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BRIEF RESEARCH REPORT

Pediatrics

Safety of early norepinephrine infusion through peripheral vascular access during transport of critically ill children

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Abstract

Study objective: In prehospital and emergency settings, vasoactive medications may need to be started through a peripheral intravenous catheter. Fear of extravasation and skin injury, with norepinephrine specifically, may prevent or delay peripheral vasopressor initiation, though studies from adults suggest the actual risk is low. We sought to study the risk of extravasation and skin injury with peripheral administration of norepinephrine in children in the prehospital setting.

Methods: We performed a retrospective study of pediatric patients (≤18 years) who received a vasopressor during prehospital transport. We collected data from retrieval and hospital records from 2 pediatric medical retrieval teams in the Paris/Ile-de-France region. Patients were eligible if they had documentation of distributive or obstructive shock and administration of norepinephrine through a peripheral catheter (intravenous or intraosseous) during retrieval. The primary outcomes were the occurrence of extravasation and evidence of skin injury. We also examined approach to norepinephrine administration (concentration, duration, proximal vs distal site) and hospital outcomes.

Results: Over a 3-year-period, 37 pediatric patients received norepinephrine through a peripheral catheter (33 intravenous, 4 intraosseous). Median patient age was 1.8 years. Thirty-two patients (86.5%) had septic shock. The median total duration of norepinephrine infusion was almost 4 hours. One patient (2.7%, 95% confidence interval 0.5%, 13.8%) had suspected extravasation from a 24-gauge intravenous catheter in the hand, with local skin hypoperfusion. Skin changes were noted after 135 minutes of norepinephrine infusion. Perfusion normalized after catheter removal, and there were no other sequelae.

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Conclusions: In a 3-year sample of pediatric patients from a large metropolitan area, we found only 1 patient with evidence of any harm with peripheral administration of norepinephrine. This finding is consistent with the adult literature but requires multicenter and multiyear investigation before a firm recommendation for this practice can be made.

KEYWORDS
norepinephrine, pediatric, sepsis, shock, transport, vascular access

1 | INTRODUCTION

1.1 | Background

Shock is associated with substantial morbidity and mortality, and early reversal of shock is a priority of initial care. The latest guidelines from the 2020 Pediatric Surviving Sepsis Campaign (SSC) suggest starting epinephrine or norepinephrine within the first hour if intravenous fluids fail to resolve evidence of shock.[1] Central venous access is the preferred route for vasopressors, but the technical requirements may prevent or delay the use of central access, especially in the prehospital setting. Clinician inexperience with central access has also been associated with delays in vasopressor administration.[2]

1.2 | Importance

The 2020 SSC guidelines recommend peripheral vascular access for the initial management of sepsis. Because of a lack of sufficient evidence, the guidelines were unable to issue a recommendation about initiating vasopressors through peripheral vascular access. In a post-hoc analysis of data from the Australasian Resuscitation In Sepsis Evaluation (ARISE) study, adult patients with septic shock received vasopressors 2.5 hours earlier if norepinephrine was initiated through peripheral vascular access, without increasing the risk of complications.[3] In a systematic review of extravasation and skin injury with peripheral vasopressors in hospitalized adults, Loubani and Green reported 270 patients from 85 case reports.

The pediatric literature is even more limited, with only 1 published study on the safety of peripheral vasopressors. In a cohort of 27 children in a pediatric intensive care unit (PICU), Lampin et al found no cases of adverse events associated with norepinephrine infusion through peripheral vascular access.[4] No study has examined peripheral vasopressors in the prehospital setting. Pediatric transport teams and emergency medical service personnel are commonly the first clinicians to care for children with shock. Lack of experience with central access and concerns about extravasation and skin injury may delay or prevent the administration of vasopressors through peripheral vascular access. Determining the risk of peripheral vasopressors is essential to overcoming clinician hesitancy about the safety of this practice.

1.3 | Goals of this investigation

The purpose of this study was to address the gap in the literature, specifically for children in the prehospital setting. Our study objective was to determine the frequency of extravasation and skin injury with norepinephrine administration through peripheral vascular access in children in the prehospital setting.

