Safety of Early Norepinephrine Infusion Through Peripheral Vascular Access During Transport of Critically ill Children

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Research

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Abstract

Background

Reversal of hypotension is a priority in the management of a collapsed child. The pediatric Surviving Sepsis Campaign advocates for the rapid use of epinephrine or norepinephrine for sepsis related myocardial or vascular dysfunction following 40-60ml/kg of fluid resuscitation. Vasoactive drugs should be started within the first hour after sepsis recognition in a patient with shock. In such a short delay, central venous access can be difficult to obtain, and infusion may be initially started through a peripheral catheter. Hereby, we reported the safety of norepinephrine infusion through a peripheral catheter in retrieved shocked patients.

Methods

Multicentric retrospective analysis of medical pediatric retrieval teams experience of vasopressors infusion through a peripheral vascular access. Medical pediatric retrieval teams (SMUR) and Pediatric Intensive care units (PICU) of the Paris urban region. Children 0 to 18 years necessitating norepinephrine infusion during retrieval. Modalities of infusion (drip concentration, duration, site of infusion), incidence of complication and outcome at PICU discharge were reviewed.

Results

Thirty-seven children in shock received a norepinephrine infusion for a median time of 4 hours. No local adverse event was noted. One patient had transient blanching of the skin which improved after appropriate care. The overall mortality was 10.8% with one death (2.7%) during transport and 3 (8.1%) in PICU.

Conclusions

During transport of critically ill patients requiring vasopressor infusion by a specialized pediatric retrieval team, the use of norepinephrine on a non-central catheter was safe among all patients.

Background

Shock and hypotension are associated with substantial mortality in critically ill children. Early reversal of shock is a priority. Sepsis and septic shock or hemorrhagic shock may require vasoactive treatment with minimal delay. The latest recommendation from the Pediatric Surviving Sepsis Campaign (SSC), suggests starting epinephrine or norepinephrine (NE) within the first hour following sepsis recognition in children with septic shock (1). An increasing number of studies supports the early use of vasopressors (2–6). It is admitted that the infusion route of vaso-active treatment is preferably a central venous access (CVA). Use of peripheral venous access (PVA) is recommended in the latest pediatric SSC guidelines, but reluctance may delay its use, mainly due to concern of local tissue injury (7). In adults, Ricard et al. found an increase in adverse effects when a PVA was preferred compared to a CVA in ICU (8). The insertion of a

CVA in a critically ill child is challenging to non-trained specialists (9). Pediatric specialized transport teams and emergency medical service (EMS) personnel are the first responders in critical situations; their lack of experience in CVA placement might delay vasopressor initiation, thus delaying shock reversal. The administration of vasopressors on a PVA in children was reported in a small cohort (10), but not in the context of transport. In Paris, pediatric retrieval teams consist of at least one senior medical officer/fellow, a pediatric transport nurse and a specialized ambulance driver. Local guidelines advocate the use of NE for reversal of hypotension and shock. This study aimed to assess the safety of NE use on a PVA in children retrieved by a specialized pediatric transport team.

Methods

Design and inclusion

We performed a retrospective multicenter study of children and neonates who received NE on a PVA during transport by two Parisian pediatric transport teams (SMUR 92/Antoine Béclère and SMUR 75/Robert Debré) to neonatal or pediatric ICUs between January 1st, 2015 and December 31st, 2017. Patients were identified using electronic institutional medical coding records and all consecutive patients aged 0 days to 18 years at the time of transport were included. A PVA was defined as either a peripheral intravenous catheter (PIVC) or an intra-osseous catheter (IOC). The safety profile of norepinephrine administration was assessed with the presence of local tissue injury as described by Loubani et al. (11). In case of infusion related complications (extravasation, local and loco-regional tissue injury), clinical evaluation from both the transport and the ICU teams was systematically reported. All the data were de-identified and secured on a password-protected file in a dedicated research computer. Initial data screening was performed by VO and SJ, data were then collected by RC and VO). When data were present, it was encoded numerically based on the variable present. We examined medical records of retrieval team as well as corresponding ICUs looking for reports of local and regional tissue injury including, but not limited to, diffusion, local necrosis, hematoma, thrombophlebitis and osteitis (11), during or after the administration of NE on a PVA. Patients characteristics included age, sex, weight, type of shock, maximum lactate level and volume expansion prior to initiation of NE. We also documented the site of NE administration, the concentration of the solution, the maximum infusion rate and duration of infusion as well as transport duration. The legal representatives of the children were informed of the possibility that data concerning their child could be analyzed and published by the mean of an information leaflet with possibility of refusal and ulterior opposition. The ethical committee of the French Intensive Care Society reviewed the protocol and agreed to the study (CE SRLF 18-24) and the data registry was declared in conformity with the General Data Protection Regulation. Data were presented as medians and interquartile ranges. A univariate analysis of causes for tissue injury was planned in the presence of more than 5 complications.

