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ORIGINAL RESEARCH

Safety of peripheral administration of vasopressor medications: A systematic review

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Abstract

Objective: Vasopressor medications have traditionally been administered via central venous catheters (CVCs), primarily due to concerns of peripheral extravasation of vasoconstrictive medications. Recent studies have suggested that vasopressor administration via peripheral intravenous catheters (PiVCs) may be a feasible and safe alternative. This systematic review evaluates the safety of delivering vasopressor medications via PiVCs.

Methods: We performed a systematic review to assess the frequency of complications associated with the delivery of vasopressors via PiVCs. A literature search for prospective and retrospective studies of vasopressor infusions in adults was performed. We included studies of continuous infusions of vasopressor medications (noradrenaline, adrenaline, metaraminol, phenylephrine, dopamine and vasopressin) delivered via a PiVCs that included at least 20 patients. Data on patient factors, cannulation approach, monitoring protocols, vasopressor dosing and dilutions and adverse events were collected and summarised.

Results: Seven studies were identified that fulfilled the inclusion criteria, including 1382 patients. No study fulfilled all of the validity criteria. Noradrenaline was the most commonly administered agent (n = 702 episodes of administration), followed by phenylephrine (n = 546), dopamine (n = 108), metaraminol (n = 74) and vasopressin and adrenaline (<5 patients). Mean duration of infusion was 22 h (95% confidence interval [CI] 8–36 h). Extravasation occurred in 3.4% (95% CI 2.5–4.7%) of patients. There were no reported episodes of tissue necrosis or limb ischaemia. All extravasation events were successfully managed conservatively or with vasodilatory medications.

Conclusions: Reports of the administration of vasopressors via PiVCs, when given for a limited duration, under close observation, suggest that extravasation is uncommon and is unlikely to lead to major complications.

Key findings

- Administration of vasopressors via peripheral intravenous catheters for a limited duration and under close observation is unlikely to cause major complications.
- Extravasation occurred in 3.4% of 1382 patients with no reported incidents of tissue necrosis or limb ischaemia.

Key words: *central venous access, extravasation, infusion, peripheral access, tissue injury, vasopressors.*

Introduction

Intravenous vasopressors have been used to treat shock states since the early 1900s,[1] and remain a mainstay in the management for patients with distributive shock. Due to concerns of potential extravasation and subsequent tissue necrosis, vasopressors have conventionally been delivered via a central venous catheter (CVC).[2]

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Placement of a CVC is not without risk, including vascular injury, pneumothorax, and even death.[3] Safely inserting a CVC in a critically ill patient can be time-consuming, with a majority of emergency physicians surveyed recently reporting that the time required to safely place a CVC was the most significant barrier to placement in the ED.[4] There is a growing recognition that earlier commencement of vasopressors may be associated with reduced mortality in certain patient cohorts and delays related to CVC insertion may hinder the administration of vasopressors.[5,6]

Due to these concerns, there has been growing use of vasopressors via peripheral intravenous catheters (PiVCs), rather than a CVC, when vasopressors are required in a time-critical fashion.[7] Guidelines have recommended the short-term use of vasopressors via peripheral catheters, noting however that there is little robust evidence to support this practice.[8] The only published review article to address the safety of the delivery of vasopressors via PiVCs included only case reports and small case series reporting adverse events.[9] In recent years, more rigorous cohort studies have emerged to describe the frequency of adverse events of peripheral vasopressors,[10,11] though there is no formal systematic evaluation of this topic.

To address this gap in the literature, this systematic review aims to assess the frequency of adverse events associated with the delivery of vasopressors via PiVCs.

Methods

The present study is reported in a manner consistent with the preferred reporting items for systematic reviews and meta-analyses statement.[12]

Literature search

Electronic searches were performed using Medline, Embase, PubMed, Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature and Cochrane databases, between dates of database inception to February 2019 to identify studies that investigated the use of peripheral vasopressors. The search terms ('noradrenaline' OR 'norepinephrine' OR 'adrenaline' OR 'epinephrine' OR 'phenylephrine' OR 'ephedrine' OR 'metaraminol' OR 'vasopressin' OR 'methylene blue') AND ('peripheral infusion' OR 'peripheral cannula' OR 'peripheral administration' OR 'catheterisation, peripheral') were used either as key terms or MeSH headings. All identified records were evaluated by two independent researchers (DHT and CS) according to the inclusion/exclusion criteria. Conflicts were resolved by the senior researcher (AD). References of the included studies were also reviewed for additional relevant studies. To expand the sensitivity of the literature search and data collection, abstracts for three large annual scientific conferences were also searched separately (Society for Academic Emergency Medicine Annual Meeting 1994–2018, Annual Scientific Meeting of the Australasian College for Emergency Medicine 2000–2018, American College of Emergency Physicians Research Forum 2000–2018).

