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Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis

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ABSTRACT

Background: Vasopressors are mainstay treatment for patients in shock and are usually infused through central venous catheters (CVCs). However, CVCs are associated with risk of infection or delay from the needs of confirmation of placement. Infusing vasopressor through peripheral venous catheter (PIVs) could be an alternative in the Emergency Departments (ED) but data regarding complications is inconclusive. We performed a random-effects meta-analysis to assess literature involving prevalence of complications from infusing vasopressors via PIVs.

Methods: We searched PubMed, EMBASE and Scopus databases from beginnings to 02/02/2020 to identify relevant randomized control trials, cohort, case-control studies. We excluded case reports. Authors assessed studies' quality with Newcastle-Ottawa Scale and Cochrane Risk of Bias tool. Kappa score was used to assess interrater agreement. Outcome was complications as direct results from infusing vasopressors through PIVs.

Results: We identified 325 articles and included 9 studies after reviewing 16 full text articles. Our analysis included 1835 patients whose mean age was 63 (Standard Deviation 12) years and 48% was female. There were 122 (7%) complications, of which 117 (96%) were minor. The meta-analysis with random effects showed the pooled prevalence of complications as 0.086 (95%CI 0.031–0.21). Studies reporting infusion safety guidelines had significantly lower prevalence of complications (0.029, 95%CI 0.018–0.045), compared to those not reporting a safety guideline (0.12, 95%CI 0.038–0.30, $p = 0.024$).

Conclusion: There was low prevalence of complications as a direct result from infusing vasopressors through PIVs. Studies with safety guidelines were associated with significantly lower prevalence of complications. Further studies are needed to confirm our observations.

1. Introduction

Vasopressors such as norepinephrine, phenylephrine, epinephrine, are usually administered in the emergency departments (ED) or intensive care unit (ICU) to treat critically ill patients in shock status. Vasopressors are commonly given through a central venous catheter (CVC) due to its reported lower risk of extravasation [1] that may cause skin necrosis [2].

Early administration of vasopressors in patients with septic shock was associated with improved outcomes [3,4]. However, the process of inserting CVCs may take longer than placing peripheral venous catheters (PIV). Inserting CVCs requires the deployment of sterile barriers and placement confirmations if the CVCs are placed in subclavian or internal jugular veins and this process may be prolonged. In a meta-analysis by Ablordeppey et al. [5], the average time interval from placement of above-diaphragm catheter to completion of chest radiography was 64 min, while the average time intervals from catheter placements to radiologists' interpretations were 143 min.

Delayed initiation of vasopressor was associated with increased mortality [3,4,19]. Each hour of delay was associated with 2% increase

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of in-hospital mortality in a multicenter study involving 8670 patients [19]. Besides infusing vasopressors, central venous catheters are usually used for rapid infusion of crystalloids, blood products, but they are associated with certain risks such as mechanical complications, and catheter-associated blood stream infection [20]. A meta-analysis showed significant delay of time interval between catheter placement to completion or radiologists' interpretations of chest radiograph [5]. The meta-analysis by Ablordeppey et al. [5] also showed that using point-of-care ultrasound could reduce the wait time. However, a survey study suggested that ED clinicians still do not frequently use point-of-care ultrasound for confirmation of central venous catheters [22]. This long wait time would mean significant delay before vasopressors can be infused through central venous catheters, while using peripheral venous catheters were associated with significant shorter intervals to initiation of vasopressor [21].

Information about complications caused by vasopressors infusing through peripheral venous catheters was inconclusive [6-8]. Since inserting central venous catheters in critically ill patients in the ED may be associated with significant delay [5] of treatment, which may result in poor outcomes [3,4], infusing vasopressors through peripheral venous catheters potentially provides an effective alternative for time-sensitive patient care in EDs and ICUs. We performed a systematic review and meta-analysis to assess current relevant literature about the prevalence of complications of vasopressor infusions via peripheral venous catheters.

2. Methods

2.1. Search strategy and selection criteria

We conducted the study in accordance with the 2015 Preferred Reporting Items for Systemic Review and Meta-Analyses statement (PRISMA) [9]. We searched PubMed, MEDLINE (OVID), EMBASE and Scopus databases from their beginning up to February 2nd, 2020.

We included prospective randomized control trials, quasi-randomized control trials, observational prospective or retrospective studies. We included studies of adult patients (age 18 years or greater) and studies reporting any complications as direct result from infusion of vasopressors through peripheral venous catheters. We excluded case reports as they represented publication bias and not reporting the true incidence of complications. We also excluded non-English language studies, non-full text studies including conference abstracts. References of included studies for full text screening were also searched for possible eligible studies. We did not contact authors for more data.

Each title and abstract were reviewed by 2 investigators before being included in full text reviews. Each title and abstract needed to have 2 agreements prior to be included for full text reviews. A third investigator served as an arbitrator when there were disagreements. We applied the same process for full text reviews to include articles in the final inclusion list. Disagreements between investigators were adjudicated by discussions between the investigators and the principal investigator.

