Extensive symmetrical skin necrosis and cutaneous blisters after vasopressin infusion in a 5-year-old child with catecholamine-resistant cold shock

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Vasopressin is recommended as a rescue vasoconstrictive agent in severe pediatric vasodilatory shock. Still there are no convincing literature on the use of vasopressin in high-systemic vascular resistance shock and in pediatric cardiac arrest. The authors report a case of catecholamine-resistant cold shock developing extensive skin necrosis with multiple blisters after high-dose vasopressin use via a central venous catheter. A 5-year-old previously healthy female child presented to emergency department unresponsive with no central pulse. The child required cardiopulmonary resuscitation multiple times in pediatric ICU for intractable hyperkalemia and for mixed cardiogenic and catecholamine-resistant cold shock. Emergency hemodialysis was done, starting high-dose vasopressin to maintain cardiac perfusion. Vasodilator milrinone infusion was started after 12 h. Cardiac output gradually improved, and vasoconstrictive inotropes were weaned off on day 3. However, the child developed bilateral extensive skin necrosis and multiple bullae on both hands and foot on days 2–3, which required multiple debridements. Skin and digital perfusion then gradually improved in next 72 h avoiding the need for amputation. Vasopressin has been included in Adult Cardiopulmonary Resuscitation Guideline as a second vasopressor to epinephrine. Although vasopressin is used widely in pediatric vasodilatory shock, its use in cardiac arrest resuscitation and cold shock scenario remains questionable. Many cases of extensive skin necrosis after peripheral vasopressin extravasation have been reported in adults. In our case, vasopressin infusion was given through a central venous line. We observed that concomitant use of vasodilators may reduce skin and digital gangrenous complications of vasopressin. We conclude that vasopressin infusion should be used with extreme caution in catecholamine-refractory septic cold shock.

Keywords:
blisters, digital gangrene, septic shock, skin necrosis, vasopressin infusion

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Introduction

Vasopressin has been used primarily to treat patients with diabetes insipidus and to control gastrointestinal bleeding. Only in the past decade, its role as a potent vasoconstrictor in septic shock has been recognized.

Vasopressin is a nonapeptide and is most commonly known as antidiuretic hormone. It is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus as a prohormone and is then transported (bound to neurohypophysis) along the supraoptichypophyseal tract to the posterior pituitary gland. Approximately 10–20% is released initially; the remainder is secreted following various stimuli [1]. The primary role of vasopressin is fluid homeostasis, and the strongest release stimuli are increasing plasma osmolarity and severe hypovolemia [2]. Several mechanisms responsible for vasopressin deficiency in septic shock have been proposed, including the depletion of neurohypophyseal stores, impaired baroreflex-mediated release of vasopressin attributable to autonomic dysfunction, and downregulation of vasopressin production by increased central nitric oxide production and by cytokine storm [3]. Because of the potent vasoconstrictor action of vasopressin, the possibility of impaired capillary blood flow and tissue oxygenation with vasopressin administration remains a concern [4]. Even though ischemic skin necrosis has commonly been reported in adults in connection with vasopressin, case reports in pediatric population are lacking [5–7]. Herein, we report a 5-year-old child with persistent cold septic shock, who developed severe ischemic skin necrosis with blisters after infusion of high-dose vasopressin via a central venous catheter.

Case report

A 5-year-old female child came unresponsive without central pulse to the emergency department at crack of

dawn. Cardiopulmonary resuscitation was initiated, and return of spontaneous circulation (ROSC) was achieved after 10 min. Arterial blood gas (ABG) done showed severe metabolic acidosis with severe hyperkalemia and severe hypoglycemia. Crystalloids upto 40ml/kg,10 % Dextrose bolus 2ml/kg,stat dose of 1ml/kg 10% Calcium gluconate,1ml/kg 8.4% sodium bicarbonate, 0.1 U/kg Insulin with 10%Dextrose and 20% albumin were started. In view of persistent shock and hyperkalemia, infusions of calcium gluconate, sodium bicarbonate, insulin with glucose, and 20% albumin infusion were started. The child had an episode of ventricular tachycardia in emergency room, which was successfully resuscitated, and ROSC was achieved after 7 min of cardiopulmonary resuscitation (CPR). The case study has been approved by ethics committee and informed consent has been taken from parents.