Inclusion/exclusion criteria

Eligible studies for the present systematic review included randomised clinical trials or prospective/retrospective cohort or case series studies that included at least 20 participants, involving patients receiving vasopressor agents via a PiVC as a continuous infusion that reported the incidence of adverse events. Studies with less than 20 participants were excluded as they were considered to likely provide unreliable estimates of the frequency of adverse events. Studies using peripherally inserted central catheters were also excluded as were studies where the patients were not in shock (i.e. laboratory studies), cardiac arrest, use of 'push-dose' vasopressors or intraoperative use of vasopressors. All publications were limited to the English language. Letters, editorials, database registrations and review articles were excluded.

Outcomes of interest

The primary outcome was the occurrence of any adverse events related to the use of peripheral vasopressors, in particular, extravasation, skin necrosis, limb ischaemia, compartment syndrome, infection and any other reported complications that required treatment. Secondary outcomes included details of administration protocols, policies and guidelines regarding the management of the infusion (for example frequency of observation). All data were extracted independently from abstracts, texts, figures and tables, by two independent researchers (DHT and CS) into Microsoft Excel. Discrepancies between the two researchers were resolved by consensus, or by referral to a third team member if consensus could not be reached.

Risk of bias assessment

The risk of bias in the included studies was assessed using a modified schema used for assessing case series, developed by the Institute of Health Economics (Alberta, Canada)[13] (Table S1). This checklist examines the suitability of study objective, design, population, intervention, outcome measure, statistical analysis, appropriateness of results and conclusions and competing interests.

Statistical analysis

Descriptive statistics were calculated for all collected variables. Categorical or continuous variables were aggregated using random-effects meta-analysis of proportions or means, as appropriate. Data are presented as n (%) with 95% confidence intervals (CIs) or mean $\pm$ standard deviation (SD). Data that were reported as median and interquartile ranges were converted into mean $\pm$ SD using the methods of Wan *et al.*[14] All statistical analyses were performed in R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Literature search

The literature search identified 5074 records, of which seven studies fulfilled the inclusion/exclusion criteria.[10,11,15–19]

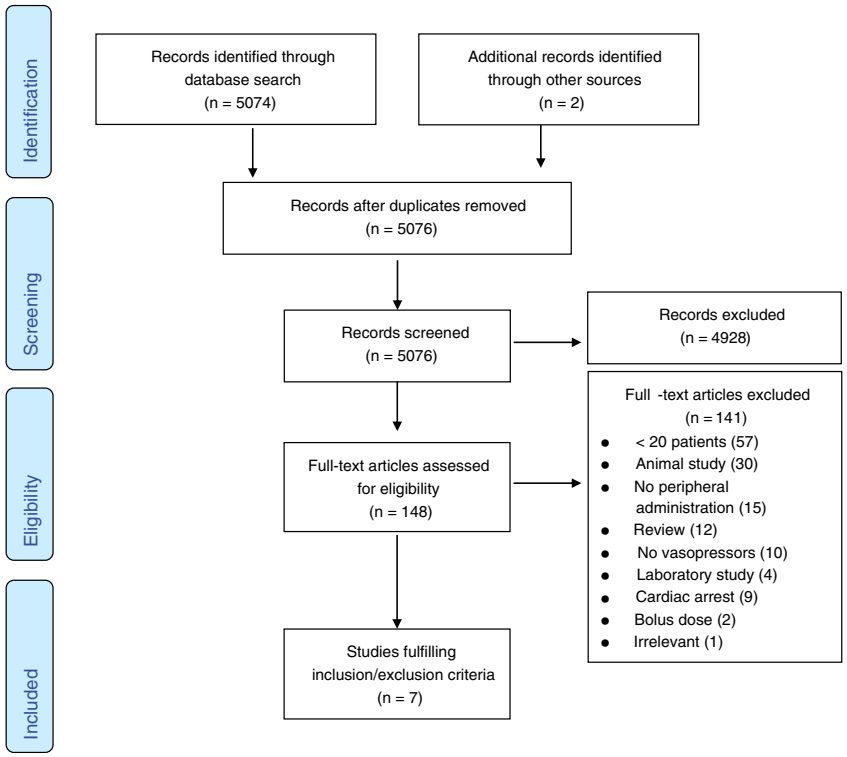

Figure 1. *Preferred reporting items for meta-analysis and systematic reviews (PRISMA) flow chart of literature search.*

The reasons for exclusion are shown in Figure 1. Agreement on the inclusion of studies was reached without the need for a third reviewer. All included studies were case series studies without comparison groups, published between 2009 and 2018, with a total of 1382 patients and 1436 episodes of peripheral vasopressor administration.

