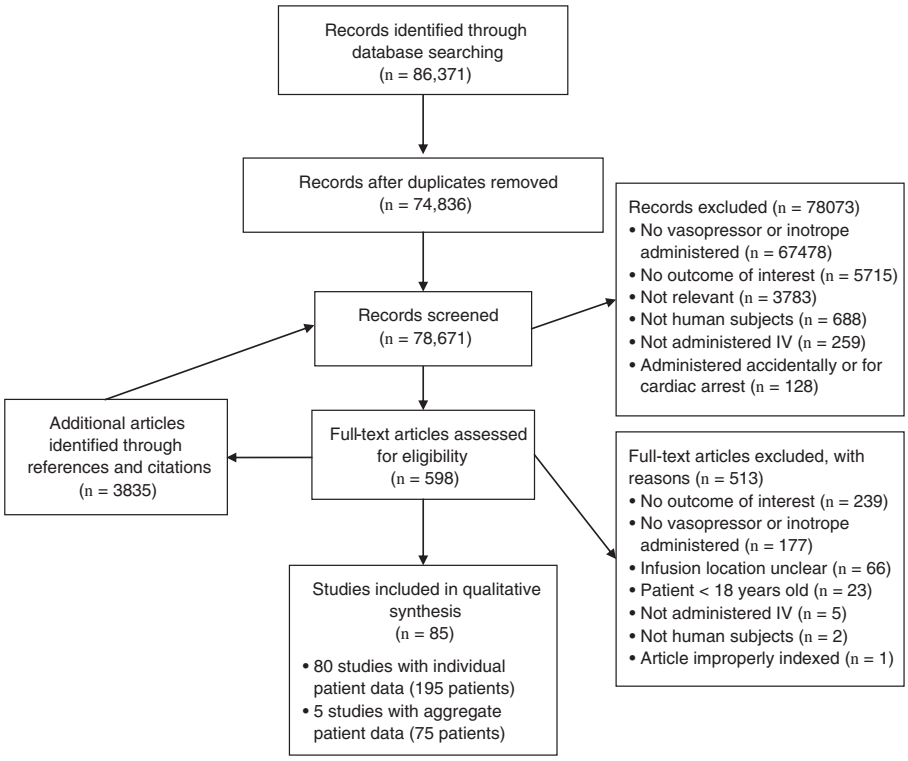

Fig. 1. Flowsheet showing inclusion of references.

Table 1
Characteristics of included studies and individual cases of extravasation or local tissue complications from peripheral or central administration of vasopressor