2.2. Search terms

PubMED and Medline:

"Infusions, Intravenous"[Mesh] OR "Catheterization, Peripheral"[Mesh]) AND "Vasoconstrictor Agents"[Mesh].

EMBASE, and Scopus:

(vasoactive AND agent OR vasopressor) AND ((peripheral AND vein OR peripheral) AND intravenous AND access OR peripheral AND IV)

2.3. Outcome measures

Our primary outcome was any complications as a direct result peripheral infusion of vasopressors at the longest time of follow up in the studies. The included vasopressors in this study are norepinephrine (noraderanaline), epinephrine (adrenaline), phenylephrine, vasopressin, dopamine, terlipressin, ephedrine. Complications were categorized as minor adverse events (extravasation, infiltrations, cellulitis, thrombophlebitis), major adverse events (ischemic limb, necrosis of tissue, venous thrombosis), as reported in previous studies [1,6]. Secondary outcome was any treatment for complications (amputation, debridement, cold compression, hot compression, pain medication, observation, local infiltration of phentolamine).

2.4. Quality assessment / heterogeneity

Two investigators analyzed each included study for study quality. Disagreements were resolved by discussion between the investigators and adjudication by a third investigator. We analyzed qualities of observational cohort studies using the Newcastle-Ottawa Scale [10] and randomized control trials using the Cochrane Risk of Bias tool [11]. We used weighted Kappa scores to assess interrater agreements. A Kappa score ≤ 0.2 was considered a poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as good and 0.81–1.00 as very good agreement. Heterogeneity was assessed by calculating I-square statistic which provides the percentage of total variance as difference in effect size across studies. We also measured the Q-statistic, which provides a test for the null hypothesis that all studies in the analysis would share a common effect size.

2.5. Data extraction

We used a standardized Excel spreadsheet (Microsoft Corp, Redmond, Washington, USA) to collect data. We collected the following data: author, year of publication, study design, sample size, age, gender, number of patients receiving vasopressor types and dosage of vasopressors, length of vasopressor infusion, time intervals from infusion to adverse events, if any. To assess quality of data extraction, we again used Kappa score to assess interrater agreements based on type of vasopressor, size of peripheral venous catheters, rate of vasopressor infusion.

2.6. Statistical analysis

We used random-effect models to evaluate the prevalence of complications among patients who received vasopressor through peripheral venous catheters. Any 2 studies reporting similar outcomes would be included in the meta-analysis. Additionally, we performed subgroup analyses to identify potential sources of heterogeneity. These subgroup analyses would also compare the prevalence of complications among subgroups. Based on available information from the studies, we defined the moderator variables for subgroups as: study design (prospective vs retrospective), publication year, clinical settings (ED vs ICU), disease states (mixed shocked state vs. spinal shock vs cardiac, etc.), study sample size, presence of safety guidelines as explicitly reported by authors, etc. Appendix 2 contains the full list of moderator variables for each study. We a priori defined a study reporting the use of safety guidelines as a study that explicitly reported the authors' institutional guidelines to ensure safe initiation of vasopressor via peripheral venous catheters. Based on Cardenas-Garcia et al.'s previous report, we defined the safety guideline as containing directions about catheters' sizes, location of catheters, nursing assessment for extravasation, treatment after complications etc.

We performed meta-regressions, using continuous independent variables, as reported by each study, to assess potential factors associated with risk of complications. These continuous independent variables included length of vasopressor infusion (hours), percentages of catheter sizes in each study (22-gauge catheters, 20-gauge catheters or 18-gauge catheters), percentages of catheter locations per studies (forearms vs. hand and wrist). In studies that reported the use of multiple vasopressors, we selected the infusion of length of norepinephrine, which is the first-line treatment for patients with septic shock, in our

meta regression. Knowing whether the length of infusion for norepinephrine would associate with complications would provide more clinically relevant information to clinicians. Prior to dividing continuous variables into groups, we inspected their histograms and divided them into groups according to their frequencies of distributions.

Meta-analysis was performed with the software Comprehensive Meta-Analysis (www.meta-analysis.com; Englewood, New Jersey, USA).

3. Results

3.1. Study selection

Our electronic search identified 325 studies (Appendix 1). After reviewing 16 full text articles, we included 9 studies in our final analysis. Eight of the studies were observational [7,8,12-17]. One study was a randomized control trial [1] and its outcome was not only complications as a direct result from vasopressor infusion medication through peripheral venous catheters, but also comparing mechanical complications from central venous catheters, such as arterial puncture, hematoma. Our search also identified 20 case reports. We excluded 18 of these case reports in the initial screening (Title and Abstract) phase and 2 case reports in the full-text review phase.

The Kappa's score for data extraction was 0.93 (95% CI 0.8–1.0), which demonstrated "very good" interrater agreement.

