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ORIGINAL ARTICLE

Utilisation of peripheral vasopressor medications and extravasation events among critically ill patients in Rwanda: A prospective cohort study

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ABSTRACT

Introduction: In high-income settings, vasopressor administration to treat haemodynamic instability through a central venous catheter (CVC) is the preferred standard. However, due to lack of availability and potential for complications, CVCs are not widely used in low- and middle-income countries. This prospective cohort study evaluated the use of peripheral vasopressors and associated incidence of extravasation events in patients with haemodynamic instability at the Centre Hospitalier Universitaire Kigali, Rwanda.

Methods: Patients ≥18 years of age receiving peripheral vasopressors in the emergency centre (EC) or intensive care unit (ICU) for >1 hour were eligible for inclusion. The primary outcome was extravasation events. Patients were followed hourly until extravasation, medication discontinuation, death, or CVC placement. Extravasation incidence with 95% confidence intervals (CI) were calculated using Poisson exact tests.

Results: 64 patients were analysed. The median age was 49 (Interquartile Range [IQR]:33-65) and 55% were female. Distributive shock was the most frequent aetiology (47%). Intravenous (IV) location was most commonly antecubital fossa/upper arm (31%) and forearm/hand (43%). IV gauges ≤18 were used in 58% of locations. Most patients were treated with adrenaline (66%) and noradrenaline (41%), and 11% received multiple vasopressors. The median treatment duration was 19 hours (IQR:8.5-37). Treatment discontinuation was predominantly due to mortality (41%) or resolution of instability (36%). There were two extravasation events (2.9%), both limited to soft tissue swelling. Extravasation incidence was 0.8 events per 1000 patient-hours (95% CI:0.2-2.2).

Conclusion: Extravasation incidence with peripheral vasopressors was low, even with long use durations, suggesting peripheral infusions may be an acceptable approach when barriers exist to CVC placement.

African relevance:

- The use of peripheral vasopressor medications in critically ill patients has not been well studied in the Rwandan context.
- In limited resource settings, access to and use of central venous catheter is relatively reduced due to availability and expense.

Introduction

Vasopressor medications are pharmacological agents used in patients with haemodynamic instability, particularly patients with inadequate tissue perfusion states, or shock [1–3]. Vasopressors can be administered via peripheral intravenous lines (PIV) or central venous catheters (CVC). Administration of vasopressors via CVC has been the preferred practice in emergency centre (EC) and intensive care unit (ICU) settings in high-income countries (HICs). Despite CVCs being the mainstay for vasopressor treatment, they require trained staff, sterile technique, specialised equipment and placement confirmation all of which can take significant time [4]. Initiation of these medications are time sensitive and their delayed initiation has been linked with increased mortality [4].

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Across both HIC and low middle-income countries (LMICs) settings limited data exists on the risk of extravasation when vasopressors are administered via PIV. The adverse effects of extravasation are not benign and range from minor localised tissue swelling and pain to possible severe tissue damage or ischemia [5, 6]. Similarly, there is limited data on the risk of extravasation when vasopressors are administered via PIV. The majority of the data that exists is based on low-quality evidence from case reports and case series [5, 6]. The limited results from studies that have examined the administration of vasopressors administered through PIV have found rates of extravasation of 2-4% [6–11]. This limited data is derived predominantly from HICs, with a paucity of research from LMICs with associated higher mortality from critical illness [6, 12]. In LMICs, access to and the use of CVCs is relatively low due to availability and expense [13]. As a result, the administration of vasopressors through PIV may be preferred in patients with haemodynamic instability in LMICs.

However, the use and risks with this approach in such settings has not been well studied. The examination of vasopressors given through PIV can guide safe use protocols in LMICs. Furthermore, data from LMICs can be compared with similar studies to assess generalisability across clinical settings. This prospective cohort evaluated the use of vasopressor medications administered via PIV and the occurrence of extravasation events among patients in both an EC and ICU clinical setting at a public tertiary care referral hospital in Rwanda.