Results

Between January 1st 2015 and December 31st 2017, 8 890 critically ill children were transported by the two pediatric retrieval teams. We identified 37 children aged 0 days to 8 years (median 1.8 months) who required NE infusion through a PVA. Thirty-two (86.5%) were treated for septic shock, 4 (10.8%) for hemorrhagic shock and 1 (2.7%) had a tension pneumothorax. They received a median of 45 ml/kg of resuscitative fluids prior to NE infusion. Mechanical ventilation was needed in 78% of the cases. Median lactate was 8.8 mmol/L [3.6-12.9] (Table 1). NE was administered through a PIVC in 32 patients (86%) and on an IOC in 5 patients. The PIVC was located preferentially on the upper distal limb and IOC on the proximal tibia. During administration, NE concentration ranged from 10 µg/ml to 1271 µg/ml (median 154 [40-245] µg/ml) and maximum doses ranged from 0,03 µg/Kg/min to 2,00 µg/kg/min (median 0.3 [0.2-0.6] µg/kg/min). Before NE, the patients received a median fluid volume of 45 ml/kg [20-60]. Median transport duration was 20 minutes [15-41]. Median duration of NE infusion through a PVA before a CVA was inserted was 230 minutes [160-270]. Twenty-seven patients received NE only infusion and 10 (27%) received another vasopressor or inotrope concomitantly (7 had dobutamine and 3 had epinephrine). Children were transferred from emergency departments or pediatric wards to the ICU (N=34, 92%) and some were primary retrieved from home (N=3, 8%).

No patient but one had any perfusion-related complication. This patient, aged less than a day and weighing 2270 g, received a NE infusion (concentration = 160 µg/ml) at a maximum rate of 0.3ml/h on a 24-Gauge PIVC located on the left hand and showed signs of local tissue altered perfusion at the site of puncture with suspected extravasation. This was noted 135 minutes after initiation. NE infusion was immediately moved to another PVA as per local protocols for perfusion-related complications. The local tissue perfusion returned to normal within minutes and there were no local nor systemic sequelae after the catheter removal.

Discussion

Early **start** of inotrope or vasopressor is a mainstay of the management of pediatric septic shock (1). Norepinephrine and epinephrine are both recommended as first line therapy when a child is hypotensive or in shock. To date, NE administration through a PVA is feared in children due to concern of local injury. We report a cohort of 37 patients who received NE through a PVA during retrieval transport for a median duration of 4 hours. No local adverse event occurred. One neonate had transient limb hypoperfusion. Given the scarcity of complications, we were unable to identify any direct relationship between any of the criteria and the incidence of local injury. Few studies described NE use on PVA. Lampin et al. reported a monocentric study on 27 patients who received NE on a PVA in PICU without complications (10). Turner et al. reported the use of vasoactive drugs (mostly dopamine) during transport of ill children (12). They found a 15% rate of intravenous infiltrate without any severe complication. Higher infusion rate and longer duration of infusion were associated with risk of infiltrate. Hereby, we show in a multicenter retrospective study that NE can be safely used on a PVA.

The main risk of NE vascular extravasation remains soft tissue ischemia and necrosis due to its vasoconstrictive alpha-adrenergic effect. It is recommended that in case of soft tissue infiltrate with

suspected NE extravasation the infusion be instantly stopped and transitioned to another PVA or a CVA. If the infiltrate is confirmed, best practices for tissue salvage include leaving the cannula on site, aspirating as much as possible both the drug and blood while removing it slowly, discussing with a pharmacist the use of sub-cutaneous injection of phentolamine (5–10 mg in 10 mL of saline) at the extravasation site (13) or discussing with plastic surgeons the use of saline flushes through multiple incisions around the extravasation site (14). Nevertheless, given the high benefit of the early administration of NE in pediatric septic shock and the difficulty obtaining an early CVA, peripheral infusion of NE can prove beneficial in restoring hemodynamic stability and complying with the pediatric SSC guidelines (1). Some patients with hemorrhagic shock may benefit from NE in addition to conventional fluid resuscitation (15).

Our study has some limitations. As with any retrospective cohort, ours is limited by reporting bias. Although we have identified patients included in the coding software and collected data logged into those patients' files, it is possible some relevant events were not logged, which weakens this study. Our results may have a positive bias as the retrieval teams are specialized in both critical care and pediatric and neonatal transport, hence preventing our findings from being generalized to all settings.