3.2. Study quality

Table 1A and B described the quality of the studies included in our meta-analysis. All studies were rated as having Moderate quality. The weighted Kappa scores for the Newcastle-Ottawa scale was 0.70 (95% CI 0.4–0.97) which reflected good agreement between authors.

One randomized control trial in our study was rated with 2 domains having Low risk of bias and 3 domains as having some concerns for risk of bias (Table 1B). The weighted Kappa score for the quality of this study was 0.71 (95% CI 0.31–1.0), which also reflected good interrater agreement.

3.3. Summary of studies

Our meta-analysis included a total of 1835 patients who received vasopressors through peripheral venous catheters. Two studies reported initiation of vasopressors in the ED [13,15] while other studies initiated vasopressors in the ICUs. Two studies [7,17] reported the details of their safety guidelines for peripheral infusion of vasopressors (Table 2).

Seven studies [7,8,12,14-17] reported peripheral venous catheters' size (Table 3). The most common size of peripheral venous catheter in our pooled patient population was 20-gauge catheters (56%). Peripheral catheters with sizes of 18-gauge or larger were used in 33% of patients. Seven percent (7%) of catheter was 22-gauge.

Eight studies, except the randomized trial [1], reported types of vasopressors. Norepinephrine was the most commonly used vasopressor (65%), followed by epinephrine (12%) and phenylephrine (12%) (Table 3).

The mean length of infusion with standard deviation (± Standard Deviation) ranged from 9.7 (12) hours to 49 (2) hours, with the pooled mean length of infusion was 25 (12) hours The maximum rate of vasopressors was as high as 0.13 μg/kg/min for norepinephrine or 3.06 μg/kg/min for phenylephrine.

Table 1A
Study Quality Assessment Of Observational Studies Included In the Meta-Analysis Using The Newcastle-Ottawa Scale.

Study (Year)	Newcastle-Ottawa quality assessment scale				
	Selection (4)	Comparability (2)	Outcome (3)	Total	Grade
1997 Dugger	3	0	1	4	Moderate
2006 Putland	3	0	3	6	Moderate
2015 Cardenas-Garcia	3	0	3	6	Moderate
2016 Delgado	3	0	3	6	Moderate
2018 Datar	3	0	2	5	Moderate
2018 Medlej	3	0	2	5	Moderate
2019 Ballieu	3	1	2	6	Moderate
2019 Lewis	3	0	2	5	Moderate

Kappa's score: 0.70 (95% CI 0.4–0.97).

3.4. Primary outcome: any complications

There was only one randomized control trial, so we did not perform meta-analysis to assess the odds of developing adverse events from infusing vasopressors through peripheral venous catheters compared to central venous catheters, as there were not enough studies. We performed a random-effects meta-analysis of proportion to assess the prevalence of any complications in our pooled patient population.

There was a total of 122 (7%) adverse events, including 117 (96%) minor events and 5 (4%) major events (Table 3) among the pooled patient population. Results from meta-analysis of proportion using random effects showed that the proportion of all complications in the pooled patient population was 0.086 (95% Confidence Interval [CI] 0.031–0.21) (Fig. 1). The Q-statistic was 190 with 8 degrees of freedom, the p-value was <0.001, which suggested that the true effect sizes were different across the studies in our meta-analysis. The I-square statistic was 96%, which suggested that 96% of variance in the observed effects was due to variance in true effects. Five of the studies [1,8,13-15,17] reported that no treatment was necessary for adverse events occurring during their study periods while 2 studies used phentolamine [7,12], one study reported heat application [16].

The Prediction Interval (Fig. 1) demonstrated that the mean effect size for any complications 122 (7%) was 0.086 (95% CI 0.02–0.81). This Prediction Interval suggested that 95% of comparable studies would report prevalence of complications from 2% to 81%. As a result, some studies will report small prevalence of complications while other studies would report rather large number of complications.

The most common type of complications was infiltration (72%), erythema was listed as second common adverse events (21%). There were 5 (4%) major adverse events (peripheral venous thrombosis). Most studies reported no treatment for their patients' complications.

3.5. Subgroup analyses

We used subgroup analyses to identify potential sources of heterogeneity and to compare the prevalence of complications from studies in different settings (Table 4A).

Subgroups containing studies that were published between 2016 and 2020 ($I^2 = 0$), studies having more than 250 patients ($I^2 = 0$), ED settings ($I^2 = 0$) or studies involving only patients with neurogenic shock ($I^2 = 33\%$) were associated with less heterogeneity (Table 4A). Similarly, studies that explicitly reported safety guidelines were also associated with lower heterogeneity ($I^2 = 28\%$). In contrast, both subgroups containing either retrospective or prospective studies were associated with high heterogeneity. Studies about mixed types of shock ($I^2 = 97\%$) were associated with high heterogeneity, likely because heterogenous patient population. We did not assess heterogeneity in patients with asthma or cardiogenic shock because there was one study in each subgroup.

