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RESEARCH ARTICLE

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Feasibility and Safety of Peripheral Intravenous Administration of Vasopressor Agents in Resource-limited Settings

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Abstract

Background: Vasopressors are conventionally administered through a central venous catheter (CVC) and not through a peripheral venous catheter (PVC) since the latter is believed to be associated with increased risk of extravasation. Placement of a CVC requires suitably trained personnel to be on hand, and in resource-limited settings, this requirement may delay placement. Because of this and in cases where suitably trained personnel are not immediately available, some clinicians may be prompted to utilise a PVC for infusing vasopressors. The objective of this study is to assess the feasibility and safety of vasopressors administered through a PVC. **Materials and methods**: Patients who received vasopressors through a PVC for more than one hour were included in a single centre, consecutive patient observational study. Patients with a CVC at the time of initiation of vasopressors were excluded. Data regarding the size, location of PVCs, dose, duration and number of vasopressors infused were recorded. The decision to place CVC was left to the discretion of the treating physician. Extravasation incidents, severity and management of such events were recorded. **Results**: One hundred twenty-two patients age 55(4) years [mean (SD)] were included in the study. The commonest PVC was of 18G calibre (57%), and the most common site of placement was the external jugular vein (36.5%). Noradrenaline was the most common vasopressor used at a dose of 10.6 (7) mcg/min [mean (SD)] and the median duration of nine hours (IQR: 6-14). CVC was placed most commonly due to an increasing dose of vasopressors after 4.5(4) hours [mean (SD)]. Grade 2 Extravasation injury occurred in one patient after prolonged infusion of fifty-two hours, through a small calibre (20G) PVC, which was managed conservatively without any sequelae. **Conclusion**: Vasopressors infused through a PVC of 18G or larger calibre into the external jugular, or a forearm vein is feasible and safe. Clinicians need to balance the safety of peripheral vasopressor infusion with the additional costs and complications associated with CVC in resource-limited settings.

Keywords: vasopressors, central venous catheter, peripheral venous catheter, hemodynamic emergencies

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Introduction

Hemodynamic emergencies are one of the most common reasons for admission to an intensive care unit (ICU). Vasopressor agents are initiated if the initial fluid resuscitation fails to meet resuscitation targets or when a patient presents with life-threatening hypotension. Administration of vasopressors has traditionally warranted the insertion of a central venous catheter (CVC). This is because of a perceived risk of extravasation and resulting tissue injury while infusing them through a peripheral venous catheter (PVC) [1,2]. The use of CVCs has also been associated with significant morbidity and complications including infection which has been reported in approximately 15% of the patients [3,4] There is, a heightened awareness to assess CVCs daily to minimise patient line days and reduce associated risks.

Moreover, CVC placement incurs additional cost. In resource-limited settings there is often a delay in the placement of a CVC due to the lack of suitably trained personnel, resulting in the postponement of vasopressor initiation.

With current evidence suggesting a delay in the administration of vasopressors in septic shock to be associated with poor outcomes, early initiation of vasopressors is essential [5].

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A systematic review showed that extravasation and tissue injuries could occur with peripheral IV administration of vasopressors, especially with prolonged infusions (>24 hours) and distal location of PVCs. Furthermore, it was observed that tissue injuries were often minor, and significant debilitating injuries were rare. The authors concluded that since such case reports of incidents suffer from publication bias, it is not possible to comment on the actual incidence of such events [6].

Recent evidence from observational studies report risks of extravasation of 2% - 5% [7,8]. Most of the events were minor, and the patients did not require antidote administration or surgical intervention. This suggests that the risks of extravasation may be overestimated and PVC underutilised for vasopressor infusions.

The present study aimed to assess the feasibility and safety of administering vasopressors through a PVC with the rationale that this would help reducing CVC use.

Materials and Methods

This is a single centre, consecutive patient observational study conducted from 1st January to 31st December 2018 in an intensive care unit (ICU) of a cancer speciality hospital in Chennai, India.

All patients who received vasopressors through a PVC during the study period were included in this study. Patients who had a CVC at the time of initiation of the vasopressor or those patients who received vasopressors for durations of less than one hour were excluded. Patients in whom a proper PVC could not be secured were also excluded.

PVCs were placed according to the hospital's standard protocol by either a physician or a skilled nurse.

However, during the period of the study, the institute did not have any protocol in place to guide clinicians with the initiation, administration and dose titration of vasopressors.