Methods

This prospective observational cohort study was conducted at the Centre Hospitalier Universitaire Kigali (CHUK), the main public referral health facility and university teaching hospital in Rwanda. CHUK is located in Kigali, the capital city of Rwanda, and has access to critical care and specialty consulting services, as well as Rwanda's sole emergency medicine, critical care and anaesthesia training programs [14].

CHUK has approximately 500 inpatient beds, 40 EC beds, and 7 ICU beds, and sees a volume of approximately 20,000 EC visits and 300 ICU admissions annually [14, 15]. The EC and ICU at CHUK treat critically ill patients with haemodynamic instability who frequently require vasopressor medications.

The research activities were approved by the CHUK ethics committee and the institutional review board of Rhode Island Hospital. Patients ≥18 years of age receiving peripheral vasopressors in the EC or ICU for >1 hour were eligible for inclusion. Patients who were pregnant, refused consent, or did not have a consenting adult or caretaker were excluded. Patients who were on peripheral vasopressors for less than 1 hour were also excluded. Informed consent for participation was obtained from the patient directly by trained research assistants. If the patient was unable to consent due to incapacity, a legally authorised patient representative provided informed consent. Research assistants were on site for data collection from 07:00-19:00 daily during study enrolment. If a patient meeting inclusion criterion arrived during hours when the research assistants were not present, the study staff were alerted. If the patient or accompanying family member provided consent at the beginning of the subsequent research assistant shift, they were approached for enrolment and data were extracted from the medical records.

Prospective data were collected from a convenience sample from January through October 2019. Following enrolment, data were collected using standardised instruments on sociodemographic and anthropomorphic patient characteristics, aetiology of shock, type of vasopressor, size of PIV catheter, location of PIV catheter, duration of vasopressor use, extravasation events, and management of extravasation. For reporting of vasopressor dosages (mg/kg/min), dosage levels for adrenaline (1:1 ratio) and dopamine (1:100 ratio) were converted to "noradrenaline equivalents" following earlier research [16]. Evaluations for extravasation events were completed hourly until peripheral use of vasopressor medication were discontinued, the patient had a CVC placed or the patient died.

The primary outcome of interest was extravasation events with PIV administration of vasopressor medications, consistent with prior literature [6–11]. Extravasation was treated as a binary outcome of yes or no. At the time of this study, there was no institutional protocol on placement of PIV catheters for vasopressor administration. Therefore, standardised protocols based on prior research and guidelines were used for monitoring and treatment of extravasation events (Appendix 1) [9, 17, 18]. The protocols included grading scales and management approaches adapted to the available resources in the study setting such as the use of nitroglycerin paste instead of phentolamine as this medication was not available at the study site [18, 19]. Any patient with an extravasation event, was monitored for 48 hours to evaluate for possible progression. If no progression in severity was noted, monitoring was discontinued at that time.

Shock aetiologies were categorised based on clinical assessments by the independent primary treatment teams and pathophysiological mechanisms of hypovolemic, cardiogenic, obstructive or distributive [2, 3]. There were four vasopressors medications with differing pharmacological mechanisms of action available and evaluated in the study population: adrenaline, noradrenaline, dopamine, and dobutamine [3]. The size of the PIV catheters was categorised as large bore (18 and 16 gauge) or small bore (20 and 22 gauge), respectively. Anatomic location of PIV was coded in the following categories: antecubital fossa or upper arm, hand or wrist, forearm, external jugular, lower extremity.

Analyses were performed using Stata Version 15 (StataCorp^{TM}, College Station, USA). Data were analysed descriptively. Frequencies and percentage were reported for categorial variables. Medians with interquartile ranges (IQR) and means with standard deviations (SD) were calculated for continuous variables. A histogram was constructed for durations of vasopressor administration, and box plots for durations of treatments were stratified by shock aetiologies and types of vasopressors used.

A Poisson distribution was used to calculate the prevalence and incidence of extravasation events along with 95% confidence intervals (CIs) [20]. Extravasation incidence was calculated for every 1000 patient-hours of vasopressor administration. A secondary incidence was also reported following the removal of two extreme outlier cases that had administration durations over tenfold higher than the median population value, in order to reduce the risk of underestimation.