In our subgroup analyses, studies that were published between 2016 and 2020 (pooled rate 5%, 95% CI 1%–20%, Prediction Interval 1%–29%), studies with >250 patients (pooled rate 3%, 95% CI 0.4%–17%) and studies reporting safety guidelines (pooled rate 3%, 95% CI 2%–5%) reported

Table 1B
Study Quality Assessment of Randomized Trial Using the Cochrane Collaboration's Risk of Bias Tool 2.

Study (year)	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result
2013 Ricard	Low	Some Concerns	Low	Some Concerns	Some Concerns

Kappa's score 0.71 (95% CI 0.31–1.0.)

significantly lower rate of complications when compared to their respective subgroups (Table 4A).

3.6. Meta-regressions to assess factors associated with risk of complications (Table 4B)

We performed meta-regressions to assess correlation between independent variables and risk of complications from infusing vasopressors via peripheral venous catheters. In multivariable meta-regression containing the percentages of catheter sizes, higher percentages of patients receiving vasopressors via 18-gauge catheters (Correlation Coefficient [corr. Coeff. -5.6, *p*-value = 0.02) and 20-gauge catheters (corr. Coeff. -7.3, p-value = 0.01) were negatively associated with the prevalence of complications. In other words, catheters' sizes of 20-gauge or larger would be associated with lower rates of complications. Multivariable meta-regression using catheter location or univariate meta-regression using length of infusion (in hours) suggested that catheter locations and infusion length were not correlated with higher rates of complications.

4. Discussion

Our meta-analysis of prevalence of complications as a direct result from infusing vasopressors through peripheral venous catheters showed that the pooled prevalence of any complications in our patient population was low. As a result, we demonstrated evidence that infusing vasopressors through peripheral venous catheters is a safe alternative, regardless of the clinical settings where it was infused in the emergency departments or intensive care units.

We included in our meta-analysis one randomized control trial [1] which compared the complications between central venous catheters and peripheral venous catheters. As a result, the authors included many outcome measures, such as arterial puncture, hematoma, pneumothorax, etc. that were not associated with peripheral venous catheters. Furthermore, Ricard et al. [1] also considered difficulty with insertion as a complication, which contributed significantly toward the overall number of complications from peripheral venous catheters. As a result, this study reported that peripheral venous catheters were associated with higher rates of complications than central venous catheters. We did not consider these complications, such as difficulties of insertion, hematoma, pneumothorax, etc., as a direct result from infusing vasopressors through peripheral venous catheters and did not include them as complications in our study.

Our meta-analysis revealed a trend toward significantly lower prevalence of complications in studies that were recently published between 2016 and 2020. The Precision Interval for this subgroup of studies was also narrower than other subgroups, despite the facts that the study characteristics of this subgroup were similar to the entire group: variety of study designs, clinical settings, sample size, disease states. Although further studies are needed to confirm our observations, we hypothesized that, clinicians in more recent years have been able to use available information from earlier publications to improve patients' safety in their clinical practice. For example, observation from previous study in 2015 [6] suggested that infusing vasopressor less than 24 h would be associated with lower risk of complications. Based on reported data from studies within the 2016–2020 subgroup, we observed that vasopressors were infused for less than 24 h (Table 3). Additionally, with the more widespread use of point -of -care ultrasound -guided-peripheral -intravenous insertion (ultrasound-guided IV access) in recent years [18], clinicians should consider ultrasound more frequently for peripheral catheter insertion, which could be associated with lower prevalence of complications from vasopressor infusion. Cardenas-Garcia et al. reported that the authors' institution mandated the use of ultrasound to establish peripheral access before infusing vasopressors. This study also reported low rate of complications [7] among their patients. Furthermore, according to this subgroup's result, any future studies with characteristics resembling patients from this subgroup would have a prevalence of complications from as low as 1% and up to 29%.

Being able to identify patients' demographic or clinical factors that may predict higher risks of complications from infusing vasopressors via peripheral venous catheters would be important for clinicians. None of the included studies in our meta-analysis performed any statistical analyses to measure association between patients' characteristics and risks of complications, while taking in account various patients' demographic or clinical factors. A narrative review by Reynolds et al. suggested certain risk factors for extravasation of vasopressor when

Table 2
Characteristics of included studies.