The treating physician team made any decision to initiate treatment with vasopressors through a PVC. PVCs were placed in the critical care unit (ICU), emergency room, operation theatre or wards.

The decision to place a CVC or transition the infusion from a PVC to a CVC was left to the discretion of the treating physician as the study was observational and non-interventional. When there was a need for renal replacement therapy, a dialysis catheter with an additional port for administering medications was placed. CVC placed in the operation room was undertaken at the discretion of the anaesthetist, depending on the perioperative risks.

Characteristics of the PVC including size, site and number are given in Figure 1, vasopressor characteristics including the number of vasopressors, concentration, dose (initial, mean and maximum dose) and duration of use are given in Table 1. The strengths of vasopressors used are given in Table 2.

The time to transition from a PVC to a CVC was observed, and the reason observed by clinicians for placing a CVC was also recorded.

The patients were monitored for the incidence of extravasation events three times daily.

Table 1. Vasopressor details

	Noradrenaline	Vasopressin	Adrenaline	Dopamine
Number of Patients	118/122	29/122	6/122	2/122
Duration-median(IQR)	9 hours (6 – 14)	4 hours (2.7 –9)	6 hours (4-10)	7.5hrs
Initial dose-mean(SD)	5.9(5.5)mcg/min	1.9(0.2)U/hr	5.2(1.7)mcg/min	10mcg/kg/min
Maximum dose- mean(SD)	14.8(8.8)mcg/min	2 (0.3)U/hr	10.5(7.8) mcg/min	10mcg/kg/min
Total dose- mean(SD)	10.6 (7) mcg/min	1.9(0.25) U/hr	6.3(2.8) mcg/min	8.3mcg/kg/min

Table 2. Vasopressor strengths

Vasopressor	Dilution	Dose
Noradrenaline*	Single strength-2mg/48ml NS Double strength-4mg /46ml NS	1ml=40 mcg 1ml=80 mcg
Adrenaline **	Single strength-3mg/47ml NS Double strength-6mg /44 ml NS	1ml=60 mcg 1ml=120 mcg
Dopamine***	5ml/45ml NS, 5ml=200 mg	1ml=4000 mcg (4mg)
Vasopressin****	20 units in 20 ml NS	1ml=1 unit

*Noradrenaline – Adrenor (Samarth Life sciences, Mumbai, India); **Adrenaline- Vasocon (Neon Laboratories, Palghar, India); ***Dopamine- Domin (Neon Laboratories, Palghar, India); ****Vasopressin- Cpressin-P (Samarth Life sciences, Mumbai, India)

Table 3 lists the extravasation events graded according to the scale provided the infusion nursing standards of practice scale [9].

In the case of such events, data regarding the severity and management of the injury was recorded.

Extravasation injuries were managed following the standard protocols used in the hospital [10]. (Appendix 1)

Patients with extravasation injuries were followed until discharge. In patients without extravasation injuries, data collection was terminated twenty-four hours after the vasopressors were tapered or stopped or twenty-four hours after the transition to a CVC to record any delayed incidence of tissue injury.

Table 3. Infusion nursing standards of practice Infiltration Scale

Grade	Clinical severity
0	No symptoms
1	Skin blanched Oedema <1 inch in any direction Cool to touch With or without pain
2	Skin blanched Oedema 1-6 inches in any direction Cool to touch With or without pain
3	Skin blanched, translucent Gross oedema >6 inches in any direction Cool to touch Mild–moderate pain Possible numbness
4	Skin blanched, translucentSkintight, leaking Skin discoloured, bruised, swollen gross oedema >6 inches Deep pitting tissue oedema Circulatory impairment Moderate–severe pain Infiltration of any amount of blood product, irritant, or vesicant

Results

A total of 122 patients, aged 55(4) years [mean(SD)], 54% males and 46% females, with a body mass index (BMI) of 24(4.4) [mean (SD)] were included in the study (Table 4).

A total of 178 PVCs were placed.

The PVC was most commonly placed in the ICU (46%), the emergency room (40%) and less commonly in the operation theatre or wards.

The most commonly placed PVC was size 18G (57%), followed by 20G (34%) (Figure 1a).

The most common site of the PVC was an external jugular vein (36.5%) followed by the forearm (32.5%) (Figure 1b).

Fifty-five% of patients had a single PVC, while 45% of the patients had two or more PVCs.