Characteristics	Overall	Peripheral administration	Central administration
Total no. of publications (% total)[a]	85	80 (94.1)	6 (7.1)
Dates of publication (% total)[a]			
1950-1959	28 (32.9)	28 (35.0)	1 (16.7)
1960-1969	21 (24.7)	21 (26.3)	0 (0.0)
1970-1979	9 (10.6)	9 (11.3)	0 (0.0)
1980-1989	10 (11.8)	9 (11.3)	1 (16.7)
1990-1999	5 (5.9)	5 (6.3)	0 (0.0)
2000-2009	9 (10.6)	6 (7.5)	3 (50.0)
2010-2014	3 (3.5)	2 (2.5)	1 (16.7)
Region of event (% total)[a]			
North America	39 (45.9)	38 (47.5)	2 (33.3)
Europe	35 (41.2)	31 (38.8)	4 (66.7)
Asia	5 (5.9)	5 (6.3)	0 (0.0)
South America	4 (4.7)	4 (5.0)	0 (0.0)
Australia	2 (2.4)	2 (2.5)	0 (0.0)
Africa	0 (0.0)	0 (0.0)	0 (0.0)
No. of patients (% total patients)	270	263 (97.4)	7 (2.6)
Age (years ± SD)	53.0 ± 15.6	53.0 ± 15.5	53.6 ± 19.3
Sex (% male)	54.0	53.8	60.0
Vasopressor used (% of events)[b]			
Norepinephrine	219 (74.5)	217 (75.6)	3 (42.9)
Dopamine	36 (12.2)	36 (12.5)	0 (0.0)
Vasopressin	16 (5.4)	14 (4.9)	2 (28.6)
Epinephrine	18 (6.1)	17 (5.9)	1 (14.3)
Terlipressin	4 (1.4)	3 (1.0)	1 (14.3)
Phenylephrine	6 (2.0)	6 (2.1)	0 (0.0)
Ephedrine	2 (0.7)	2 (0.7)	0 (0.0)
Reason for presenting to medical attention (% of events)[b]			
Sepsis/septic shock	49 (16.7)	45 (15.7)	4 (57.1)
Gastrointestinal	62 (21.1)	59 (20.6)	3 (0.0)
Cardiac	61 (20.7)	61 (21.3)	0 (0.0)
Respiratory	21 (7.1)	21 (7.3)	0 (0.0)
Genitourinary	13 (4.4)	13 (4.5)	0 (0.0)
Central nervous system	16 (5.4)	16 (5.6)	0 (0.0)
Oncologic	10 (3.4)	10 (3.5)	0 (0.0)
Trauma	4 (1.4)	4 (1.4)	0 (0.0)
Obstetric or gynecologic	4 (1.4)	4 (1.4)	0 (0.0)
Endocrine	3 (1.0)	3 (1.0)	0 (0.0)
Autoimmune	2 (0.7)	2 (0.7)	0 (0.0)
Psychiatric	1 (0.3)	1 (0.3)	0 (0.0)
Metabolic derangement	1 (0.3)	1 (0.3)	0 (0.0)
Vascular	1 (0.3)	0 (0.0)	1 (14.3)
Anaphylaxis	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol dependence or abuse	0 (0.0)	0 (0.0)	0 (0.0)
Other substance dependence or abuse	0 (0.0)	0 (0.0)	0 (0.0)
Other	45 (15.3)	45 (15.7)	0 (0.0)
Not reported	28 (9.5)	28 (9.8)	0 (0.0)
Reason for vasopressor administration (% of events)[b]			
Elevation of blood pressure	246 (83.7)	241 (84.0)	5 (71.4)
Control of gastrointestinal hemorrhage	15 (5.1)	13 (4.5)	2 (28.6)
Increasing urine output	17 (5.8)	17 (5.9)	0 (0.0)
Asthma or other immune reaction	11 (3.7)	11 (3.8)	0 (0.0)
Chronotropy	3 (1.0)	3 (1.0)	0 (1.3)
Heart failure	1 (0.3)	1 (0.3)	0 (0.0)
Inotropy	0 (0.0)	0 (0.0)	0 (1.3)
Reversal of anaphylaxis	0 (0.0)	0 (0.0)	0 (0.0)
Renal perfusion	1 (0.3)	1 (0.3)	0 (0.0)
Evaluation of cardiac status	0 (0.0)	0 (0.0)	0 (0.0)
Vasoconstriction	0 (0.0)	0 (0.0)	0 (0.0)
Other (all were for hepatorenal syndrome)	1 (0.3)	1 (0.3)	0 (1.3)

[a] Note: sum of papers presenting complications from peripheral and central catheters is greater than total as some papers presented complications of both central and peripheral catheters.
[b] Note: column sum may be greater than 100% because some patients may have had multiple events or may have been given multiple vasopressors.

data and articles that presented aggregate data are reported in Web Appendices 4 and 5 respectively. We collected data on study date and location, patient characteristics including comorbidities and reason for presenting to medical attention, information regarding the vasopressor(s) used including reason for administration, location of administration, dose used, gauge of IV, duration of infusion, and any complications suffered by the patient. In cases where information was missing from articles published after 1990, authors were contacted by phone or e-mail, and information was obtained using a standardized form (Web Appendix 6).