Author, year	Design	Clinical setting	Total patients	Patients with PIV vasopressor N (%)	Any adverse events N (%)	Presence of safety guidelines
1997 Dugger	Retrospective	ICU	25	25 (100)	17 (100)	No
2006 Putland	Retrospective	ED	220	220 (100)	11 (5)	No
2013 Ricard	Prospective/RCT	ICU	263	128 (49)	45 (35)	No
2015 Cardenas-Garcia [a]	Prospective	ICU	953	783 (82)	19 (2)	Yes
2016 Delgado	Retrospective	ICU	20	20 (100)	1 (5)	No
2018 Datar	Retrospective	ICU	277	277 (100)	9 (3)	No
2018 Medlej	Prospective	ED	55	55 (100)	3 (5)	No
2019 Ballieu	Retrospective	ICU	125	125 (100)	9 (7)	No
2019 Lewis [b]	Retrospective	ICU	202	202 (100)	8 (4)	Yes

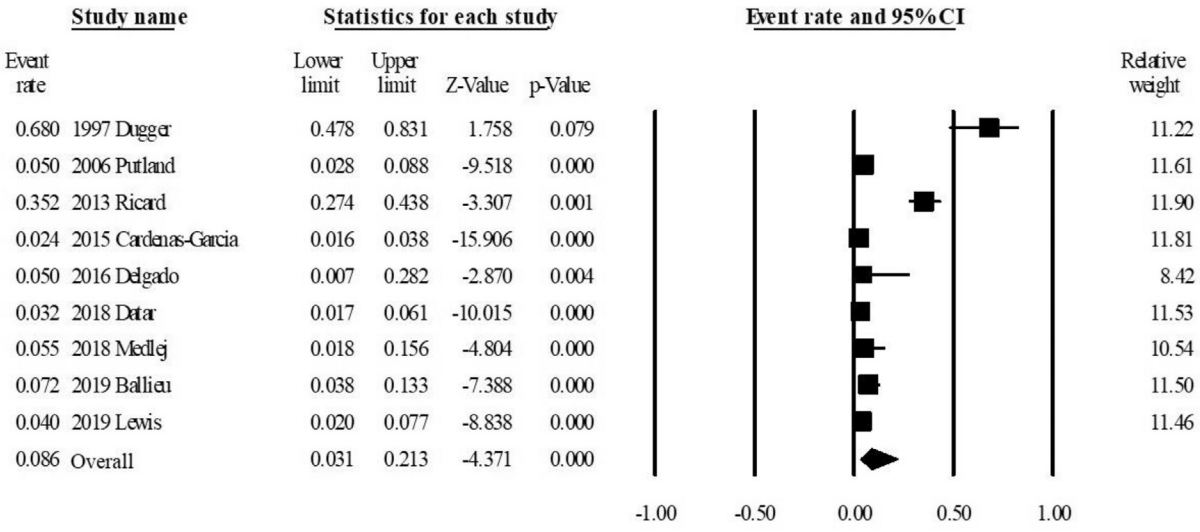
[a] safety guidelines mandated size of veins (>4 mm as measured by point of care ultrasound), mode of insertion (guided by point of care ultrasound), size of catheters (18-gauge or 20-gauge), locations of catheter (upper arms only), frequent assessment of catheters' functions every 2 h, duration of infusion (maximum of 72 h), immediate initiation of treatment if extravasation was detected.

[b] safety guidelines emphasized the multidisciplinary collaborations between clinicians, pharmacists and nurses. The authors' guidelines specified: sizes of catheters (20-guage catheters or larger), quality of catheters (blood return must be present, flushing easily with 10 mm of normal saline), locations of catheters (antecubital fossa, upper arms), frequent assessment of catheters' function every hour, dosage (not exceeding maximum dose of 25 microgram per minutes for norepinephrine or epinephrine), duration of infusion (maximum of 24 h), immediate treatment (terbutaline and topical nitroglycerine).

Table 3
Patients Characteristics.