The external jugular vein was the site of choice for vasopressor administration when multiple PVCs were used.

The details and strengths infused vasopressors are given in Tables 1 and 5.

A single vasopressor was used in 72% of patients and dual vasopressors in 28% of patients. Noradrenaline was the most common vasopressor used, and vasopressin was the most commonly added second agent. During the study, no patient received vasopressin infusion alone or three vasopressor infusions.

Noradrenaline was infused at 10.6(7) mcg/min, [mean (SD]. The median duration of noradrenaline infusion was nine hours (IQR 6-14). The maximum dose of noradrenaline infused to a patient was 48 mcg/min, and the maximum duration infused was eighty-eight hours. Single strength solutions of noradrenaline were used in 73.7% of cases, and double strength dilution was used in 26.2% of the patients.

Table 4. Baseline patient characteristics

Total no of patients	122
Male	66
Female	56
Age	55(4) years;[mean(SD)]
BMI	24.1(4.4); [mean(SD)]
Indications for vasopressor administration	
Septic shock	89
Cardiogenic shock	7
Stroke/Subarachnoid haemorrhage	12
Other	14

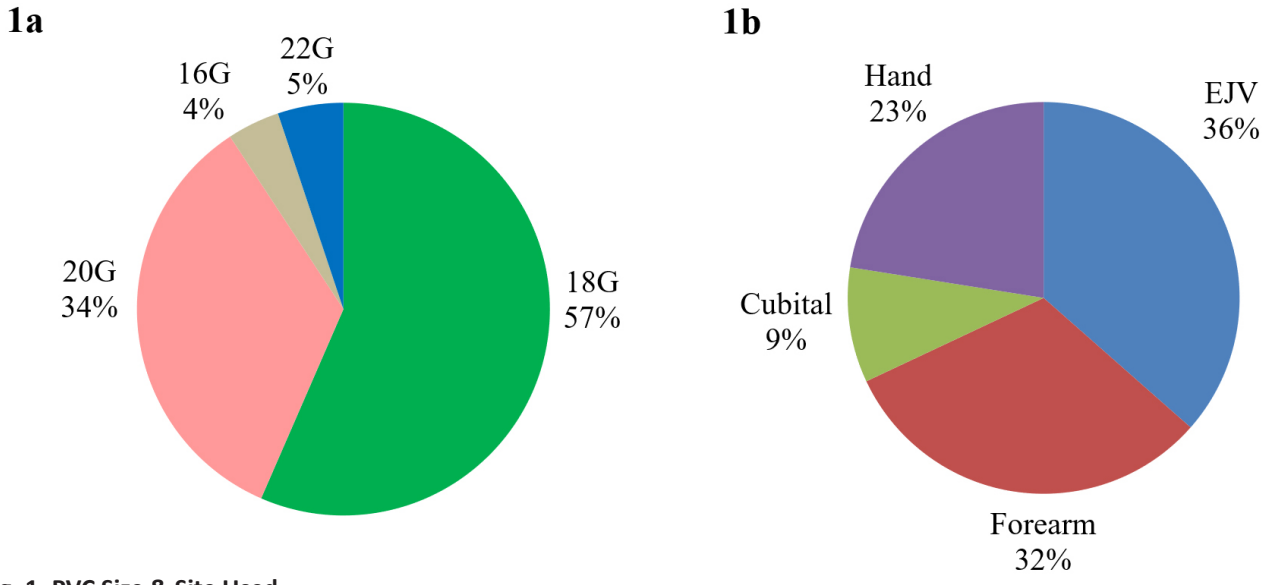

Fig. 1. PVC Size & Site Used

Table 5. Vasopressor combinations

Vasopressor combinations used	Number (n) of patients used
*Noradrenaline alone	85
**Adrenaline alone	2
***Dopamine alone	2
Noradrenaline + ****Vasopressin	29
Noradrenaline + Adrenaline	4

*Noradrenaline – Adrenor (Samarth Life sciences, Mumbai, India); **Adrenaline- Vasocon (Neon Laboratories, Palghar, India); ***Dopamine- Domin (Neon Laboratories, Palghar, India); ****Vasopressin- Cpressin-P (Samarth Life sciences, Mumbai, India)

Of the 122 patients who were started using vasopressors through a PVC, 83 (68%) patients did not require a CVC. The median duration of vasopressor infusion in patients who did not transition to a CVC was eleven hours (IQR 7-18). Only 32% of patients needed a CVC to be inserted.