Differences in vasopressor medication administration were assessed based on aetiology of shock and the type of vasopressor the patient received. Significant differences in vasopressor medications were assessed using chi-squared tests or Kruskal-Wallis tests, as appropriate. Additionally, differences in vasopressor administered and reason for discontinuation were evaluated in an exploratory analysis comparing patients with and without distributive shock, the most common observed aetiology. A post-hoc logistic regression model was used to evaluate for an association between IV bore size and odds of extravasation events. IV gauge was analysed as a dichotomised variable as small bore (>18g) or large bore (≤18g).

Results

A total of 69 patients were screened for study inclusion. Of those, 64 were consented and enrolled. Among participants, 51.5% were enrolled in the EC and 48.5% were enrolled in the ICU. The majority of patients were female (55%). The median age was 49 years (IQR: 33-65, 95% CI: 44.3–53.9). Patients transferred from outside hospitals made up 59% of cases. A small proportion of cases were trauma patients (8%) (Table 1).

There were extravasation events in two cases, both of which were limited to localised soft tissue swelling. One patient was treated for distributive shock with an 18g IV gauge in the wrist. Their extravasation event occurred after 47 hours of peripheral infusion. The second patient was treated for cardiogenic shock with a 20g IV and their extravasation event occurred after 93 hours of infusion. For this case, the anatomic PIV location was not documented. Each had an extravasation severity score

Table 1
Characteristics of Study Population.

	n (%) or Median [IQR]
Gender	
Male	29 (45%)
Female	35 (55%)
Age (years)	49 [33, 65]
Height (cm)	167 [162, 171]
Weight (kg)	62 [60, 68]
Arrival method	
Ambulance	23 (36%)
Private vehicle	15 (23%)
Walk-in	13 (20%)
Other	3 (5%)
Unknown	10 (16%)
Transfer from another health facility	
Yes	40 (63%)
No	24 (37%)
Case type	
Medical	33 (52%)
Trauma	5 (8%)
Unknown	27 (42%)

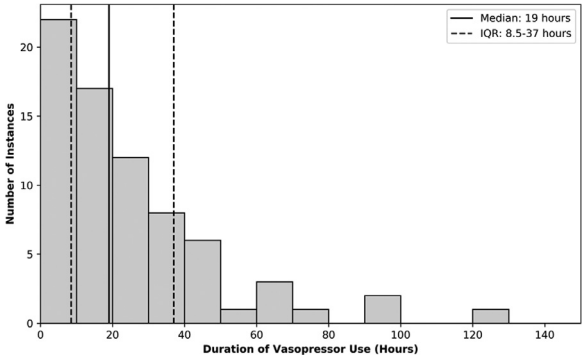

Fig. 1. Frequency Distribution of Duration of Vasopressor Medication Administration*
*Vertical solid line identifies median duration (19 hours) and vertical dashed lines identify the IQR (8.5, 37 hours). Two outlier cases with prolonged administration of 264 hours and 465 hours) were excluded.

of one on a scale of zero to four (Table A.1) [17]. A score of one represented mild localised tissue swelling less than one inch in either direction [17]. Both patients had their extravasation treated with elevation and warm compresses as per the standardised extravasation protocol (Table A.2). Both patients were followed for 48 hours after extravasation, during which time there was no progression of severity.

Using a Poisson analysis, the prevalence of extravasation events in the study population was 2.9% (95% CI: 1.0-8.7%). The total duration of follow up time with peripheral vasopressor administration in the cohort was 2,544 patient-hours. The extravasation incidence in the study population was 0.8 events per 1000 patient-hours (95% CI: 0.2-2.2 events per 1000 patient-hours). After removal of two outliers with a vasopressor administration duration of over 200 hours each, (which did not involve extravasation events), the extravasation incidence remained similar at 1.1 events per 1000 patient-hours (95% CI: 0.4-3.4 events per 1000 patient-hours). No significant association was found with large bore IV as compared to small bore IV use with the odds of extravasation events (odds ratio=0.69, 95% CI: 0.04–11.11, P=0.80). The dosage of vasopressor administration was also not associated with extravasation events (odds ratio=1.14 per +1 mg/kg/min, 95% CI: 0.06–20.55, P=0.929). The incidence of extravasation events was also not associated with patient age (odds ratio=1.10, 95% CI: 0.76–1.59, P=0.63).

