Intensive Care Society

Guidance For:

The use of Vasopressor Agents by Peripheral Intravenous Infusion in Adult Critical Care Patients

Version 1.1

Contents

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List of Contributors

Standards and Guidelines Committee (ICS)

Dr Sam Clark – Trainee in Intensive Care Medicine (Mersey School of Intensive Care Medicine, Health Education England – North West), Trainee Advisory Group Member (Intensive Care Society)

Mr Greg Barton FRPharmS FFRPS MPhil – Specialist Pharmacist in Critical Care & Burns (St Helens and Knowsley Teaching Hospitals NHS Trust)

Dr Paul Dean – Chair of Standards and Guidelines Committee (Intensive Care Society), Consultant in Intensive Care and Anaesthesia (East Lancashire Hospitals NHS Trust)

Dr Yun Mei Lau – Medical Fellow (Intensive Care Society)

Ms Andrea Baldwin – Network Director, Lancs and South Cumbria Critical Care Network and Nursing Professional Affairs Group (Intensive Care Society)

List of Abbreviations

PVC Peripheral Venous Cannula

CVAD Central Venous Access Device

CVC Central Venous Cannula

Introduction

This document aims to provide guidance to adult critical care professionals on the administration of vasopressor agents via a peripheral venous cannula (PVC) to adult critical care patients and to set out safe principles and standard concentrations in order to inform local policy.

We anticipate that in most circumstances this would be done as a bridging measure as an adjunct to good patient management, until such a time that a central venous access device (CVAD) is available; or used for a short term under specific circumstances.

Whereas traditionally it has been commonplace to only administer vasopressor agents via a CVAD (with the risks of peripheral extravasation often cited as the reason for this), the practice of administering vasopressor agents peripherally is emerging (as it is in anaesthetic practice in the perioperative period) with a recent systematic review of over 1300 patients suggesting the risk of doing so being lower than is anecdotally cited [1]. This review reported that extravasation events were uncommon (event rate 3.4%), with no reported incidents of tissue necrosis or limb ischaemia.

The most common alternative to a PVC is the insertion of a central venous cannula (CVC) [2] [3]. Whilst the use of ultrasound-guided insertion will aid in the reduction of the incidence of such risks, many remain clinically significant (such as pneumothorax, arterial injury, arrhythmias and catheter-related infection) and so it seems sensible to consider circumstances wherein administration via PVC may be preferable.

Such situations might include, but are not limited to, stabilisation of critically unwell patients awaiting transfer to a critical care area; short term post-operative use; patient preference; or where central venous access would prove problematic. The decision will ultimately come down to local policy and the responsible senior decision-maker at the time.

Standards

1. Critical care units must have clear policies detailing the use of vasopressor agents administered by peripheral intravenous infusion. These policies must include details on concentration, dose and infusion of selected vasopressor agents and highlight that these concentrations may differ from the recommended standard concentrations for administration via a CVAD.
2. Critical care units must provide clear guidelines on the choice of peripheral venous access devices and their siting for the administration of vasopressor agents by peripheral intravenous infusion.
3. Critical care units must specify a protocol for regular assessment, and documentation of assessment, of indwelling intravascular catheters using a suitable scoring system.
4. Critical care units must use an infusion pump for the administration of vasopressor agents by peripheral intravenous infusion.
5. Critical care units must have clear policies for the management of extravasation events relating to vasopressor agents administered by peripheral intravenous infusion.
6. Vasopressor agents must only be administered by professionals trained in their use and competent to do so.

Recommendations

1. Peripheral venous access should ideally be of size 20G or more; be sited proximal to the wrist in the arm; avoid sites of flexion in awake patients; avoid sites requiring more than one venepuncture; and there should be a return of blood following insertion and flush easily with 5-10mL of 0.9% sodium chloride.
2. A second peripheral venous cannula should be sited as a contingency in case of a primary site failure.
3. Trusts should use standard concentrations for infusions of peripheral vasopressor agents, and these should be standardised across all clinical areas. We recommend following the standard concentrations detailed in the monographs below. Please note that these concentrations may differ from the recommended standard concentrations for administration via a CVAD.
4. Local policy should detail clinical practitioners who can initiate the use of vasopressor agents by peripheral intravenous infusion.
5. Local policy should detail in which clinical areas practitioners can initiate and/or maintain the use of vasopressor agents by peripheral intravenous infusion.
6. Local policy should detail any maximum rate and/or duration of administration of vasopressor agents by peripheral intravenous infusion.
7. Local policy should detail who, if anyone, may decide to deviate from the local policy.
8. Local policy should detail the required time interval to review the administration of vasopressor agents by peripheral intravenous infusion.
9. Invasive blood pressure monitoring is recommended but it is acknowledged that it might not be considered appropriate in all cases. Regular interval non-invasive blood pressure monitoring must be ensured in these cases.
10. Where an adverse event occurs (for example, extravasation of vasopressor agent), this should be reported and investigated using the local healthcare organisation’s incident reporting system. All learning should be widely shared.