Author, Year	Total Patients with PIV	Age (years)	Female N (%)	Disease State	Name of Vasopressor Name, N (%)	PIV Location Name, N (%)	PIV Size Name, N (%)	Length of Infusion Hour, mean (SD)	Max Rate of Vasopressor	Mean rate of Vasopressor	Major Adverse Events Name, N (%)	Minor Adverse Events Name, N (%)	Any Treatment Name, N (%)
1997 Dugger	17	Not reported	Not reported	Cardiogenic shock	Dopamine, 25 (100)	Forearm, 17 (100)	18-gauge, 1 (6) 20-gauge, 7 (41) 22-gauge, 7 (41) 24-gauge, 1 (6)	9.7 (12)	DE 5 mcg/kg/min	Not reported	None	Infiltration, 17 (100)	Phentolamine, 17 (94)
2006 Putland	220	36 (16)	132 (60)	Asthma	epinephrine	Not reported	Not reported	19.5	Epi 13.3 mcg/min	Epi 1.5 mcg/min	None	infiltration 11 (5)	None
2013 Ricard	128	65 (16)	43 (33)	Mixed type of shock	not reported	Not reported	Not reported	Not reported	Not reported	not reported	Thrombosis 5 (4)	infiltration 19 (15); erythema, 20 (16); phlebitis 1 (0.01)	None
2015 Cardenas-Garcia	783	72 (15)	36 (46)	Mixed type of shock	Norepinephrine	Not reported	18-gauge,192 (25) 20-gauge, 590 (75) 22-gauge, 1 (0)	49 (2)	Not reported	DE 12.7 (5.23) NE 0.70 (0.23) PE 3.25 (1.69)	None	infiltration, 19 (2)	Phentolamine 19 (2) and nitroglycerin paste, 19 (2)
2016 Delgado	20	62 (28)	9 (45)	Neurogenic shock	phenylephrine, 20 (100)	Forearm, 20 (100)	18-gauge, 19 (95) 20-gauge, 1 (5)	14.3 (13)	PE 2 mcg/kg/min	0.53 mcg/kg/min	None	infiltration, 1 (5)	None
2018 Datar	277	65 (15)	148 (53)	Neurogenic shock	phenylephrine, 277 (100)	Upper arm, 139 (50) Wrist/ hand, 87 (32) other, 3 (1) Unknown, 48 (17)	16-gauge, 13 (5) 18-gauge, 98 (35) 20-gauge, 113 (41) 22-gauge, 5 (2) unknown, 48 (17)	19 (18)	PE 1.04 mcg/kg/min	Not reported	None	infiltration, 9 (3)	None
2018 Medlej	55	70	21 (38)	Mixed type of shock	Norepinephrine 50 (91)	hand 20 (36) forearm 10 (18) antecubital fossa/upper arm 23 (42) external jugular 2 (4)	16-gauge, 6 (11) 18-gauge, 20 (36) 20-gauge 28 (51) 22-gauge, 1 (2)	NE 16 (7) DE 58 (28)	NE 30 mcg/min; DE 15 mcg/min	NE 10 mcg/min	None	infiltration, 2 (4); thrombophlebitis, 1 (1)	None
2019 Ballieu	125	59	73 (58)	Neurogenic shock	phenylephrine	upper extremity	18-gauge, exact numbers not reported	19 (13)	PE 3.06 mcg/kg/min	PE 0.64 mg/kg/min	None	erythema, 6 (5); infiltration, 2 (2); thrombophlebitis, 1 (1)	heat application
2019 Lewis	202	75 (5)	95 (47)	Mixed type of shock	Norepinephrine 146 (72); Phenylephrine 73 (36); Epinephrine 2 (1); Vasopressin 4 (2); Dopamine 2 (1)	Forearm 145 (72) antecubital fossa 109 (54) hand 81 (40) other 5 (2)	18-gauge, 46 (23) 20-gauge, 149 (74) 22-gauge, 103 (51) other 6 (3)	16 (6)	NE 0.13 mcg/kg/min; PE 95 mcg/min	NE 0.07 (0.2) mcg/kg/min PE 25 mcg/min	None	8 (4)	None

DE, dopamine; Epi, epinephrine; NE, norepinephrine; mcg/kg/min, microgram per kilogram per minute; mcg/min, microgram per minute; PE, phenylephrine.



Prediction Interval	0.086 (95% CI 0.02-0.81)
Q	190
Degree of Freedom	8
p-value	<0.001
I-square	96%

Fig. 1. Meta-analysis of Prevalence of Any Complications From Infusing Vasopressors Through Peripheral Intravenous Catheters.

infusing via peripheral venous catheters [23]. These risk factors included duration of infusion, infusion rate, catheter size, locations (elbow, hands). However, these risk factors were not derived from statistical analyses that controlled for patients' characteristics. Our meta-analysis, by using meta-regression, was able to suggest that catheters' size of 20-gauge or larger would be associated with lower risk of complications, although further testing is necessary to confirm our observations. Furthermore, the subgroup of studies reporting explicitly the use of safety guidelines [7,17] while infusing vasopressors via peripheral venous catheters were also associated with significant lower prevalence of complications than other studies. Until more studies validate these safety guidelines, clinicians may consider establishing similar detailed guidelines at their institutions for safely infusion of vasopressors through peripheral venous catheters.

4.1. Implications for further research

Our study raised many potential areas for further research in this area. All studies included in our meta-analysis focused on identifying the prevalence of complications. However, clinicians should investigate

Table 4A
Results from subgroup analysis to identify potential sources of heterogeneity and to compare prevalence of complications between subgroups.

Moderator variables	Number of Study included	Complication rate	95% CI	P	Q-value	df (Q)	*P*	I^2	Between group comparison *P*
Study Design									0.99
Retrospective	6	9%	2%–28%	0.001	70	5	0.001	93%	
Prospective	3	9%	1%–40%	0.001	110	2	0.001	98%	
Publication Year									0.001
<2010	2	25%	3%–79%	0.37	49	1	0.001	97%	
2011–2015	2	10%	1%–57%	0.083	107	1	0.001	99%	
2016–2020	5	5%	1%–12%	0.001	3	4	0.51	0	
Study Sample size									0.001
<100 patients	3	18%	4%–56%	0.088	29	2	0.001	93%	
101–249 patients	4	9%	3%–28%	0.001	74	3	0.001	95%	
>250 patients	2	3%	0.4%–17%	0.001	0.54	1	0.47	0	
Clinical Settings									
ED	2	5%	3%–8%	0.001	0.02	1	0.89	0	0.32
ICU	7	9%	3%–28%	0.001	181	6	0.001	96%	
Disease State									0.26
Asthma	1	5%	3%–9%	0.001	NA	NA	1	NA	
Cardiogenic shock	1	68%	48%–83%	0.079	NA	NA	1	NA	
Mixed type of shock	4	12%	9%–14%	0.001	122	3	0.001	97%	
Neurogenic shock	3	5%	3%–7%	0.001	2.9	2	0.22	33%	
Reporting safety guidelines									
Yes	2	3%	2%–5%	0.001	1.4	1	0.24	28%	0.02
No	7	12%	4%–30%	0.001	119	6	0.001	95%	