There was a history of fever, loose stools, and disorientation, and the child was talking irrelevantly since evening the day before admission. The parents thought it was some demonic possession and continued doing prayers.

Blood investigations revealed total white blood cells count 23 000 cells/cm^3 with 80% neutrophils, platelet count 25 000 cells/cm^3, C-reactive protein 7.55 mg/dl, serum potassium 7.3 mmol/l, total serum calcium 6.4 mg/dl, ionized 0.85 mg/dl, serum magnesium 2.37 mg/dl, serum urea 58 mg/dl, serum creatinine 2.15 mg/dl, serum glutamic-oxaloacetic transaminase 8712 IU/l, lutamic-pyruvic transaminase 2492 IU/l, total serum bilirubin 2.6 mg/dl, lactate dehydrogenase 6171 IU/l, serum ferritin 800 ng/ml, prothrombin time, and partial thromboplastin time more than 180 s. Peripheral smear showed neutrophilic leukocytosis, thrombocytopenia, and echinocytic red blood cells with spherocytes. Viral hepatitic markers were negative.

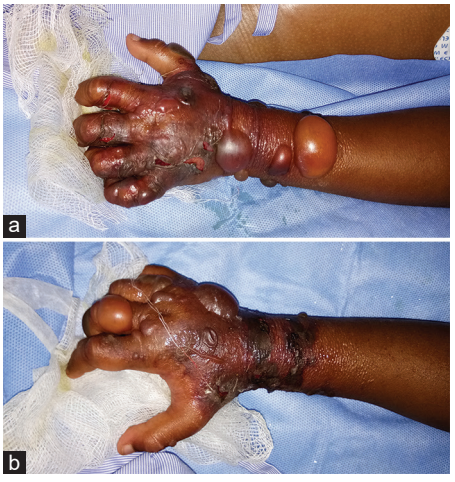
The child was then shifted to pediatric ICU and put on mechanical ventilatory support. On examination, the child was comatose with unrecordable SpO_2 and had cold and clammy peripheries without palpable peripheral pulses. Noninvasive blood pressure was 52/36 (mean arterial pressure 40 mmHg). Echocardiogram showed severe left ventricular dysfunction (ejection fraction 20%). The child was started on injection of meropenam, adrenaline infusion injection, Vit-K injection, stress dose hydrocortisone, and other supportive medications. Femoral arterial line and right internal jugular vein were catheterized, and hemodialysis catheter was inserted in left internal jugular vein. Emergency hemodialysis was initiated. Vasopressin infusion injection was started though in persistent catecholamine-resistant cold shock to maintain cardiac perfusion. The child had two further episodes of cardiac arrest on the same day, which was resuscitated successfully.

Oxygenation index was greater than 45 for 6 h after admission. Pediatric sequential organ failure assessment score was 19 at 6 h of admission. Extracorporeal membrane oxygenation (ECMO) was deferred because of deranged coagulation profile. Differential diagnoses such as acute gastroenteritis with shock worsening to multiorgan dysfunction syndrome, acute encephalitis with nonconvulsive status epilepticus leading to shock and multiorgan dysfunction syndrome, atypical hemolytic uremic syndrome, macrophage activation like syndrome were considered.

Vasopressin infusion injection was continued at the rate of 0.04 Ul/kg/min along with high-dose adrenaline infusion. Milrinone infusion injection was started to counteract high systemic vascular resistance with cold peripheries. The child had two further episodes of bradycardia with nonrecordable intra-arterial blood pressure overnight, which was revived. Over the next 48 h, the child required multiple units of single donor platelets, fresh frozen plasma, cryoprecipitate, and PRBCs in view of continuous oronasal bleed and severely deranged coagulation profile with thrombocytopenia (disseminated intravascular coagulation). Hemodialysis with ultrafiltration (SLED) was done daily. Gradually, ventricular function, cardiac output, and peripheral perfusion were improved, and vasoconstrictive inotropes were managed to wean off on day 3.