Adrenaline

PHarmacological Properties

Adrenaline is a direct-acting sympathomimetic agent with both alpha- and beta-adrenergic activity, the former being predominant at higher doses. Its effect on blood pressure ceases about 2-3 minutes after discontinuing the infusion.

Presentation

Adrenaline 1mg/mL (1:1000) solution for injection.

Dilution

For dilution in either 0.9% sodium chloride injection or 5% glucose.

The recommended standard concentration in an adult critical care area for administration via peripheral venous cannula is 16microgram/mL.

Example dilution: Dilute 4mg Adrenaline (4mL of Adrenaline 1mg/mL) with 246mL 0.9% sodium chloride to provide a concentration of 16microgram/mL.

Method of Administration & Dose

Administer via an infusion pump at a rate of 210microgram/hour (13mL/hour of the standard concentration given above, based on a 70kg patient at a starting dose of 0.05microgram/kg/min). Titrate to desired effect.

Special Considerations

After discontinuation, flush the peripheral cannula with sodium chloride 0.9% at the same rate the medicine was infused to avoid adverse haemodynamic effects.

The concomitant administration of adrenaline and other medicines via a Y-site should be avoided to prevent inadvertent bolus administration of adrenaline.

Sources of Information

Electronic Medicines Compendium available at **http://www.medicines.org.uk** [4]

Medusa Injectable Medicines Guide available at **http://medusa.wales.nhs.uk** [5]

Medicines Complete available at **http://www.medicinescomplete.com** [6]

Noradrenaline

Pharmacological Properties

Noradrenaline is a sympathetic agent with both alpha- and beta-adrenergic activity, the former being predominant at the concentrations used in clinical practice. Its effect on blood pressure ceases 1-2 minutes after discontinuing the infusion.

Presentation

Noradrenaline 1mg/mL concentrate for solution for infusion.

Dilution

For dilution in either 0.9% sodium chloride injection or 5% glucose.

The recommended standard concentration in an adult critical care area for administration via peripheral venous cannula is 16microgram/mL.

Example dilution: Dilute 4mg Noradrenaline (4mL of Noradrenaline 1mg/mL) with 246mL 0.9% sodium chloride to provide a concentration of 16microgram/mL.

Method of Administration & Dose

Administer via an infusion pump at a rate of 210microgram/hour (13mL/hour of the standard concentration given above, based on a 70kg patient at a starting dose of 0.05microgram/kg/min*). Titrate to desired effect.

Special Considerations

After discontinuation, flush the peripheral cannula with sodium chloride 0.9% at the same rate the medicine was infused to avoid adverse haemodynamic effects.

The concomitant administration of noradrenaline and other medicines via a Y-site should be avoided to prevent inadvertent bolus administration of noradrenaline.

Sources of Information

Electronic Medicines Compendium available at **http://www.medicines.org.uk** [4]

Medusa Injectable Medicines Guide available at **http://medusa.wales.nhs.uk** [5]

Medicines Complete available at **http://www.medicinescomplete.com** [6]

*Starting dose based on CENSER study [7]

Metaraminol

None of the recent observational studies cited above investigated the use of metaraminol as a vasoactive agent, nor could we find any publications pertaining to it in the context of this guidance. However, it is commonly used in practice therefore has been included in this guidance. Recommendations are made from the summary of product characteristics and consensus opinion.

Pharmacological Properties

Metaraminol is a sympathetic agent with direct and indirect effects on adrenergic receptors. It has both alpha- and beta-adrenergic activity, the former being predominant. The effects of metaraminol are similar to those of noradrenaline but it is much less potent and has more prolonged action – the effect of a single dose lasts from about 20 minutes up to one hour (therefore effects taper off when therapy is stopped). Its onset is around one or two minutes.

Presentation

Metaraminol 10mg/mL Solution for injection or infusion.

Dilution

For dilution in either 0.9% sodium chloride injection or 5% glucose.

The recommended standard concentration in an adult critical care area for administration via peripheral venous cannula is 0.5mg/mL.

Example dilution: Dilute 20mg Metaraminol (2mL of Metaraminol 10mg/mL) with 38mL 0.9% sodium chloride to provide a concentration of 0.5mg/mL.

Method of Administration & Dose

Administer via an infusion pump at a rate of 0.5mg to 10mg/hour (1 to 20mL/hour of the standard concentration given above).

Special Considerations

After discontinuation, flush the peripheral cannula with sodium chloride 0.9% at the same rate the medicine was infused to avoid adverse haemodynamic effects.

