Refractory hypotension in neonates is defined as hypotension with signs of inadequate perfusion despite volume expansion and administration of inotropic agents and/or corticosteroids. This condition is associated with severe intraventricular hemorrhage, a high mortality rate of about 50%, hearing loss, and adverse neurodevelopmental outcomes.

Terlipressin (TP), a long-acting analog of vasopressin (VP), is indicated for treating hemorrhage from esophageal varices and hepatorenal syndrome. Several randomized and retrospective studies in adults and children (> 1-month-old) have shown its clinical benefits in the treatment of refractory hypotension. However, TP as a rescue treatment for neonatal hypotension is considered off-label use. We report our experience with the use of TP in a case of neonatal refractory hypotension resulting from septic shock.

Case Report

A boy was born via normal vaginal delivery at 37 weeks and 6 days, with a birth weight of 3,700 g and an Apgar score of 10 at 1, 5, and 10 min. The neonate was transferred to our neonatal intensive care unit owing to the appearance of signs of facial cyanosis 4 h after birth. After tracheal intubation and sputum suction, we found bloody sputum. Chest radiograph suggested pulmonary hemorrhage. His oxygen saturation was 85-90% and pulmonary artery pressure (PAP) was 55 mmHg. Treatment was initiated using high-frequency oscillatory ventilation combined with nitric oxide inhalation. Then the blood pressure was 75/43 mmHg with a mean arterial pressure (MAP) of 53 mmHg, the knees and elbows were cold, the femoral arteries were weak, the complexion was pale, the capillary refill time (CRT) was 3 seconds, and the shock score was 5 points. Dopamine and dobutamine infusions were administered to improve his microcirculation. Twenty-two hours after admission, the blood pressure had dropped to 40/32 (Mean Arterial Pressure (MAP): 35) mmHg despite dopamine treatment of 8.8 µg/kg/min. Thus, dopamine...
was replaced with epinephrine, which was gradually increased to a dose of 0.66 µg/kg/min. In addition, hydrocortisone was administered at a dose of 10 mg four times daily. Under this treatment regime, the neonate’s MAP increased to 50 mmHg, with mild fluctuations.

Routine blood testing revealed a white blood cell count of 16.08×10⁹/L and a C-reactive protein level of 51.5 mg/L. His prothrombin and activated partial thromboplastin times were extended by >1.5-fold. Chest radiography revealed pneumonia, and the newborn was diagnosed with septic shock. Fifty-one hours after admission, he developed hypotension with a blood pressure of 49/32 (MAP: 38) mmHg. His hypotension did not respond to high-dose inotropic drug treatment (epinephrine at 0.82 µg/kg/min and milrinone at 0.5 µg/kg/min) and transfusion therapy, and his oliguria did not respond to furosemide treatment. Thus, TP rescue therapy (20 µg/kg every 4 h) was started after obtaining approval from the parents. About 15 minutes after the first dose of TP treatment, the blood pressure increased to 52/43 (MAP 46) mmHg. After the second dose of TP, the values for MAP (maintained at 50-55 mmHg), blood oxygen saturation (90-93%), blood pH (7.12-7.25), lactate levels (15.26-14.33 mmol/L), base excess in the extracellular fluid compartment (-20.9 to -1.73 mmol/L), and urine output (0.3-4.7 mL/kg·h) also improved. Therefore, we decreased the positive inotropic drug support by discontinuing the milrinone treatment. The epinephrine treatment was gradually discontinued starting 72 h after

Fig. 1. Male neonate with refractory hypotension: blood pressure values and medications administered during the entire hospitalization process.

MAP: mean arterial pressure, PAP: pulmonary artery pressure, TP: terlipressin.
the first dose of TP. MAP was maintained at approximately 64 mmHg. Blood pressure values and medication administered during the hospitalization process have been given in Figure 1. However, genetic testing revealed mitochondrial gene defects four days after the first dose of TP, and the parents subsequently elected to stop the TP treatment. The newborn died shortly afterward.

Informed consent was obtained from the parents of the patient for the publication of this report.

Discussion

The hypothalamus produces vasopressin (VP), a powerful vasoconstrictor, used to treat cardiac arrest, advanced hemorrhagic shock, and hypotension caused by orthostasis or hemodialysis. In addition to its antidiuretic effect, which is mediated by the V2 receptor, VP can mediate vasoconstriction of vascular smooth muscle by binding to the V1 receptor. The TP molecule, a synthetic analog of the VP molecule, has a higher selectivity for the vascular V1 receptor and consequently a stronger vasoactive and weaker antidiuretic effects than VP. Its pharmacokinetics involve the continuous conversion of the TP prodrug to a vasoactive lysine-VP by endopeptidase, providing a long-lasting and dose-dependent effect. The half-life of TP is 6 h (2-10 h of drug action) while that of VP is 6 min (with 30-60 min of drug action). This difference allows TP to be administered at greater intervals without the rebound hypotension that is usually observed after stopping a VP infusion. However, the relatively long half-life requires adjustment of the TP dose in clinical practice, which may also be a disadvantage.