Risk of bias assessment

Studies were rated between 6 and 12 points, out of a total of 13 points, as shown in Table 1. Table S2 shows the detail of the risk of bias scoring. Points were lost as studies were not multi-centre (six studies), unclear regarding consecutiveness of patient inclusion (five studies), lack of reporting of competing interests (three studies), and poor description of patient characteristics, interventions, outcome measures and/or adverse events (two studies). Scarcity of primary outcomes precluded sub-group analysis of higher-quality studies.

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. All but two studies were conducted in either in the USA or UK.[11,17] Most were in the intensive care/high dependency unit environment, with one study conducted in the pre-hospital retrieval setting[17] and another in the ED.[11] All but three studies were retrospective in nature.[10,11,19] There was a range of indications for vasopressor support, including sepsis, hemodynamic augmentation post-neurosurgery and cardiogenic shock. The mean age of the patients included in the reports was 69 years (95% CI 65–73), with males representing 52% of patients (95% CI 48–56%).

Administration of vasopressors via a peripheral intravenous catheter

Only four of seven studies detailed their protocols for PiVC insertion (Table 2). Most catheters were either 18 or 20G in size. Some centres restricted PiVC insertion only to the antecubital fossa or upper arm. Due to the low event rate, the association between complications and PiVC site or size could not be reliably assessed. Only two studies provided detailed protocols regarding management of extravasation, which included subcutaneous injection of phentolamine or terbutaline, with topical nitroglycerin paste. The details of the vasopressor agents used are shown in Table 3. Noradrenaline was the most frequently administered agent (three studies, n = 702 episodes of administration), followed by phenylephrine (four studies, n = 546), dopamine (two studies, n = 108), metaraminol (two studies, n = 74), vasopressin (one study, n = 4) and adrenaline (one study, n = 2). Median infusion durations ranged between 4.5 and 60.5 h (mean 22 h; 95% CI 8–36 h).

Adverse events

There were 35 episodes of vasopressor extravasation (3.4%, 95% CI 2.5–4.6%) reported, none of which resulted in limb ischaemia or tissue necrosis (Table 3). One study administered a local injection of phentolamine and application of nitroglycerin paste in all cases of extravasation per protocol, while all other studies did not need to provide active treatment to cases of extravasation. Complications apart from extravasation were reported by only two studies, including one case of localised swelling, pain and erythema,[16] and another study which had one case of thrombophlebitis and two cases of localised erythema due to extravasation.[11] There were no reported incidences of compartment syndrome or any requirement for surgical intervention.

Discussion

We conducted a systematic review to assess the frequency of adverse events associated with the delivery of vasopressors via PiVCs. We found a small number of observational studies including more than 1300 patients. Overall the quality of the included studies was mixed with variable levels

TABLE 1. *Characteristics of included studies*

Lead author	Year published	Institution	Country	Study period	Study type	Population	Indication	Quality	Patients	Age	Males
Cardenas-Garcia[10]	2015	Long Island Jewish Medical Center, New York	USA	2012–2014	Prospective/ retrospective	General ICU	NR	12/13	734	72 ± 15	398 (53%)
Datar[15]	2018	Wake Forest University Health Sciences, North Carolina	USA	2012–2015	Retrospective	Neuro ICU	Haemodynamic augmentation (48%), post-op hypotension (6%); other hypotension (22%), sepsis (6%)	12/13	277	65 ± 15	129 (47%)
Delgado[16]	2016	University of Utah, Utah	USA	2013–2014	Retrospective	Neuro ICU	NR	10/13	20	57 ± 19†	11 (55%)
Joynes[17]	2016	Multiple Australian rural hospitals	Australia	2011–2014	Multi-centre, retrospective	Rural hospitals/ retrieval	Sepsis (100%)	7/13	27	NR	NR
Lewis[18]	2017	NYU Langone Medical Center, New York	USA	2015–2016	Retrospective	General ICU	Sepsis (73%), cardiogenic shock (14%), stroke/ neurological (7%), other (6%)	11/13	202	74 ± 14†	107 (53%)
Makowski[19]	2010	Medway Foundation Trust, Gillingham	UK	2008–2009	Retrospective, abstract	Surgical HDU	Sepsis (34%), neuraxial opioids (28%), haemorrhage (17%), spinal (7%), cardiogenic shock (6%), dehydration (6%), amiodarone infusion (2%)	5/13	47	73 ± 13†	22 (47%)
Medlej[11]	2018	American University of Beirut Medical Center, Beirut	Lebanon	2013–2015	Prospective	ED	Sepsis (84%), cardiogenic shock (11%), hypovolaemic shock (5%)	10/13	55	70	34 (62%)

†Data converted from median/interquartile. HDU, high dependency unit; ICU, intensive care unit; NR, not reported.