ED, emergency department; ICU, intensive care unit.

Table 4B
Results from meta-regressions to identify potential predictors for risk associated with complications from infusing vasopressor via peripheral venous catheters. Univariate meta-regression was performed with infusion length while multivariable meta-regressions were performed for percentages of catheter sizes and percentages of catheter locations

Covariate	Number of study	Correlation coefficient	95% CI	*P*	Adjusted R-square
Infusion length [a]	8	−0.06	−0.14 to 0.02	0.13	0.08
Catheter size [b]	7				
18-gauge catheter		−5.6	−10.4 to 0.9	0.02	0.61
20-gauge catheter		−7.3	−12.2 to 2.4	0.01	
22-gauge catheter		1.7	−2.38 to 5.7	0.42	
Catheter Location [c]	6				
Forearm		4.49	−24.7 to 33.7	0.76	0.25
hand/wrist		1.03	−35.8 to 37.9	0.96	

[a] Length of infusion in hours was entered in the univariable meta-regression. If a study reported the use of multiple vasopressors, we used the length of norepinephrine.
[b] percentages of each catheter's size were entered into the multivariable meta-regression containing only catheter sizes.
[c] percentages of each location of catheters were entered into the multivariable meta-regression containing only catheter locations.

risk factors for complications in future studies, as there is adequate literature to suggest safe infusion of vasopressor through peripheral venous catheters. Future studies should also validate the use of safety guidelines while using peripheral venous catheters for vasopressors. Consequently, externally-validated safety guidelines would allow more widespread acceptance of this clinical practice while ensuring patients' safety and outcomes.

4.2. Limitation

There are several limitations to our study. Our meta-analysis reported high heterogeneity between studies. This was most likely due to different methodologies, different patient populations and clinical settings, etc. However, the meta-analysis of prevalence with high heterogeneity across different patient populations, clinical settings offers a benefit: the prevalence of complications from infusing vasopressor through peripheral IV was low, even across different patient populations and settings. The risk of bias in our study was high as only one study reported objective measurements to assess infiltrations and other types of complications [17]. Furthermore, we could not perform meta-regression assessing maximum concentrations of vasopressors as many studies reported these concentrations in non-weight-based formats. Future studies should report the concentration of vasopressors in weight-based format. Even in the recently published studies in our meta-analysis, vasopressor concentrations were still reported in non-weight-based format as microgram per minute. Adopting weight-based concentrations should allow for more generalizability of each study's results.

5. Conclusion

The prevalence of complications as a direct result from infusing vasopressors through peripheral venous catheters in our study's pooled population was low. Recently published studies, studies with large sample sizes and studies which reported the use of safety guidelines were associated with significantly lower incidence of adverse events, compared to other subgroups. Using catheters with larger size was also associated with lower risk of complications. Due to the quality and characteristics of the included studies, more randomized controlled studies are needed to confirm our observations and to investigate the risk factors for complications from infusing vasopressors through peripheral venous catheters.

Authors' contribution

Conceptualization: QKT, AP, AM, KA.
Data Collection: LZA, SA, ZA, VB, GM. AW, AM, KA.
Data Analysis: LZA, SA, ZA, VB, GM. AW, QKT.
Preparing manuscript: LZA, SA, ZA, VB, GM. AW, QKT, AP, AM, KA.
Critical revision of manuscript: LZA, SA, ZA, VB, GM. AW, QKT, AP, AM, KA.