Amongst cases enrolled in the study, the most common aetiology of shock was distributive (56%), followed by hypovolemic (30%), cardiogenic (11%) and neurogenic (2%). IV location was antecubital fossa or upper arm in 31% of cases and forearm or hand in 43%. IV gauges ≤18 were used in 58% of peripheral vasopressor administration locations. The majority of cases were treated with adrenaline (66%) followed by noradrenaline (41%) (Table 2). In 11% of cases, multiple peripheral vasopressors were administered, with up to four being administered in two cases. Discontinuation of treatment was most frequently due to mortality (41%), resolution of instability (36%), or CVC placement (11%). The type of vasopressor administered (P=0.401) and reason for discontinuation of treatment (P=0.899) did not differ significantly between patients with and without distributive shock, the most common aetiology (Table 3). For patients with and without distributive shock, adrenaline was the most common vasopressor administered (47% vs. 61%), and patient death or clinical improvement were the two most common reasons for discontinuation.

The median duration of treatment with peripheral vasopressor administration was 19 hours (IQR: 8.5, 37, 95% CI: 20.2–48) (Fig. 1) and the duration ranged from 1 hour to a maximum of 451 hours. Among the four aetiologies of shock, patients with cardiogenic shock had the highest mean duration of peripheral vasopressor administration of 85.1 hours (mean=23, IQR=9–51; Fig. 2A). However, the observed median duration of vasopressor administration did not differ significantly between aetiologies of shock (P=0.172). Similarly, median duration of vasopressor use did not differ significantly (P=0.810) between patients administered adrenaline (median=18, IQR=8–33.5), noradrenaline (median=19.5, IQR=10.3–37.0), or dopamine (median=17, IQR=5–53; Fig. 2B). Additionally, there were no significant differences in median vasopressor dosage between adrenaline (median=0.12, IQR=0.06–0.38), noradrenaline (median=0.10, IQR=0.01–0.48), and dopamine (median=0.06, IQR=0.05–0.09; P=0.305).

Finally, there was no difference in location of peripheral vasopressor administration (P=0.777), duration of administration (P=0.112), and vasopressor dosage (P=0.760) between survivors and non-survivors in the study population (Table 4).

Discussion

In the studied cohort, the incidence of extravasation events was low, even with relatively prolonged use of peripheral vasopressor medications. Of the cases experiencing extravasation, no pharmacological or surgical interventions were required. This data supports the safe use of vasopressor medications through PIV in LMIC settings where barriers to CVC use exist. Regardless of income setting, this data could also support the peripheral use of vasopressors as a safe temporising measure when prompt pressor support is warranted for critically ill patients. However, further research in larger populations on the safety of peripheral vasopressors administration is still needed to enhance the evidence base.

This is among the first prospective studies examining vasopressor administration via PIV access in LMICs. The current findings are concordant with prior literature which describes use of PIV with low extravasation events and few associated severe complications [6, 10, 11, 21]. Vasopressor medications are a crucial clinical tool in the management of patients with haemodynamic instability and shock [9, 22]. Prior studies have shown that early initiation of vasopressor medications can reverse the shock state and improve patient outcomes [1, 9, 13, 22–24]. However, a majority of these studies originate in HIC settings where resources are vastly different than in LMIC settings [6, 13, 25].