TABLE 2. *Summary of peripheral intravenous catheter (PiVC) insertion and monitoring protocols*

	PiVC size				PiVC insertion site					
Study	16G	18G	20G	22G	Hand	Wrist/ forearm	ACF	Upper arm	Frequency of observations	Management of extravasation
Cardenas-Garcia[10]	0	192 (25%)	590 (75%)	1 (<1%)	Prohibited	Prohibited	Prohibited	734 (100%)	Q2hr aspirates	S/C phentolamine + nitroglycerin paste
Datar[15]†	13 (5%)	98 (35%)	113 (41%)	5 (2%)	87 (32%)		139 (50%)		NR	NR
Delgado[16]	NR	20 (95%)	1 (5%, prohibited)	Prohibited	Prohibited	Prohibited	20 (100%)		Q1hr site inspection	NR
Joynes[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lewis[18]‡	NR	46 (23%)	149 (74%)	103 (51%)	81 (40%)	145 (72%)	109 (54%)	NR	Q1hr site inspection, q2shift aspirate	i.v. + s.c. terbutaline, nitroglycerin paste
Makowski[19]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Medlej[11]	6 (11%)	20 (36%)	28 (51%)	1 (2%)	20 (36%)	10 (18%)	22 (40%)	1 (2%)	NR	NR

†48 records had incomplete data. ‡Study reported data from multiple PiVCs per patient. ACF, antecubital fossa; i.v., intravenous; NR, not reported; s.c., subcutaneous.

TABLE 3. *Vasopressor administration protocols*†

	Number of infusions	Dilution	Effective dose/mL	Peak dose	Duration (h)	Extravasation
Noradrenaline						
Cardenas-Garcia[10]	506	8–16 mg in 250 mL N/S	32–64 μg/mL	0.70 ± 0.23 μg/kg/min	49 ± 22	16 (2.3%)
Lewis[18]	146	4 mg in 250 mL N/S	16 μg/mL	0.13 μg/kg/ml	11.2 ± 15‡	4 (2.7%)
Medlej[11]	50	8 mg in 250 mL D5W	32 μg/mL	30 μg/min	16.9 ± 18.9‡	2 (4.0%)
Metaraminol						
Joynes[17]	27	NR	NR	NR	NR	NR
Makowski[19]	47	NR	NR	NR	NR	NR
Phenylephrine						
Cardenas-Garcia[10]	176	80–160 mg in 500 mL N/S	160–320 μg/mL			0
Datar[15]	277	NR	120 μg/mL	1.04 ± 0.74 μg/kg/min	19 ± 18	9 (3.2%)
Delgado[16]	20	NR	40 μg/mL	2.0 μg/kg/min	21 ± 13‡	0
Lewis[18]	73	100 mg in 250 mL N/S	400 μg/mL	>150 μg/kg/min	19.7 ± 24.2‡	4 (5.5%)
Dopamine						
Cardenas-Garcia[10]	101	400–800 mg in 250 mL D5W	1.6–3.2 mg/mL	NR	NR	3
Lewis[18]	2	200 mg in 250 mL D5W	0.8 mg/mL	9 μg/kg/min	23.5	0
Medlej[11]	3	NR	NR	15 μg/kg/min	60.5 ± 98.5‡	0
Vasopressin						
Lewis[18]	4	0.16 units/mL	0.16 units/mL	0.06 units/min	13.2 ± 19	0
Adrenaline						
Lewis[18]	2	4 mg in 250 mL N/S	16 μg/mL	0.06 μg/kg/min	4.5	0
Overall	**1436**				22 (8–36)	38 events (3.4%; 95% CI 2.5–4.7%)

†Patients may have received concurrent infusions. ‡Data converted from median/interquartile. Overall results presented as *n* (%) or mean (95% confidence interval), using randomised-effects meta-analysis of proportions or means. D5W, 5% dextrose; N/S, normal saline; NR, not reported.

of information provided regarding adverse events and processes of care. These observational studies reported the use of a variety of vasopressor agents, at differing concentrations and durations of administration, as well as varying details regarding the frequency of and types of observation required to ensure the safety of the infusions. The major finding of this systematic review is that extravasation events were uncommon, with no reports of significant tissue necrosis or distal ischaemia. The present systematic review demonstrates that based on the limited available evidence, the administration of vasopressors via a peripheral venous catheter is associated with a low rate of complications, particularly if the duration of administration is limited.