Descriptive statistics were calculated for all collected variables and subgrouped by location of vasopressor administration being either central or peripheral. Categorical variables were reported as percentages, and continuous variables were reported as mean ± standard deviation. Median values for continuous variables were also reported. Microsoft Excel 2010 was used for all calculations. Neither assessment of bias

Table 2
Data for incidents of local tissue injury and extravasation resulting from administration of vasopressor via peripheral IVs

Data from events	Local tissue injury (n = 204)[a]	Extravasation (n = 114)
Description of reported event (no./100)		
Skin necrosis	179 (87.7)	23 (20.2)
Gangrene	20 (9.8)	5 (4.4)
Tissue necrosis	5 (2.5)	0 (0.0)
Blister	0 (0.0)	0 (0.0)
Ulcer	0 (0.7)	0 (0.0)
No injury	NA	86 (75.4)
Vasopressor (no./100) and dose (reported as range)[b]		
Norepinephrine	164 (80.4), 2-48 μg/min	74 (64.9), 2-40 μg/min
Dopamine	19 (9.3), 2-12 $\mu g\ kg^{-1}\ min^{-1}$	26 (22.8), 0.4-8 $\mu g\ kg^{-1}\ min^{-1}$
Vasopressin	14 (6.9), 0.04-0.66 U/min	4 (3.5), 0.2-0.4 U/min
Epinephrine	6 (2.9), NR	11 (9.6), 1.5 μg/min
Terlipressin	3 (1.5), 1mgq6h-1.5mgq4h	0 (0.0), NA
Phenylephrine	6 (2.9), NR	0 (0.0), NA
Ephedrine	2 (1.0), NR	0 (0.0), NA
Location of infusion		
Distal	174 (85.3)	39 (34.2)
Saphenous vein	116 (56.9)	15 (13.2)
Hand	15 (7.4)	14 (12.3)
Forearm	17 (8.3)	6 (5.3)
Leg	12 (5.9)	1 (0.9)
Wrist	6 (2.9)	2 (1.8)
Foot	6 (2.9)	0 (0.0)
Arm	2 (1.0)	1 (0.9)
Proximal	120 (9.8)	13 (11.4)
Antecubital fossa	18 (8.8)	13 (11.4)
Neck	1 (0.5)	0 (0.0)
Thigh	1 (0.5)	0 (0.0)
Scalp/head	0 (0.0)	0 (0.0)
Trunk	0 (0.0)	0 (0.0)
Not reported	10 (4.9)	62 (54.4)
Gauge of IV used		
14	0 (0.0)	1 (0.9)
16	1 (0.5)	0 (0.0)
18	1 (0.5)	1 (0.9)
20	4 (2.0)	3 (2.6)
22	0 (0.0)	17 (14.9)
24	1 (0.5)	1 (0.9)
Not reported	197 (96.6)	100 (87.7)
Intervention provided[b]		
Conservative management[c]	74 (36.3)	8 (7.0)
Medication[d]	9 (4.4)	81 (71.1)
Stopping vasopressor	40 (19.6)	19 (16.7)
Skin graft	63 (30.9)	4 (3.5)
Change/manipulation of insertion site	27 (13.2)	26 (22.8)
Tissue debridement	39 (19.1)	5 (4.4)
Amputation	9 (4.4)	2 (1.8)
Dialysis	0 (0.0)	0 (0.0)
Cardiac intervention	0 (0.0)	0 (0.0)
None	0 (0.0)	1 (0.9)
Not reported	16 (7.8)	1 (0.9)
Long-term sequelae		
Mortality—unrelated to pressor event	56 (27.5)	17 (14.9)
Minor disability from pressor event	36 (17.6)	1 (0.9)
Major disability from pressor event	9 (4.4)	3 (2.6)
Mortality—pressor event contributed	4 (2.0)	1 (0.9)
No long-term sequelae	77 (37.7)	90 (78.9)
Not reported	22 (10.8)	2 (1.8)

NA indicates not applicable; NR, not reported.
[a] Event attributed to vasopressor occurring within close proximity (ie, the same extremity) to the infusion site.
[b] Sum may be greater than 100% because some patients received multiple vasopressors or interventions.
[c] Conservative management included skin compresses, observation, and dressings of any kind.
[d] Administered to reverse the effects of vasopressor.

nor meta-analysis of the data was performed due to significant heterogeneity in study populations and designs.