Patients with septic shock have low VP levels and particularly a sensitive pressor response. Thus, single, intermittent, or continuous doses of TP can provide most patients with adequate blood pressure levels for >5 h, with a decreasing need for positive inotropic support after the first dose of TP. Yildizdas et al. studied 58 children with septic shock and refractory hypotension (randomized enrolment for TP treatment) and found that TP significantly increased MAP and survival time, but did not improve the mortality outcomes. Furthermore, a retrospective study of 14 children with septic shock revealed significant improvements in respiratory and hemodynamic parameters after TP treatment, with a rapid increase and maintenance of adequate blood pressure levels. A prospective study of children also indicated that continuous infusion of TP was effective in improving and maintaining blood pressure. Thus, there appears to be a role for TP treatment in childhood cases of hypotension.

Although these results suggest that TP treatment may also help improve the clinical symptoms and prognosis of neonatal refractory hypotension, there are limited high-quality data regarding this indication. Matok et al. were the first to report TP as rescue therapy in an 8-day-old neonate with septic shock and hypotension who did not respond to dopamine, milrinone, and epinephrine treatment. In that case, the newborn experienced a rapid improvement in both blood pressure and tissue perfusion after starting TP treatment, without any significant side effects. In another study in refractory hypotension in newborns and infants, TP appeared to help correct serum pH and lactate levels, promote the recovery of cerebral vascular tone, improve blood oxygen saturation, and reduce or eliminate the need for catecholamines, which may alleviate the adverse reactions caused by long-term high-dose catecholamine treatment. In our case, the newborn experienced improvements in his clinical, physiological, and biochemical parameters after starting TP treatment, including normalization of cardiac preload and peripheral resistance, improvement of blood oxygen saturation and blood gas parameters, increased urine output, and rapid elevation of MAP from 38 to 55 mmHg, with consecutive maintenance of this level. The limited improvement in lactate levels may have been associated with a mitochondrial metabolic disorder.
The reported TP doses for neonates range from 7 µg/kg twice daily to 20 µg/kg every 4 h. Some studies have indicated that TP treatment provides the greatest benefit when the norepinephrine requirements are between 0.8 and 2.5 µg/kg/min. Our patient received TP treatment for a 100-h period divided into 25 doses of 20 µg/kg after the adrenaline dose was increased to 0.82 µg/kg/min. Thus, given the pharmacokinetics of TP, the dosing interval might be extended, and the dose might be decreased to reduce the incidence of adverse reactions, depending on the clinical efficacy and positive inotropic support in an individual case. Nonetheless, there are no conclusive data regarding whether TP administration before the occurrence of catecholamine resistance can improve outcomes in neonates, and additional research is needed to determine the optimal dose, dosing interval, and duration of TP treatment. However, Radicioni et al. reported that TP may be associated with the over-contraction of coronary vascular in neonates (weighing 3,800 g and born at 40 weeks). Thus, in cases with high-dose catecholamine administration, it may be prudent to consider a small starting dose of TP.

The V2 receptor mediates vasodilation in some blood vessels, and animal experiments have indicated that TP treatment may result in pulmonary vasodilation. This is slightly different from our experience, as our patient experienced a continuous increase in PAP after starting TP treatment. We suspect that this might have been related to a down-regulation of nitric oxide. Furthermore, TP treatment may induce hyponatremia in children with postoperative catecholamine-resistant hypotension, possibly via its effect on V2 receptors. In contrast, our patient had high sodium levels during treatment, which may be related to renal dysfunction and the high selectivity of TP for V1 receptors, as well as the inhibition of V2 receptor-mediated antidiuretic effects.

In conclusion, in our case of sepsis-induced neonatal refractory hypotension, TP rescue treatment improved the hypotension. The promising findings in our case require further investigation in future studies to examine their safety and efficacy. Given the risk of adverse reactions, we cannot recommend the replacement of catecholamines with TP as a first-line treatment. However, children who are considered for TP treatment are already in a critical state and have a high mortality rate. Thus, we recommend carefully weighing the pros and cons. If TP is administered, care should be taken to avoid excessive vasoconstriction through monitoring of the patient’s heart, lung, kidney function, electrolytes, and hemodynamic status.

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REFERENCES