Use in caution in patients on digoxin since the combination can cause ectopic arrhythmic activity.

Sources of Information

Electronic Medicines Compendium available at **http://www.medicines.org.uk** [4]

Medusa Injectable Medicines Guide available at **http://medusa.wales.nhs.uk** [5]

Medicines Complete available at **http://www.medicinescomplete.com** [6]

Phenylephrine

Pharmacological Properties

Phenylephrine is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity. It is effective for up to 20 minutes.

Presentation

Phenylephrine 10mg/mL Solution for injection or infusion.

Dilution

For dilution in either 0.9% sodium chloride injection or 5% glucose.

The recommended standard concentration in an adult critical care area for administration via peripheral venous cannula is 100microgram/mL.

Example dilution: Dilute 50mg Phenylephrine (5mL of Phenylephrine 10mg/mL) with 495mL 0.9% sodium chloride to provide a concentration of 100microgram/mL.

Method of Administration & Dose

Administer via an infusion pump at a rate of up to 10.8mg/hour initially (108mL/hour of the standard concentration given above) reduced according to response to between 1.8-3.6mg/hour (18-36ml/h of the standard concentration).

Special Considerations

After discontinuation, flush the peripheral cannula with sodium chloride 0.9% at the same rate the medicine was infused to avoid adverse haemodynamic effects.

Metabolised by monoamine oxidase therefore contraindicated in patients on monoamine oxidase inhibitors.

Sources of Information

Electronic Medicines Compendium available at **http://www.medicines.org.uk** [4]

Medusa Injectable Medicines Guide available at http://medusa.wales.nhs.uk [5]

UK Clinical Pharmacy Association Minimum Infusion Volumes For fluid restricted critically ill patients. 4ed. [8]

Background

Many publications describing extravasation and local tissue injury resulting from administration of vasopressor agents via a peripheral or central route pre-date 1969 and such reports may not accurately reflect current practice [9]. A more recent retrospective case note review in the United States of 202 patients found an extravasation event rate of 4% (2 patients receiving noradrenaline and 2 patients receiving phenylephrine via a PVC), with all events being of lower severity grading and requiring only conservative management [10]. This is supported by four other studies (two retrospective case note reviews and two prospective observational studies) reporting event rates of 2% [11], 3% [12], 5% [13] and 5.5% [14], again without any tissue injury or requiring any surgical intervention. Another retrospective chart review of 91 patients treated with noradrenaline, with the majority (86.8%) administered via a peripheral cannula, reported "no signs of ischaemia or necrosis around the area of infusion" in either group [15]; and another more recently reported an exceptionally low event rate of 0.035% (5/14,385 patients) when administering noradrenaline peripherally in elective peri-operative patients – whilst acknowledging that this is a different patient population to other studies cited [16]. One study however did report higher adverse event rates with PVC versus CVC, although on closer inspection the most frequently reported event was difficulty in inserting the line itself [17].

For comparison we sought complication rates for CVC, however, studies are very much heterogeneous. Two recent small observational studies found complication rates of between 1.9% (mechanical complications only) and 5.9% [18] [19]. We consider that these rates are at least comparable, however as stated previously, complications associated with CVC insertion remain clinically significant, therein lying the case for the use of PVC outlined in this document.

Choice of size and site of peripheral venous cannula

There is no persuasive evidence to suggest a link between the choice of site for PVC and extravasation events. Cardenas-Garcia et al 2015 reported the in the majority of cases (75%) vasoactive agents were administered through a 20G cannula and they reported the lowest event rate of 2% [11]. Other studies reported variability regarding PVC size and location where extravasation events occurred [10], or had implemented specific requirements for inclusion
(such as vein diameter measured on ultrasonography, upper extremity only, 18G or 20G cannula size etc.) [11] [14].

We would suggest that clinicians choose a site in which they are confident and consider the use of ultrasound in their assessment. Some of the studies that we have cited employed common-sense guidance on choice of size and site of PVC which we feel would be wise to follow:

- Choose at least a 20G PVC size
- Locate in a site in the arm, proximal to the wrist
- Avoid sites of flexion in awake patients due to the risk of occlusion
- Avoid sites requiring more than 1 venepuncture
- Ensure there is a return of blood following insertion of the PVC and that the PVC flushes easily with 5-10mL of 0.9% sodium chloride
- Site a second PVC in case of failure of the primary site

Midline catheters may also be considered (peripherally inserted catheters which can be inserted into larger veins where blood flow is generally faster and duration of use can be up to 28 days) as an alternative where appropriate training and experience is available [20].