2.4. Event definitions

For the purposes of this study, we used the following definitions: (*a*) local complication—adverse event attributed to vasopressor administration occurring within close proximity (ie, the same extremity) to the infusion site; (*b*) extravasation of vasopressor—escape of solution containing vasopressor from vessel through which it is infused into surrounding tissue or body cavity; (*c*) tissue necrosis—death of any tissue deep to the skin as determined by pathological or visual observation; (*d*) skin necrosis—death of the epidermal or dermal layers of skin as determined by pathological or visual observation; (*e*) gangrene—death and putrefaction of tissue; (*f*) limb ischemia caused by extravasation of vasopressor—hypoperfusion of areas of tissue into which extravasation of vasopressor solutions has occurred that does not lead to tissue necrosis; (*g*) blister—visible accumulations of fluid within or beneath

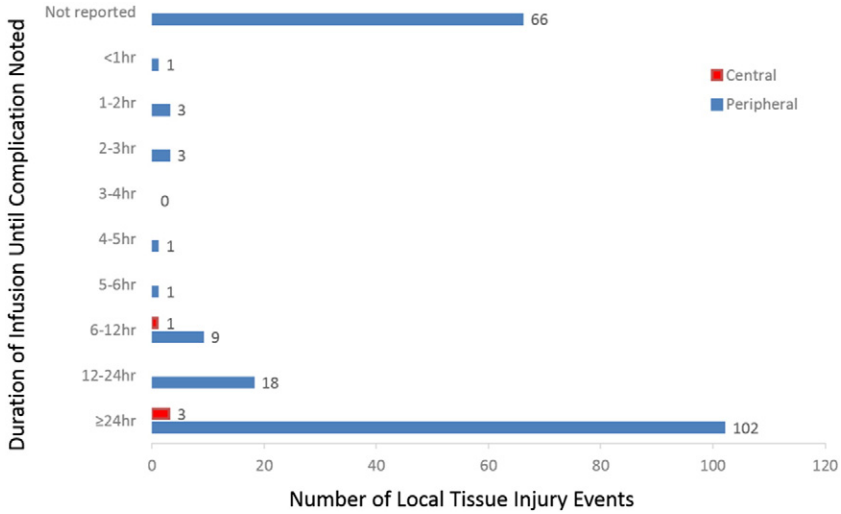

Fig. 2. Duration of infusion of peripherally and centrally administered vasopressors, in hours, for events where local tissue injury occurred.

the epidermis; (*h*) ulcer—lesion on surface of skin or a mucosal surface produced by sloughing of inflammatory necrotic tissue; (*i*) amputation of limb or digit—removal of limb or other appendage or outgrowth of the body; (*j*) distal catheter location—IV catheters placed distal to the antecubital fossa of the upper extremity or the popliteal fossa of the lower extremity; (*k*) no long-term sequelae—patient returned to previous level of function without deficits; (*l*) minor disability from pressor event—patient returned to previous level of function, but with minor deficits; (*m*) major disability—patient unable to return to previous level of function because of severe deficits from event; (*n*) mortality contributed from pressor event—patient died, and pressor event was felt to be major contributor causing death; and (*o*) mortality unrelated to pressor event—patient died, and pressor event was felt not to be important contributor in causing death.