There were several indications for insertion of a CVC including increasing dose of vasopressors (51.6%), need for dialysis (36.8%), during high-risk surgical procedures (10.5%) and administration of total parenteral nutrition (1%). The mean time for transitioning from a PVC to a CVC was 4.5(4) hours, [mean (SD)].

The central line-associated bloodstream infection (CLABSI) rates in the ICU was 0.85 per 1000 line days during the study period.

Only one extravasation related tissue injury was observed during the study. This patient developed a Grade 2 injury after fifty-two hours of a single strength noradrenaline infusion at a mean dose of 6.5 mcg/min and a maximum dose of 9 mcg/min. This was infused through a 20G ante-cubital catheter. The injury was managed by aspirating the remaining vasopressor and removal of the catheter. No antidotes were required to be administered. The affected limb was kept elevated with warm compression, and the daily dressing was undertaken for five days by the plastic surgery team, but no surgical intervention was required. The patient was on the end of life care for inoperable neuro-malignancy and had opted out of a CVC. Following removal of the PVC, a new PVC was placed. The vasopressor was reinitiated through the new catheter and was tapered off after thirty-eight hours. The patient was discharged without any sequelae or morbidity.

Discussion

Vasopressors are an integral part of shock management, especially septic shock [11]. It has been shown by retrospective analysis of data of patients with septic shock that delay in vasopressor initiation causes increased mortality and hence vasopressors need to be initiated early [5,12]. Bai et al. (2014) reported that with every hour's delay in noradrenaline initiation after the onset of septic shock, mortality increased by 5.3% [13]. Although CVC has long been considered necessary by clinicians for initiating vasopressors, delay in placement due to non-availability of skilled personnel may be associated with prolonged hemodynamic instability and its related complications [14]. It is possible to initiate vasopressors early if the infusion is initiated through a PVC and even forestall the use of a CVC. CVC insertion is significantly more expensive and also time-consuming. Often CVC placement may not be

aligned with the goals of care as is the case in our study, which was performed in a cancer speciality hospital. CVC placement necessitates a skilled physician often not available in night shifts in intensive care unit or emergency rooms in resource-limited settings while a skilled nurse can competently place PVC.

There are a few recent observational studies that have evaluated the incidence of extravasation injuries. A prospective observational study by Cardenas-Garcia et al. (2015) of 734 patients receiving vasopressors through PVCs in a single centre showed the incidence of extravasation events in 19 (2%) of the patients [7]. All the injuries were managed conservatively in these patients. The study followed a strict protocol for PVC insertion, which included ultrasound guidance, retention of the catheter for a maximum of 72 hours, the use of no distal lines and strict surveillance and assessment of all patients. This may not be necessarily reproducible, particularly in resource-limited settings. A similar observational study by Delgado et al. (2016) also with a protocolised insertion of PVC and administration of phenylephrine, showed an incidence of 5% extravasation injuries which were managed conservatively [15]. Another observational study of 55 patients receiving vasopressors through a PVC done in an emergency department showed three tissue injury events. The injuries were managed conservatively too, and no morbidity was observed [16]. A retrospective chart review of 202 patients who had received vasopressors through a PVC in a New York hospital showed an incidence of extravasation events of 4%. None of the patients had severe injuries. In fact, in many of these patients, vasopressors were resumed through another PVC. There were no protocols in place for PVC placement, as in the previous observational studies [8].

Regarding the comparison of the characteristics of the PVC, vasopressors and the injury risks with other observational studies, in the present study, patients received a lower dose and shorter duration of vasopressors which could explain the lower incidence of complications. The lower dose could be because 32% of the patients initially receiving vasopressors through a PVC transitioned to a CVC on many occasions because they required an increasing dose of vasopressor. The clinicians in our study transitioned to the placement of CVC whenever patients required higher doses or longer duration of infusion of Vasopressors. The rates of CVC placement (32%) were moderate in comparison to earlier studies by Lewis et al. (2019), in which 50% of the patients were transitioned to a CVC and the study by Cardenas-Garcia et al. (2015) in which 13% required CVC.

It was also not possible to establish the median duration of infusion before the development of extravasation injuries due to wide variations in many of the studies. In the systematic review by Loubani (2015), the mean duration of infusion was 55.9 hours (0.08-528hrs)[6].