Our literature search did not yield any studies which evaluated the incidence of extravasation per patient hours. The finding of 0.8 events per 1000 patient hours could serve to inform the use of vasopressors through peripheral means. Additionally, the study patient population employed different PIV sites and sizes indicating that even with small and distal sites, extravasation events are low. However, considering the small sample size in this study, further research could provide further evidence for safe use and should focus on clinically modifiable factors

Table 2
Characteristics of Peripheral Vasopressor Medication Administration.

	n (%) or Median [IQR]
Aetiology of shock	
Distributive	36 (56%)
Hypovolemic	19 (30%)
Cardiogenic	7 (11%)
Obstructive	1 (2%)
Unknown	1 (2%)
Type of vasopressor medications administered*	
Adrenaline	42 (66%)
Noradrenaline	26 (41%)
Dopamine	7 (11%)
Dobutamine	1 (2%)
Number of peripheral vasopressors medications administered	
1	57 (89%)
2	4 (6%)
3	1 (2%)
4	2 (3%)
Duration of time vasopressors medications administered (hours)	19 [8.5, 37]
Dosage of vasopressor administration (mg/kg/min in noradrenaline equivalents)	
Adrenaline	0.12 [0.06, 0.38]
Noradrenaline	0.10 [0.01, 0.48]
Dopamine	0.06 [0.05. 0.09]
Gauge of peripheral intravenous catheter	
20 g or 22 G	26 (41%)
16 g or 18 G	37 (58%)
Unknown	1 (2%)
Location of peripheral intravenous catheter used for administration	
Antecubital fossa or upper arm	20 (31%)
Hand or wrist	17 (27%)
Forearm	10 (16%)
External jugular	6 (9%)
Lower extremity	1 (2%)
Unknown	10 (16%)
Reason for vasopressor medication discontinuation	
Death	26 (41%)
Clinically improved	23 (36%)
Placement of Central Venous Catheter	7 (11%)
Extravasation	2 (3%)
Unknown	6 (9%)

* Due to multiple vasopressors being administered in some cases the sum is greater than 100%.

Table 3
Differences in Vasopressor Medication Administration Between Distributive and Non-Distributive Shock Cases.

	Distributive Shock (n=36)	Non-Distributive Shock (n=28)	P-Value
Initial vasopressor medication administered			0.401
Adrenaline	17 (47%)	17 (61%)	
Noradrenaline	15 (42%)	10 (36%)	
Dopamine	4 (11%)	1 (4%)	
Reason for vasopressor medication discontinuation			0.899
Death	12 (43%)	14 (39%)	
Clinically improved	9 (32%)	14 (39%)	
Placement of Central Venous Catheter	4 (14%)	3 (8%)	
Extravasation	1 (3%)	1 (4%)	

Table 4
Differences in Vasopressor Medication Characteristics Based on Patient Death.

	Survivors (n=38)	Non-Survivors (n=26)	P-Value
Location of peripheral intravenous catheter used for administration			0.777
Antecubital fossa or upper arm	14 (37%)	6 (23%)	
Hand or wrist	9 (24%)	8 (31%)	
Forearm	5 (13%)	5 (19%)	
External jugular	3 (8%)	3 (12%)	
Lower extremity	1 (3%)	0 (0%)	
Unknown	6 (16%)	4 (15%)	
Duration of time vasopressors medications administered (hours)	20 [8.8–37]	18 [9.0–24]	0.112
Dosage of vasopressor administration (mg/kg/min in noradrenaline equivalents)	0.1 [0.05–0.3]	0.1 [0.03–0.4]	0.760