Standardising Concentration and Dosage

There is minimal data from the existing evidence to wholly support a single standardised concentration. However, based on consensus opinion we have provided a recommended standard concentration in order to reduce the risk of error that might occur should variable concentrations be used. Tables 1 and 2 in the appendix summarise the relevant information from the studies referenced in this document. **It should be noted that these concentrations are reduced as compared to those recommended for administration via a CVAD and as such are not interchangeable.**

Duration of Infusion

There is minimal data existing to wholly support a maximal duration of infusion with regards to safety. However, from the minimal available data, it may be that infusion via a PVC is safe for a matter of days though we acknowledge that it would be expected that the risk would increase with duration of infusion. Therefore, this should be determined locally and be at the discretion of the responsible senior decision-maker on a case by case basis. Table 3 in the appendix summaries the relevant information from the studies referenced in this document.

Extravasation

Extravasation describes the inadvertent leakage of any drug or fluid into the surrounding tissues. Events may occur due to multiple risk factors including those related to the access device, the infusion or the patient [21]. Regular monitoring of the infusion site is essential to enable early recognition and management of extravasation events.

There are only case reports to support the management of extravasation. In the studies referenced in this guideline, there was no documented tissue injury or any need for surgical intervention. Local guidelines should be followed in the event of extravasation and a conservative strategy as suggested in Figure 1 may be considered sufficient.

Figure 1. Suggested management of an extravasation event.

1. Stop the infusion immediately and disconnect the line from the PVC.
2. Attempt to aspirate 3-5mL from the PVC if able.
3. Remove the cannula and apply a dressing to the removal site.
4. Mark the extravasation area if possible, in order to allow monitoring of any developing injury.
5. Elevate the affected limb if able to do so to reduce swelling.
6. Consider application of a topical vasoactive agent to encourage local blood flow (for example nitroglycerin paste).
7. Administer analgesia if required.
8. Seek advice from a surgeon or your local tissue viability service if concerned.
9. Document the incident and report via local incident reporting system.

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Table 1. Drug concentrations reported in publications

Study	Noradrenaline Concentration range (Dilution)	Phenylephrine Concentration range (Dilution)
Pancaro et al 2020 [16]	20 microgram/ mL	Not studied
Permpikul et al 2019 [7]	16 microgram/ mL (4mg in 250mL)	Not studied
Lewis et al 2019 [10]	16 to 64 microgram/ mL	20 to 400 microgram/mL
Datar et al 2017 [12]	Not studied	120 microgram/mL
Medlej et al 2017 [14]	32 microgram/mL (8mg in 250mL)	Not studied
Delgado et al 2016 [13]	Not studied	40 microgram/mL
Cardenas-Garcia et al 2015 [11]	32 to 64 microgram/ mL (8 to 16mg in 250mL)	160 to 320 microgram/mL (80 – 160mg in 500mL)

Table 2. Drug doses reported in publications

Dose	Noradrenaline Dose range	Phenylephrine Dose range
Pancaro et al 2020 [16]	0.01 microgram/kg/min (starting dose) 0.1 microgram/kg/min (maximum dose)	Not studied
Permpikul et al 2019 [7]	0.1 microgram/kg/min (median dose); 0.05-0.18 microgram/kg/min (IQR)	Not studied
Lewis et al 2019 [10]	0.08 microgram/kg/min (median dose); 0.04-0.13 microgram/kg/min (median min/max dose)	50 microgram/kg/min (initial dose); 25-95 microgram/kg/min (median min/max)
Datar et al 2017 [12]	Not studied	1.04 (0.07-3.49) microgram/kg/min (mean max dose (range))
Medlej et al 2017 [14]	30 microgram/minute (max rate)	Not studied
Delgado et al 2016 [13]	Not studied	0.53 (0.19-1.84) microgram/kg/min (Average dose (range))
Hallengren et al 2016 [15]	0.05 microgram/kg/min (starting dose); 0.2 microgram/kg/min (maximum dose)	Not studied
Cardenas-Garcia et al 2015 [11]	0.7±0.23 microgram/kg/min (SD)	3.25±1.69 microgram/kg/min (SD)

Table 3. Duration of peripheral vasopressor infusion reported in publications

Study	Noradrenaline Median (Range), hours	Phenylephrine Median (Range), hours
Lewis et al 2019 [10]	7.45 (3-23)	15 (6-38)
Datar et al [12]	Not studied	Mean 19 (1-129)
Medlej et al 2017 [14]	13 (2-146)	Not studied
Delgado et al 2016 [13]	Not studied	14.29 (1-54.3)
Cardenas-Garcia et al 2015 [11]	Not provided for individual drugs. Duration quoted as 49±22 hours	

Intensive Care Society I Churchill House I 35 Red Lion Square I London I WC1R 4SG
T: +44 (0)20 7280 4350 E: info@ics.ac.uk W: www.ics.ac.uk

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