Very few studies comparing PVC and CVC for vasopressors infusion exist. Ricard et al. (2013), conducted a randomised controlled trial in three ICU in France in which 263 patients were randomised to receive either a PVC or a CVC.

This study did not specifically evaluate the safety of vasopressor infusion through a PVC or a CVC. The study concluded that the rate of complications was higher in the PVC group than the CVC group. As the results were analysed by intention to treat, events like the difficulty of placing a PVC and erythema at PVC site were listed as major complications. When a patient in the PVC group received a CVC, complications that would usually be associated with CVC insertion like pneumothorax were listed in the PVC group. This questions the validity of previous study results which showed a higher incidence of complications with PVC compared to CVC. While looking at extravasation events alone, the incidence was 17%, and all of which were managed conservatively [17]. Another similar study comparing PVC and CVC showed CVC to be associated with more major complications such as pneumothorax, and PVC to be associated with more minor complications such as phlebitis [18].

It has not been possible to identify the specific risk factors for injury, though the systematic review by Loubani (2015) points towards a higher incidence of injury if PVCs were placed distal to the forearm and infused more than for more than four hours [6]. In our study, 23% of the PVCs were placed distal, and 77% of the lines were proximal on the hand or wrist.

Distal lines tend to be smaller and more fragile and could be at a higher risk of extravasation. The present study demonstrates that when low to moderate doses of vasopressors were used for short durations, the incidence of complications was low. The study was non-interventional and did not employ any specific decision protocols for PVC or CVC placement or restricting vasopressor infusion levels.

After reviewing the existing literature, it is reasonable to state that infusion of vasopressors through a PVC is associated with minor risks, most commonly related to extravasation, which often do not require major interventions. Other concerns exist with regards to PVC usage. Flushing of vasopressors when bolus injections are given may cause hypertension. There is also a possibility of the patient receiving sub-therapeutic doses of drugs due to doubts about the continuity of infusions. Also, concerns remain regarding the impact of other 'venotoxic' drugs on the PVC.

The present study is probably the first study in India to report on the infusion of vasopressors through peripheral venous access. Every patient enrolled in the study was followed up, and all relevant outcome measures were registered. Objective criteria were used to grade and treat extravasation injuries. The study was limited in that it was a single centre observational study in a cancer speciality hospital with an inflexible skilled nurse to patient ratio. Extravasation event rates are likely to be different in mixed medical/surgical ICUs and in smaller community ICUs with a lower nurse to patient ratio. Since some of the patients transitioned to a CVC due to increasing dose of vasopressors, it is possible that there was an underestimation of the risks of PVC in this group. Patients who transitioned to a CVC could have received higher mean doses of vasopressors, but these could not be measured since such patients were not followed after transitioning to a CVC.

Conclusions

Vasopressors infusion through a PVC of 18G or larger calibre into proximal veins such as the external jugular or forearm veins is feasible and safe. The incidence of significant complications in the PVC group was small, can be conservatively managed and is not associated with significant morbidity. Initiation of vasopressors at low to moderate doses through a PVC with careful monitoring can be safely attempted in resource-limited settings.

Conflict of interest

None to declare.

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Appendix 1

Protocol for Management of Extravasation

- On suspecting extravasation, the infusion must be stopped immediately
- The critical care physician must be contacted immediately in order to assess the site and initiate treatment
- Leave the catheter in place
- Slowly aspirate as much drug as possible.
- Do not apply pressure to the area.
- The physician will initiate and administer both reversal agents in the following order:
  a. Terbutaline: 1 mg diluted in 10 mL of 0.9% saline. Inject 5 mL through the indwelling catheter atthe IV site. Inject the remaining 5 mL subcutaneously with a 27 gauge needle into the affected area around the leading edge of the extravasation site. Blanching should reverse immediately. Additional doses may be required if blanching returns.
  b. PLUS topical Nitroglycerin 2%. Apply 1-inch strip to the site of ischemia. May re-dose every 8 hours as needed
- Remove the catheter
- Establish a new peripheral access site for vasopressor administration and consider a central line
- Elevate the affected limb to minimise swelling
- Apply warm compresses for 20 minutes every 6 to 8 hours for the first 24 to 48 hours after extravasation occurs
- Advise patient to resume activity with an affected limb as tolerated
- Depending on the extent of the injury, debridement and excision of necrotic tissue should be considered if pain continues and plastic surgeon should be consulted.