However, she developed extensive skin necrosis with multiple blisters over both hands (Fig. 1) and foot on

Figure 1



(a) Extensive skin blisters on left hand, and (b) extensive skin blisters on right hand.

days 2–3, which required repeated debridements. Blood culture showed no growth. Skin and digital perfusion then gradually improved in next 72 h avoiding the need for amputation.

The child was shifted to another center on day 7 on parent's request, and the child finally succumbed to illness after 3 weeks.

Discussion

Vasopressin is a potent systemic vasoconstrictor, but the low-dose infusion of vasopressin concurrently causes vasodilation in pulmonary, cerebral, and coronary circulations via oxytocin receptor stimulation and endothelial NO release. Low-dose vasopressin may thus be more beneficial in preserving vital organ perfusion when compared with catecholamine pressors [8].

The American College of Critical Care Medicine-Pediatric Advanced Life Support (ACCM-PALS) guideline recommends vasopressin in warm shock with low blood pressure [9].

Vasopressin and its long-acting analog terlipressin has been in use for adult septic shock with catecholamine-resistant vasodilatory hypotension since Surviving Sepsis Guideline (SSCG) 2012 [10,11]. However, the use of these agents was not supported in children for lack of overt clinical benefits [10,12,13]. Masarwa *et al.*[14] in their systematic review in children found no association between the use of vasopressin or terlipressin and mortality, rather they pointed out a concerning tendency toward more tissue ischemia in patients treated with vasopressin/terlipressin. This difference in efficacy could be owing to variable levels of intrinsic vasopressin and copeptin in children with septic shock, contrary to relative vasopressin deficiency among adult patients [15].

Choong *et al.*[13] in their multicentric randomized control trail (RCT) have showed no beneficial effects of low-dose vasopressin infusion in pediatric shock, but again, there was a concerning trend in increased mortality in the vasopressin group. Russell *et al.*[16] in association with coinvestigators for vasopressin and septic shock trial compared vasopressin and norepinephrine in patients (>16 years) with septic shock and concluded that there was no significant difference in the 28-day and 90-day mortality rate between the two groups.

Meyer *et al.*[17] in their study on ELBW infants with catecholamine-resistant septic shock showed that systemic arterial blood pressure increased substantially with restoration of urine output after arginine vasopressin administration (dosage: 0.035–0.36 U/kg/h). Lauzier *et al.*[18] evaluated the use of vasopressin in early hyperdynamic septic shock in adults and found that vasopressin decreased the dose requirement of norepinephrine and improved organ dysfunction (evaluated by sequential organ failure assessment score scores) as compared with norepinephrine

Rosenzweig *et al.* [19], Jerath *et al.* [20], and Lechner *et al.*[21] showed a favorable role of vasopressin in postpediatric cardiac surgery hypotension. They showed that the use of vasopressin resulted in a significant increase in blood pressure and also the requirement for traditional vasopressors decreased significantly. A retrospective case series of children with cardiac arrest suggested that vasopressin 0.4 U/kg/dose is beneficial during prolonged pediatric cardiac arrest, following the failure of conventional cardiopulmonary resuscitation [22]. Another retrospective case series of pediatric cardiac arrests, unresponsive to epinephrine, found that ROSC was achieved in six of eight episodes in patients treated with 15–20 μg/kg/dose of terlipressin and four of these patients survived without neurological sequelae [23].

To conclude, there is no conclusive evidence for the use of vasopressin in pediatric septic shock. Based on the available literature, it has been used as a rescue therapy to improve the hemodynamics in a volume-optimized child, especially in cases of vasodilatory shock, despite the use of norepinephrine [24]. Case reports of ischemic skin necrosis secondary to vasopressin infusion even through a central venous line in children are currently lacking. Risk factors for developing skin necrosis in pediatric age group need to be evaluated further. Till then vasopressin infusion in children for septic shock should be used with extreme caution.

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Conflicts of interest

There are no conflicts of interest.

References

1 Sharman A,James low. Vasopressin and its role in critical care. Continuing Education in Anaesthesia Crit Care Pain 2008; 8:134–137.