Conclusions

We report our experience of NE infusion through PVA during pediatric transport without any notable complication. Research with larger cohorts is required to identify factors predisposing to local injury and to clarify the impact of a rapid peripheral infusion of NE on outcome of children with shock.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of the French intensive care society. The study is in conformity to the French Information and Liberty Commission and the European General Rule for of Data Protection

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

Ramy Charbel : Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing

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Noella Lode : Writing - Review & Editing

Pierre Tissières : Writing - Review & Editing, Project administration

Luc Morin : Conceptualization, Methodology, Data curation, Writing – Original Draft, Writing – Review and Editing, Supervision.

All authors approved and reviewed the article.

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References

1. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med.* 2020 Feb;46(Suppl 1):10–67.
2. Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care.* 2014 Oct 3;18(5):532.
3. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. *Pediatrics.* 2012 Aug;130(2):e273-280.
4. Paul R, Melendez E, Stack A, Capraro A, Monuteaux M, Neuman MI. Improving adherence to PALS septic shock guidelines. *Pediatrics.* 2014 May;133(5):e1358-1366.

5. Ranjit S, Natraj R, Kandath SK, Kissoon N, Ramakrishnan B, Marik PE. Early norepinephrine decreases fluid and ventilatory requirements in pediatric vasodilatory septic shock. *Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med*. 2016 Oct;20(10):561–9.
6. Delaney A, Finnis M, Bellomo R, Udy A, Jones D, Keijzers G, et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. *Emerg Med Australas EMA*. 2020 Apr;32(2):210–9.
7. Marx J, Hockberger R, Walls R. *Rosen's Emergency Medicine: Concepts and Clinical Practice* [Internet]. 9th ed. Saunders; 2013. 2808 p. Available from: <https://www.elsevier.com/books/rosens-emergency-medicine-concepts-and-clinical-practice/walls/978-0-323-35479-0>
8. Ricard J-D, Salomon L, Boyer A, Thiery G, Meybeck A, Roy C, et al. Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial. *Crit Care Med*. 2013 Sep;41(9):2108–15.
9. Malbezin S, Gauss T, Smith I, Bruneau B, Mangalsuren N, Diallo T, et al. A review of 5434 percutaneous pediatric central venous catheters inserted by anesthesiologists. *Paediatr Anaesth*. 2013 Nov;23(11):974–9.
10. Lampin ME, Rousseaux J, Botte A, Sadik A, Cremer R, Leclerc F. Noradrenaline use for septic shock in children: doses, routes of administration and complications. *Acta Paediatr Oslo Nor* 1992. 2012 Sep;101(9):e426-430.
11. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. *J Crit Care*. 2015 Jun;30(3):653.e9-17.
12. Turner DA, Kleinman ME. The use of vasoactive agents via peripheral intravenous access during transport of critically ill infants and children. *Pediatr Emerg Care*. 2010 Aug;26(8):563–6.
13. Plum M, Moukhachen O. Alternative Pharmacological Management of Vasopressor Extravasation in the Absence of Phentolamine. *P T Peer-Rev J Formul Manag*. 2017 Sep;42(9):581–92.
14. Gopalakrishnan PN, Goel N, Banerjee S. Saline irrigation for the management of skin extravasation injury in neonates. *Cochrane Database Syst Rev* [Internet]. 2017 Jul 19 [cited 2020 May 13];2017(7). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6483149/>
15. Beloncle F, Meziani F, Lerolle N, Radermacher P, Asfar P. Does vasopressor therapy have an indication in hemorrhagic shock? *Ann Intensive Care*. 2013 May 22;3(1):13.

Tables

Table 1. Patient characteristics

Characteristics, <i>n</i>=37	Median [IQR] or N (%)
Age, months	1.8 [0.03-12.7]
Weight, Kg	4 [3-7]
Sex	
Male	24 (65%)
Female	23 (35%)
Type of shock	
- Septic	32 (86.5%)
- Hemorrhagic	4 (10.8%)
- Tension pneumothorax	1 (2.7%)
Initial ventilation	
- Mechanical	29 (78%)
- Spontaneous	8 (22%)
Median fluid boluses, ml/Kg	45 [20-60]
Lactate, mmol/L	8.8 [3.6-12.9]
Additional inotrope	
- Dobutamine	7 (19%)
- Epinephrine	3 (8%)
NE infusion	
Dose, µg/Kg/min	0.3 [0.2-0.4]
Concentration, µg/ml	154 [40-245]
Rate, ml/h	0.9 [0.5-2]
Duration, min	230 [160-270]
Infusion site	
Intra osseous	5 (14%)
- Proximal tibia	4 (80%)
- Distal femur	1 (20%)
Intra venous	32 (86%)
- Hand	20 (63%)

-	Arm	8 (25%)
-	Foot	3 (9%)
-	Scalp	1 (3%)

Values are expressed as number (percentage) or median [interquartile range]