3. Results

3.1. Characteristics of study subjects

Our search identified a total of 86 371 references, of which 85 [5–89] met final inclusion criteria (Fig. 1). The κ statistic for agreement between reviewers for the final inclusion of papers based on full references was 0.773. Of the 85 included references, 80 [5–21,23–35,37–64,66,68–88] presented individual data and were made up of case studies and case series, while 5 [22,36,65,67,89] presented aggregate data and included 1 [67] randomized controlled trial and 4 [22,36,65,89] case series. None of these studies directly compared the administration of vasopressors via central or peripheral catheters with rates of tissue ischemia or extravasation. From the 85 included studies, a total of 270 patients with 325 separate events of local tissue injury or vasopressor extravasation arising from IV administration of vasopressors were identified. Overall, individual data were presented on 195 patients, and aggregate data were presented on 75 patients. Of the 85 studies included for review, 29 were written in 14 languages other than English. Demographic and study characteristics of included papers are presented in Table 1.

4. Main results

4.1. Studies on peripheral administration of vasopressors

Of the 325 separate events of local tissue injury or vasopressor extravasation associated with administration of vasopressors, 318 events [6–17,19–27,29–66,68–75,77–89] resulted from peripheral IV administration. Of these 318 events, there were 204 [6–14,16,17,19–21,23–27,29–60,62–64,66,69–75,78,79,81–89] local tissue injury events and 114 events [6,9,11,15,17,19,21,22,25,29,49,50,52,56,61,62,65,68,70,72–74,77,80,83–85,88,89] of extravasation of vasopressor solution. Table 2 presents data on complications that resulted from the administration of vasopressor via peripheral IV. The occurrence of extravasation was recorded independently of other complications and may or may not have been related to other tissue injury.

Of the 204 local tissue injury events, there were 179 skin necrosis events, 5 tissue necrosis events, and 20 gangrene events. Norepinephrine (80.4%), dopamine (9.3%), and vasopressin (6.9%) were most commonly administered in instances of local tissue complications. The location of the peripheral IV through which vasopressor was infused was given in 194 of 204 events. In 174 (85.3%) events, the peripheral catheter through which vasopressor was administered was located in a site distal to the antecubital or popliteal fossae. The average duration of vasopressor infusion before local tissue injury occurred was 55.9 hours ($\pm$68.1), with a median of 24 hours and a range of 0.08 to 528 hours. Fig. 2 provides a graphic representation of the local tissue injury events occurring as a function of the duration of peripheral vasopressor infusion after which local tissue injury was noted. The occurrence of long-term sequelae was reported in 182 of the 204 local tissue injury events. In many of the local tissue injury events, no long-term sequelae (77 [37.7%]) or minor disability (36 [17.6%]) was reported. However, major disability was reported in 9 (4.4%) of these events, and in 4 (2.0%), the complications arising from use of peripheral vasopressors were felt to be a major contributor to mortality.

Of the 114 events of extravasation of vasopressor solution, most (75.4%) did not result in any tissue injury. Norepinephrine (64.9%) and dopamine (22.8%) were most commonly administered in instances of extravasation. The location of the peripheral IV through which vasopressor was infused was provided in 52 of the 114 extravasation events. In most of the reported events (39/52 [75.0%]), the peripheral catheter was located distal to the antecubital or popliteal fossae. The average duration of vasopressor infusion before extravasation occurred was 35.2 hours ($\pm$51.0), with a median of 22 hours and a range of 0.25 to 240 hours. The occurrence of long-term sequelae was reported in 112 of the 114 extravasation events. Most of the patients who experienced extravasation events had no long-term sequelae (90/112 [80.4%]). In 3 (2.7%) of 112 of these events, the patient suffered major disability, and in 1 (0.9%) of 112, the event was felt to be a major contributor to mortality.