2 Russell JA. Bench-to-bedside review: vasopressin in the management of septic shock. Crit Care 2011; 15:226.

3 Kim EH, Lee SH, Byun SW, Kang HS, Koo DH, Park H-G, Hong SB. Skin necrosis after a low-dose vasopressin infusion through a central venous catheter for treating septic shock. Korean J Intern Med 2006; 21:287–290.

4 Singh VK, Sharma R, Agrawal A, Varma A. Vasopressin in the pediatric cardiac intensive care unit: myth or reality. Ann Pediatr Cardiol 2009; 2:65–73.

5 Bunker N, Higgins D. Peripheral administration of vasopressin for catecholamine-resistant hypotension complicated by skin necrosis. Crit Care Med 2006; 34:935.

6 Kwon JW, Hong MK, Park BY. Risk factors of vasopressor-induced symmetrical peripheral gangrene. Ann Plast Surg 2018; 80:622–627.

7 Dunser MW, Mayr AJ, Tür A, Pakj W, Barbara F, Knotzer H, *et al*. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med 2003; 31:13941398.

8 Treschan TA, Peters J. The vasopressin system: physiology and clinical strategies; the vasopressin system: physiology and clinical strategies. Anesthesiology 2006; 105:599–612.

9 Kawasaki T. Update on pediatric sepsis: a review. J Intensive Care 2017; 5:47.

10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580–637.

11. Belletti A, Musu M, Silvetti S, Omar S, Laura P, Fabrizio M, *et al*. Non-adrenergic vasopressors in patients with or at risk for vasodilatory shock. A systematic review and meta-analysis of randomized trials. PLoS One 2015; 10:1–13.

12. Yildizdas D, Yapicioglu H, Celik U, Sertdemir Y, Alhan E. Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. Intensive Care Med 2008; 34:511–517.

13. Choong K, Bohn D, Fraser DD, Isabelle G, James SH, Ari RJ, *et al*. Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial. Am J Respir Crit Care Med 2009; 180:632–639.

14. Masarwa R, Paret G, Perlman A,Shimon R,Bruria HR,Ilan M; Role of vasopressin and terlipressin in refractory shock compared to conventional therapy in the neonatal and pediatric population: a systematic review, meta-analysis, and trial sequential analysis. Crit Care 2017; 21:1.

15. Rios DR, Kaiser JR. Vasopressin versus dopamine for treatment of hypotension in extremely low birth weight infants: a randomized, blinded pilot study. J Pediatr 2015; 166:850–855.

16. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, *et al*. VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008; 358:877–887.

17. Meyer S, Gottschling S, Baghai A, Wurm D, Gortner L. Arginine-vasopressin in catecholamine-refractory septic versus non-septic shock in extremely low birth weight infants with acute renal injury. Crit Care 2006; 10:R71.

18. Lauzier F, Lévy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Med 2006; 32:1782–1789.

19. Rosenzweig EB, Starc TJ, Chen JM, Cullinane S, Timchak DM, Gersony WM, *et al*. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. Circulation 1999; 100 (19 Suppl):II182–II186.

20. Jerath N, Frndova H, McCrindle BW, Gurofsky R, Humpl T. Clinical impact of vasopressin infusion on hemodynamics, liver and renal function in pediatric patients. Intensive Care Med 2008; 34:1274–1280.

21. Lechner E, Hofer A, Mair R, Moosbauer W, Sames-Dolzer E, Tulzer G. Arginine-vasopressin in neonates with vasodilatory shock after cardiopulmonary bypass. Eur J Pediatr 2007; 166:1221–1227.

22. Mann K, Berg RA, Nadkarni V. Beneficial effects of vasopressin in prolonged pediatric cardiac arrest: a case series. Resuscitation 2002; 52:149–156.

23. Matok I, Vardi A, Augarten A, Efrati O, Leibovitch L, Rubinshtein M, Paret G. Beneficial effects of terlipressin in prolonged pediatric cardiopulmonary resuscitation: a case series. Crit Care Med 2007; 35:1161–1164.

24. Masutani S, Senzaki H, Ishido H, Taketazu M, Matsunaga T, Kobayashi T, *et al*. Vasopressin in the treatment of vasodilatory shock in children. Pediatr Int 2005; 47:132–136.