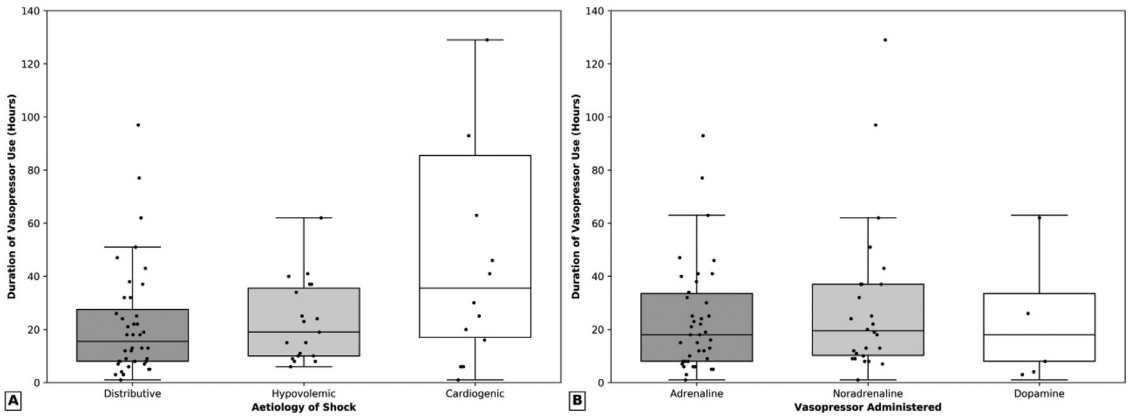

Fig. 2. Box Plots Summarising Duration of Vasopressor Administration
A) Stratified by aetiology of shock. Obstructive shock was excluded because it was present in only one case.
B) Stratified by vasopressor type. Dobutamine was excluded because it was only administered once in the study population.
* Dobutamine was excluded because it was only administered once in the study population. Box plots display the median and interquartile range of duration of vasopressor administration (in hours) for each patient subpopulation, with the whiskers denoting the median ± 1.5 times the interquartile range. Each individual point represents a unique instance of a vasopressor being administered in the study population.

such as vasopressor duration, PIV bore size, PIV location, concentration of medication, shock physiology, etc.

Although the present study represents the largest dataset from a LMIC setting, it evaluated a relatively small number of patients from a single academic teaching hospital. As the study cohort was a convenience sample of patients, there is the potential for selection bias. As noted in the methods, this was an exploratory, hypothesis generating study where a sample size was not determined. Given the lack of prior data on extravasation in similar study settings the ability to perform a power calculation was not feasible. However, the current data now may now be able to inform future research.

In this study, patients with extravasation events were followed for 48 hours after the event occurred. If there was no progression in severity, clinical monitoring was ceased. Although unlikely, it is unknown if more severe complications developed at a later stage. Additionally, as the use of peripheral vasopressors is commonplace at the study site, the low number of extravasation events may be influenced by the clinical experience of the medical staff who are adept at administering vasopressors through PIV. Thus, caution must be exercised before generalising these results to health facilities without such clinical experience. It also is not possible to know if patients not included or those who declined participation were significantly different from those included and analysed as their data were not collected. This could have introduced selection bias into the study. However, the study findings are similar to other literature pertaining to extravasation events, suggesting that this potential bias did not substantially impact the findings [6]. Patients in this study were followed hourly until peripheral use of vasopressor medication were discontinued, a CVC was placed, or the patient died. Thus, we cannot say with certainty that these patients did not develop other complications from peripheral vasopressor use after data collection ceased.

Although noradrenaline is the recommended first choice for vasoactive medications in distributive shock states secondary to sepsis, in the current cohort adrenaline was the most commonly used agent, which could limit the generalisability. Although data were collected on the IV gauge and anatomical location, given the low absolute number of extravasation events observed, it was not possible to evaluate factors which modulate risk of extravasation with use of peripheral vasopressors. Future studies with larger sample sizes would be beneficial to evaluate such factors, particularly in LMIC settings where barriers to CVC use more commonly exist.

The incidence of extravasation with peripheral vasopressors was low in the studied population, even with long durations of use, suggesting peripheral infusions may be an acceptable approach when barriers exist to CVC placement. The findings of this study should be used to further develop understanding and clinical guidance for the safe use of vasopressor medications in resource-constrained practice settings. Further research in larger populations can validate the safety of peripheral vasopressors in HICs and LMICs.

Dissemination of results

Results from this research study were shared with staff members at the data collection site through an informal presentation.

Authors' contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: CGM contributed 25%; LM 10%; and KMa, OT, CU, VN, DU, KMo, VS, SN, LJ, SCG, MN, ACL and ARA contributed 5% each. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.afjem.2022.03.006.

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