4.2. Studies on central administration of vasopressors

Information regarding the occurrence of tissue injury or extravasation resulting from vasopressor administration via CVC is presented in

Table 3
Data for incidents in which administration of vasopressor via CVCs resulted in local tissue injury or extravasation

Data from events	Local tissue injury (n = 4)[a]	Extravasation (n = 3)
Description of reported event (no./100)		
Skin necrosis	3 (75.0)	0 (0.0)
Gangrene	1 (25.0)	0 (0.0)
Tissue necrosis	0 (0.0)	0 (0.0)
Blister	0 (0.0)	0 (0.0)
Ulcer	0 (0.0)	0 (0.0)
No injury	NA	3 (100.0)
Vasopressor (no./100) and dose (reported as range)[b]		
Norepinephrine	1 (25.0), 4 μg/min	2 (66.7), 15-60 μg/min
Vasopressin	1 (25.0), 0.4 U/min	1 (33.3), 0.03 U/min
Dopamine	0 (0.0), NA	0 (0.0), NA
Epinephrine	1 (25.0), 0.38 μg/kg/min	0 (0.0), NA
Terlipressin	1 (25.0), 8 mg/24 h	0 (0.0), NA
Phenylephrine	0 (0.0), NA	0 (0.0), NA
Ephedrine	0 (0.0), NA	0 (0.0), NA
Location of infusion		
Not reported	1 (25.0)	2 (66.7)
Internal jugular	1 (25.0)	0 (0.0)
Subclavian	0 (0.0)	1 (33.3)
PICC	1 (25.0)	0 (0.0)
Femoral	1 (25.0)	0 (0.0)
Intervention provided[b]		
Conservative management[c]	2 (50.0)	0 (0.0)
Amputation	0 (0.0)	0 (0.0)
Stopping vasopressor	0 (0.0)	0 (0.0)
Tissue debridement	2 (50.0)	0 (0.0)
Medication[d]	0 (0.0)	0 (0.0)
Skin graft	1 (25.0)	0 (0.0)
Change/manipulation of insertion site	1 (25.0)	1 (33.3)
Cardiac intervention	0 (0.0)	0 (0.0)
Dialysis	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)
Not reported	2 (50.0)	2 (66.7)
Long-term sequelae		
Mortality—unrelated to pressor event	1 (25.0)	0 (0.0)
Major disability from pressor event	0 (0.0)	0 (0.0)
Minor disability from pressor event	2 (50.0)	0 (0.0)
Mortality—pressor event contributed	0 (0.0)	0 (0.0)
No long-term sequelae	1 (25.0)	1 (33.3)
Not reported	0 (0.0)	2 (66.7)

NA indicates not applicable; NR, not reported; PICC, peripherally inserted central catheter.
[a] Event attributed to vasopressor occurring within close proximity (ie, the same extremity) to the infusion site.
[b] Sum may be greater than 100% as patients may have received multiple vasopressors or interventions.
[c] Conservative management included skin compresses, observation, and dressings of any kind.
[d] Administered to reverse the effects of vasopressor.

Table 3. Of the 325 events of tissue injury or vasopressor extravasation that occurred with vasopressor administration, 7 events resulted from administration via CVCs. These included 4 [5,16,18,76] local tissue injury events and 3 [28,67] extravasation of vasopressor solution events. Of the 4 local tissue injury events reported, 3 were of skin necrosis and 1 of gangrene. Norepinephrine, vasopressin, terlipressin, and epinephrine were each administered once in these 4 events. The location of the CVC was reported in 3 of these 4 local tissue injury events (1 in internal jugular vein, 1 in femoral vein, and 1 via peripherally inserted catheter). The average duration of vasopressor infusion until local tissue injury occurred was 55.5 hours (±47.3) with a median of 48 hours and a range of 6 to 120 hours. No long-term sequelae were reported in 1 (25%) of 4 of these events, and minor sequelae resulted in 2 (50.0%) of 4 of these events. In 1 (25%) of 4 of these events, local tissue injury was felt to contribute to mortality.

Information regarding the 3 events of extravasation of vasopressor solution can be found in Table 3. In all events, no information was given regarding the duration of infusion.

A condensed summary of the results is presented in Fig. 3.