2 | METHODS

2.1 | Design and setting

We performed a retrospective study of pediatric patients who received norepinephrine through peripheral vascular access during transport by 1 of 2 Parisian pediatric retrieval teams (SMUR 92/Antoine Béclère and SMUR 75/Robert Debré). In Paris, pediatric retrieval teams consist of at least 1 senior medical officer/fellow (physician), a pediatric transport nurse, and a specialized ambulance driver. Local retrieval team guidelines advocate for the use of norepinephrine, started on peripheral catheter, for reversal of hypotension and vasoplegic shock.

The ethical committee of the French intensive care society reviewed and approved the study protocol before commencement and the data registry was declared in conformity with the General Data Protection Regulation. Legal representatives of retrieval team patients were informed of the possibility that their child's data could be used in research, with the possibility of refusal and ulterior opposition.

2.2 | Selection of participants

We included all patients who met the following criteria: (1) age 0 days to 18 years of age at the time of transport, (2) received norepinephrine prehospital and through peripheral vascular access, and (3) transported from January 1, 2015 through December 31, 2017 (36 months). Peripheral vascular access consisted of a peripheral intravenous catheter (PIV) or an intraosseous (IO) catheter. Patients were identified using the electronic medical records (EMRs) from the retrieval teams and receiving institutions.

2.3 | Data collection

Two investigators (VO and SJ) performed the initial screening for eligible patients. Two investigators (RC and VO) collected study from the EMR data using a standardized abstraction form (Microsoft Excel, Microsoft Corporation, Redmond, WA). The 2 primary data sources were the retrieval team records and PICU records. Data for extravasation and adverse events were coded as present or absent, without imputation of missing values; no documentation of an adverse event in the EMR was considered an absence of the adverse event. Patients characteristics included age, sex, weight, type of shock, maximum lactate level, and expansion volume before initiation of norepinephrine. We documented the site of norepinephrine administration, the concentration of the solution, the maximum infusion rate, and duration of infusion as well as transport duration.

2.4 | Outcomes

The main outcomes were extravasation and associated adverse events, including local and regional skin injury and abnormal perfusion. Extravasation and adverse events were defined based on the systematic review by Loubani and Green.[5] In the case of perfusion abnormalities, we relied on clinical documentation from the retrieval team and PICU.

2.5 | Statistical analysis

We tabulated all data and generated standard descriptive statistics. For the main outcomes, we report the proportion of patients with either extravasation or adverse events, with a 95% confidence interval (CI). We planned an analysis of factors associated with the main outcomes, but there were too few patients with either outcome.

3 | RESULTS

3.1 | Enrollment

Between January 1, 2015 and December 31, 2017 (36 months), 8890 critically ill children were transported by the 2 pediatric retrieval teams. Thirty-seven of these children (0.4%) received norepinephrine infusion through peripheral vascular access: 32 through a PIV and 5 through an IO. Because of missing data, we could not report on norepinephrine dilution and rate for 3 patients and time of infusion initiation and transition to central venous catheter (CVC) for 6 patients.

3.2 | Subject characteristics

Median patient age was just under 2 years (Table 1). All but 5 patients had septic shock and the median lactate was nearly 9 mmol/L. All patients received at least 1 fluid bolus before norepinephrine. Almost 80% of patients underwent tracheal intubation and mechanical ventilation.

PIVs were generally placed in the arm, and the IOs were all placed in the leg (Table 2). Norepinephrine concentrations ranged from 10 to 1271 μg/mL, and the maximum dose ranged from 0.03 μg/Kg/min to 2.00 μg/kg/min. Most transport times were ≈20–30 minutes, and the median total duration of peripheral norepinephrine infusion was almost 4 hours. Ten patients (27%) received another peripheral vasopressor along with norepinephrine.

The Bottom Line

Concerns about extravasation and skin injury may prevent the use of peripheral vasopressors in shock. The literature on harm from peripheral vasopressors, however, is very limited, especially in children. In this retrospective study from 2 prehospital groups in Paris, France, there were no serious injuries among 37 pediatric patients with peripheral norepinephrine. Multicenter investigations are needed, but the available literature suggests that serious adverse events from peripheral vasopressors are not common.