Relationship to other literature

The primary concern of administrating vasopressors peripherally remains extravasation of highly vasoconstrictive agents in the peripheral tissue, with numerous historic reports of tissue necrosis and limb ischaemia. These reports were collated in a previous review, which included only case reports and a small case series of patients with complications.[9] Due to the methods used in this prior review, the frequency that these complications occurred could not be ascertained, and those results need to be interpreted with the clear patient selection bias in mind. The present review included all cases of peripheral vasopressor administration, rather than just those who have had complications, and therefore provides a more accurate gauge of the true frequency of adverse events.

Few studies have directly assessed the relative safety of vasopressor delivery via a PiVC compared to a CVC. In a single-centre randomised clinical trial, 135 participants who were admitted to an intensive care unit and judged to require venous access were randomised to receive either a CVC or a PiVC.[20] The most common reason for inclusion in the study was the need for vasopressors, which was present in 70% of the included participants. There were 133 major complications that occurred in 135 patients randomised to initially receive a peripheral catheter compared to 87 in 128 patients who had a CVC, although the former also included 56 cases of difficulties in peripheral catheter insertion as a major complication.

Strengths and weaknesses

This systematic review used robust methods and predefined inclusion criteria to provide an estimate of the incidence of adverse events associated with the use of vasopressors via a peripheral catheter. The extensive search strategy ensures a low chance of missing studies.

There are also several limitations. First, there is a relative paucity of studies examining the use of peripheral vasopressors. Those that have been published are of mixed methodological quality. Second, the duration of vasopressor use in the included studies is relatively limited, with all but two studies receiving less than 24 h of infusion. We are unable to draw conclusion regarding the safety of more prolonged infusions. Third, the variations in the dose and concentrations of vasopressors, variation in the sites and gauge size of peripheral catheters, and monitoring protocols precludes definitive recommendations regarding what constitutes safe medical practice. There are some detailed protocols available for clinicians who were considering implementing this clinical practice.[18]

Implications for clinicians

With the caveat that the studies included in this review were not of a universally high quality, the relatively low incidence of reported complications associated with the delivery of vasopressor infusions via PiVC is reassuring for clinicians. The time taken to ensure the safe placement of a CVC can be a significant barrier to clinicians undertaking this procedure.[4] Given that a delay in the administration of vasopressors has been associated with an increase in mortality in certain clinical scenarios,[5,6] the findings of this review will provide clinicians confidence in commencing a vasopressor infusion via a peripheral catheter while the resources for the safe placement of a CVC can be mobilised. For those clinicians who undertake this mode of delivery of vasopressors, it should be stressed that the low rate of reported adverse events may be due to the mandated rigorous clinical monitoring and protocols for managing extravasation, and that these aspects of the intervention should be carefully considered at an institutional level.

Implications for further research

There is clearly a need for further research in this area. While this study has shown a low incidence of reported adverse events, direct comparisons between a strategy of commencing vasopressors via a PiVC compared to a CVC with respect to their effect on processes of care and clinically important outcomes are clearly needed. Future studies also need to thoroughly report all adverse events, including extravasation, haematoma, phlebitis, localised erythema, limb ischaemia, tissue necrosis and compartment syndrome, as well as dosing and dilutions, site and gauge of cannulation, and nursing and monitoring protocols.

Conclusion

This systematic review found in a small number of studies of variable quality that the administration of vasopressor infusions for a limited duration via a PiVC is associated with a low incidence of reported adverse events, providing that systematic efforts are undertaken to ensure regular monitoring and protocols are instituted to deal with extravasation events. Future research is required to determine the relative effectiveness of this strategy.

Competing interests

GK and SPJM are section editors for *Emergency Medicine Australasia*.

Author contributions

DHT and AD made substantial contributions to the conception and

design of the study. DHT, CS, GK, SPJM, SP, AAU and AD made substantial contributions in the acquisition, analysis and interpretation of the data. All authors were involved in drafting the manuscript and revising it critically. All authors approved the final manuscript and thereby agree to be accountable for all aspects of the work.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1. Modified quality assessment schema.
Table S2. Quality assessment for included studies. Each study (rows) is scored 1 if the relevant quality criterion (columns) is met. Explanations of each criteria is provided in Table S1.