5. Limitations

As with any review, our study is limited by reporting bias. Although we have collected published data regarding complications resulting from peripheral and central vasopressor infusion, it is likely some relevant events were not published, which weakens the conclusions of this review. As we searched only for events where complications resulted from administration of vasopressor, we cannot make conclusions comparing the frequency of these complications with instances where no complication occurred.

Another major limitation of this study is the inconsistency of reporting among published reports. Critical information necessary for analyzing the outcomes of interest for this study was often missing from published reports. Very few papers included all information we consider essential to perform an analysis of complications from vasopressor infusion—patient age, comorbidities, reason for presenting to medical attention, reason for requiring vasopressor, type of vasopressor used, location of vasopressor infusion, type of catheter used, concentration and dose of infusion, duration of infusion, complication suffered, intervention provided, and long-term sequelae. We recommend any future studies that assess complications from vasopressor administration to include all of these key data elements.

6. Discussion

Administration of vasopressors is a paramount management strategy in hemodynamically unstable patients [90]. Currently, administration of vasopressors via peripheral IVs is considered by some to be unsafe and is often discouraged, mainly due to concern of local tissue injury [2]. For this reason, administration of vasopressors via CVCs is often advocated [1,2]. In our systematic review, we have found only observational reports of complications attributable to vasopressor administration via peripheral IVs or CVCs.

Our search identified 204 local tissue injury events attributable to peripheral administration of vasopressors and 4 local tissue injury events attributable to administration via CVC. In the published reports identified in this review, local tissue injury attributable to peripheral administration tends to occur in distal IV sites following long durations of infusion. The peripheral IV catheter was located distal to the antecubital or popliteal fossae in 85.3% of local complications resulting from peripheral vasopressor administration. In patients suffering local tissue injury from peripheral vasopressor infusion, the average duration of infusion was 55.9 hours (±68.1), with a median time of 24 hours and a range of 0.08 to 528 hours. Most local tissue injuries occurring from peripheral administration occurred after more than 6 hours of vasopressor infusion. Only 1 event [23] was identified where local tissue injury occurred with infusion of vasopressor via peripheral IV for less than 1 hour and involved a 69-year-old woman presenting with septic shock who received an infusion of phenylephrine of unspecified dose via the saphenous vein of the left leg and developed necrotic skin lesions after 5 minutes of infusion.

We were unable to identify any direct comparisons of the complication rates of central and peripheral administration of vasopressors from the literature. A randomized controlled trial conducted by Ricard et al [4] randomized critically ill patients with equal central or peripheral venous access requirement to receive either central or peripheral venous catheters. This study included patients who required doses of epinephrine or norepinephrine as high as 2 mg/h but did not investigate complications related to vasopressor administration. Although this trial reported an increased complication rate in patients receiving peripheral