TABLE 1 Characteristics of 37 pediatric patients with norepinephrine administration through peripheral vascular access in the prehospital setting

Median [IQR] or n (%) shown	
Characteristics	n = 37
Age, mo	1.8 [0.03–12.7]
Weight, Kg	4 [3–7]
Male	24 (65%)
Type of transport	
Primary	3 (8%)
Transfer out to a tertiary center	34 (92%)
Type of shock	
Septic	32 (86.5%)
Hemorrhagic	4 (10.8%)
Tension pneumothorax	1 (2.7%)
Lactate, mmol/L	8.8 [3.6-12.9]
Median fluids, mL/Kg	45 [20–60]
Mechanical ventilation	29 (78%)
Additional inotrope	
Dobutamine	7 (19%)
Epinephrine	3 (8%)

IQR, interquartile range.

TABLE 2 Vascular access and norepinephrine infusion characteristics

Median [IQR] or n (%) shown	
Infusion site	
Intravenous	32 (86%)
Hand	20 (63%)
Arm	8 (25%)
Foot	3 (9%)
Scalp	1 (3%)
Intraosseous	5 (14%)
Proximal tibia	4 (80%)
Distal femur	1 (20%)
Norepinephrine	
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]

IQR, interquartile range.

3.3 | Main outcome

One patient (2.7%, 95% CI 0.5%, 13.8%) with norepinephrine through peripheral vascular access had suspected extravasation with transient local skin blanching. The patient was day of life 0 and weighed 2270 g. The norepinephrine concentration was 160 μg/mL and the maximum rate was 0.3 mL/h. The PIV was a 24-gauge in the left hand. The retrieval team documented signs of abnormal tissue perfusion at the site of the PIV 135 minutes after norepinephrine initiation, with suspected extravasation. The PIV was removed and the norepinephrine infusion moved to another peripheral vascular access. The local tissue perfusion reportedly normalized within minutes and there were no sequelae.

4 | LIMITATIONS

Our study has 2 main limitations. As with any study based on EMR review, ours is limited by the accuracy and completeness of documentation. It is possible we missed patients with norepinephrine administration and patients with related injuries because of the absence of documentation. We believe it is unlikely, however, that severe injuries would be completely absent from the medical record. Second, our study was specific to retrieval teams in Paris, France, who are specialized in pediatric and neonatal transport. Hence, our findings may not be broadly generalizable.

5 | DISCUSSION

Early vasopressors are a mainstay of the management of fluid refractory septic shock.[1] Norepinephrine and epinephrine are both options for first-line therapy. Concerns about extravasation and severe tissue injury may limit the use of vasopressors through peripheral access. The main risk of norepinephrine is extravasation with soft tissue ischemia and necrosis owing to its vasoconstrictive alpha-adrenergic effect.

We found no cases of severe skin injury from extravasation of norepinephrine through a peripheral vascular access from a series of 37 pediatric patients collected over 3 years from 2 pediatric retrieval units in Paris. The median total duration of peripheral norepinephrine administration was 4 hours. One neonate had transient limb hypoperfusion and no tissue injury occurred. Few studies describe complications of peripheral norepinephrine use in children. Lampin et al found no cases of serious skin injury among 27 patients who received norepinephrine through peripheral vascular access in a single PICU.[4] Turner et al reported the use of vasoactive drugs (mostly dopamine) during transport of critically ill children and showed a 15% rate of intravenous infiltrate without any severe complication.[6] Higher infusion rate and longer duration of infusion were associated with risk of subcutaneous infiltrate.

Loubani et al had similar findings in a systematic review of reports of extravasation and local tissue injury from administration of norepinephrine through peripheral catheter in adults. Most events occurred after >24 hours of infusion, and most of the time in a catheter located distally to the antecubital fossa. In the absence of control group, the authors could not deduce incidence nor risk factors for extravasation event.[5]

In summary, we report our experience of norepinephrine infusion through peripheral vascular access 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 norepinephrine on outcome of children in shock.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

RC and LM conceived the study and supervised the conduct of the study and data collection. GJ and NL, VO, and SJ undertook recruitment of participating centers and patients. RC and LM managed the data. LM provided statistical advice on study design and analyzed the data. RC, LM, and PT drafted the manuscript, and all authors contributed substantially to its revision. PT takes responsibility for the paper as a whole.

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