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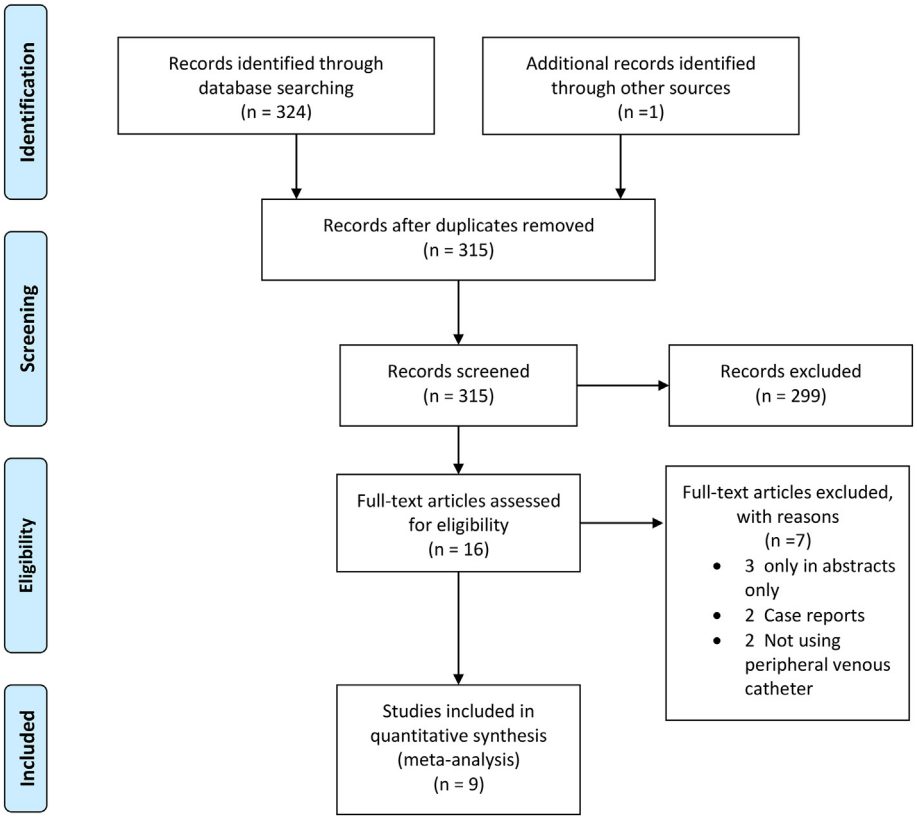
Declaration of Competing Interest

The authors declared no conflict of interest.

Appendix 1 Study selection flow diagram



Appendix 2. List of moderator variables that were used in subgroup analyses and meta-regressions

Study	*Categorical Variables*						Continuous variables					
							Catheter Size			Catheter Location		
	Study Design	Year	Study Sample Size	Clinical Settings	Disease State	Safety Guideline	% of 18gauge	% of 20gauge	% of 22gauge	% in Arm	% in Wrist or hand	Infusion length (hours)[a]
1997 Dugger	Retrospective	<2010	<100	ICU	Cardiogenic shock	No	0.06	0.41	0.47	1	0	9.7
2006 Putland	Retrospective	<2010	101–249	ED	Asthma	No	NR	NR	NR	NR	NR	19.5
2013 Ricard	Prospective	2011–2015	1010–249	ICU	Mixed Shock	No	NR	NR	NR	NR	NR	NR
2015 Cardenas-Garcia	Prospective	2011–2015	>250	ICU	Mixed Shock	Yes	0.25	0.75	0	NR	NR	49
2016 Delgado	Retrospective	2016–2020	<100	ICU	Neurogenic	No	0.95	0.05	0	1	0	14.3
2018 Datar	Retrospective	2016–2020	>250	ICU	Neurogenic	No	0.4	0.41	0.02	0.5	0.32	19
2018 Medlej	Prospective	2016–2020	<100	ED	Mixed Shock	No	0.47	0.51	0.02	0.6	0.36	16
2019 Ballieu	Retrospective	2016–2020	101–249	ICU	Neurogenic	No	1	0	0	1	0	19
2019 Lewis	Retrospective	2016–2020	101–249	ICU	Mixed Shock	Yes	0.23	0.74	0.56	0.54	0.4	16

[a] In studies with multiple types of vasopressor, we used the infusion length of norepinephrine, which is the first line treatment in patients with septic shock.

Appendix 3. PRISMA-P 2015 Checklist

Title: Infusing Vasoactive Medication Through Peripheral Venous Catheters: A Meta-analysis of Adverse Events.
This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1.

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Administrative Information					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Yes		1–2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		NA	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract		NA	NA
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes		Line 23, title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes		Line 12, page 2 of title page
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		NA	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	Yes		line 21, page 2, Title page
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		NA	NA
Introduction					
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes		Lines 55–56, Introduction Page
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes		Lines 60–62, Page 2, Introduction Page
Methods					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes		Lines 70–77, Methods, Page 2
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes		Line 66–69, Methods, Page 3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes		Line 66–69, Methods, Page 2.
Study records					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes		Line 112–118, Methods, Page 3.
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes		Lines 78–83, Methods, Page3
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes		Lines 112–118, Methods, Page 3.
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	YEs		lines 112–118, Methods section, page 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes		Lines 92–99, method section, page 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes		Lines 101–104, Methods, page 3.
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes		Lines 120–122, Methods, page 4
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	Yes		Lines 122–143, Methods, page 4.
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Yes		Lines 122–143, Methods, page 4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		NA	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Yes		Lines 102–110, Methods, page 3.

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