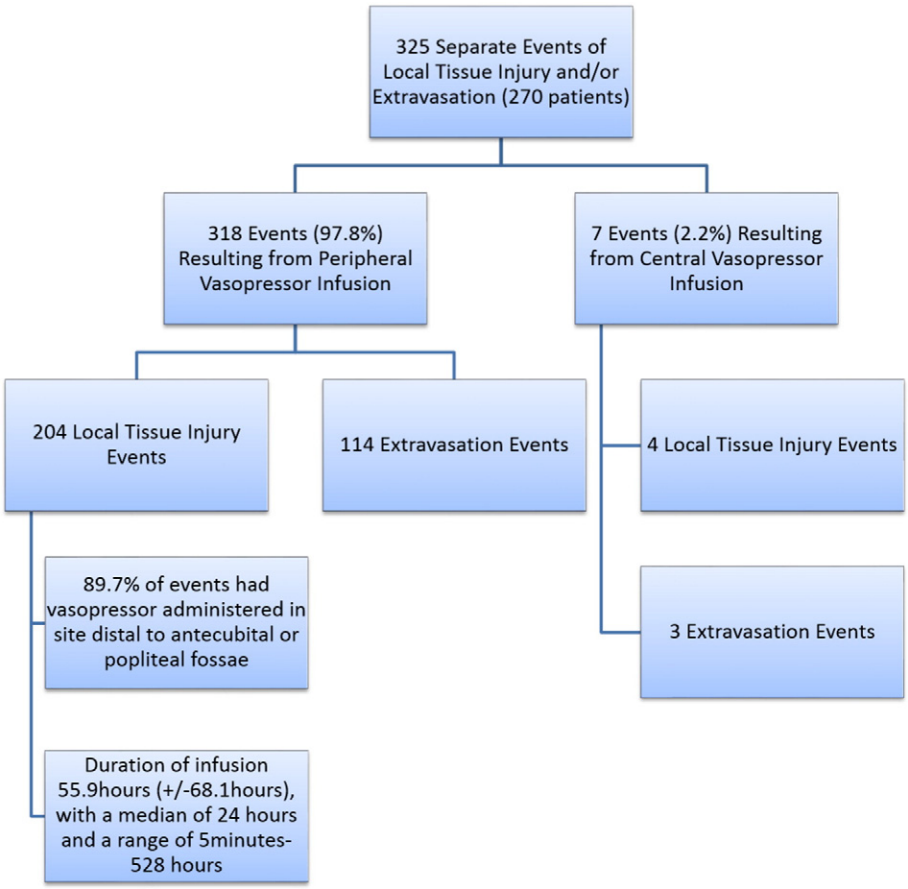

Fig. 3. Flowchart presenting condensed summary of results.

catheters, it did not provide details on location of the catheter, the nature of the vasopressor infused, or the duration of infusion.

The importance of duration and location of vasopressor infusion suggests the development of tissue injury is likely related to both the duration and degree of tissue hypoperfusion following vasopressor administration. Vasopressor medications are known to cause vasoconstriction that can lead to tissue hypoperfusion due to reduced blood delivery. We speculate that with peripheral administration of vasopressors, there is likely increased vasoconstriction local to the site of administration, leading to local tissue hypoperfusion. Tissue hypoperfusion, with time, may result in local tissue injury. The findings from this review indicate that the duration of hypoperfusion required to cause injury is in the range of 0.08 to 528 hours and most commonly after 12 to 24 hours. This effect may be further exacerbated in already hypoperfused areas (such as distal extremities) in states of shock, making it more likely infusion in these areas will cause tissue injury.

Because the data from this review are derived principally from case reports and case series, it cannot be said to be representative or typical of clinical practice. As such, no definitive conclusions can be drawn from this review regarding safety of peripheral administration of vasopressors. However, within the published reports identified by this review, peripheral infusion of vasopressors for short duration (ie, less than 2 hours) and in proximal locations (ie, antecubital fossa or external jugular vein) is unlikely to result in tissue injury. Because peripheral IVs can be inserted rapidly and easily in most cases, vasopressor administration via peripheral IVs may reduce the time it takes the medication to reach the patient and consequently the time required to achieve hemodynamic stability. In the context of emergency medicine, strategic use of peripheral vasopressor administration to quickly control and stabilize the patient may facilitate the placement of a CVC.

7. Conclusions

Vasopressor medications are strong vasoconstrictors that can cause tissue hypoperfusion and injury. Published reports of local tissue injury and extravasation from vasopressor infusion via peripheral IVs are mainly case reports, and may not be representative of true practice. However, based on published reports, the occurrence of local tissue injury requires prolonged administration of vasopressors via peripheral IVs. In emergency situations, short-term administration (<2 hours) of vasopressor infusions via proximal, well-placed peripheral IVs is unlikely to cause local tissue injury. This should only be performed as a temporizing measure until central venous access is obtained. Further research is required to clarify the impact of peripheral IV administration of vasopressors on hemodynamic stability in critically ill patients and on their clinical outcomes.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2015.01.014.

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