Is there any role for terlipressin in the extremely low birth weight infant with refractory septic shock?

Francesca Bissolo, Carlo Alberto Forcellini, Stefania Spaggiari, Marcella Gaffuri, Giuseppe Pagano, Paolo Biban

Neonatal and Pediatric Intensive Care Unit, Department of Pediatrics, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Abstract

Terlipressin, a synthetic long-acting analogue of vasopressin, has been investigated as a second line vasopressor in adults and children with refractory septic shock, i.e. not responding to fluid resuscitation and high-dose catecholamine administration. Little experience is available about the safety and efficacy of terlipressin in term and preterm newborns.

We report the case of an extremely low birth weight infant with severe septic shock, unresponsive to fluids, noradrenalin and hydrocortisone, in whom terlipressin was attempted as a rescue drug. Despite three doses of terlipressin, administered 6-hourly, the patient remained profoundly hypotensive and eventually died.

Further studies are required before any recommendation on the use of terlipressin in term or preterm newborns with septic shock can be made.

Keywords

Terlipressin, newborn, ELBW, sepsis, shock.

Corresponding author

Paolo Biban, Neonatal and Paediatric Intensive Care Unit, Department of Paediatrics, Azienda Ospedaliera Universitaria Integrata Verona, Italy; email: paolo.biban@ospedaleuniverona.it.

How to cite

Introduction

Septic shock may constitute a life-threatening condition at any age, but it may be particularly challenging in very low birth weight infants, in whom a high incidence of morbidity and mortality is still observed [1, 2]. Management is generally based on the early use of antibiotics, fluids, steroids and inotropic support, together with advanced monitoring and mechanical respiratory support.

We report the case of an extremely low birth weight infant with septic shock and hypotension, unresponsive to volume replacement and maximal inotropic support, in whom the synthetic vasopressor terlipressin was attempted as a rescue therapy.

Case report

A female baby was born by spontaneous delivery at a gestational age of 25 + 3 weeks (BW 920 g). At birth she was assisted with sustained lung inflation for 15 seconds, followed by nasal CPAP. Apgar Scores were 6, 8 and 10 at 1, 5 and 10 minutes, respectively. At day 7 of life she suffered an episode of sepsis, developing multiple organ failure and requiring invasive mechanical ventilation.

Empiric antibiotic therapy with vancomycin and cefotaxime was started; metronidazole was added as soon as mild signs of necrotizing enterocolitis (NEC) appeared. Echocardiography was negative for ductus arteriosus patency, whilst cranial ultrasound showed an IVH II.

Blood cultures yielded C. albicans and St. haemolitycus, whereas Kl. pneumoniae was found in spinal fluid cultures.

The patient developed metabolic acidosis and severe hypotension refractory to abundant fluid replacement. Mean arterial pressure (MAP) was initially maintained above 25 mmHg with dopamine and dobutamine, both at 10 mcg/kg/min. Following a transient clinical improvement, on day 14 MAP fell below 20 mmHg despite aggressive volume replacement and inotropic support. We then started adrenaline at 0.5 mcg/kg/min, progressing with noradrenalin at 1 mcg/kg/min, with scarce effect. Hydrocortisone was also initiated at 2 mg/kg/die. However, MAP remained persistently low and the patient developed oligo-anuric renal failure. At this point, after informed parental consent, administration of terlipressin was instituted, at a dosage of 0.05 mg every 6 hours. However, the patient remained extremely hypotensive and anuric, with progressively severe metabolic acidosis (serum lactate > 10 mmol/l). The patient died about 14 hours since terlipressin was started.

Discussion

Despite recent advances in understanding the pathophysiology of shock, the mortality rate due to septic shock remains relatively high, often due to refractory hypotension not responding to volume resuscitation or to high-dose vasopressors and inotropes [1-3].

In these situations, vasopressin and terlipressin, a synthetic long-acting analogue of vasopressin, can raise systemic vascular resistance and blood pressure while reducing the need for adrenaline or noradrenaline [4].

Terlipressin (triglycyl-lysine-vasopressin) is rapidly metabolized by endopeptidases to the vasoactive lysine-vasopressin. Terlipressin has a vasoconstrictive effect on the cardiovascular system that is mediated by V1 receptors on the vascular smooth muscles. Of note, the half-life of terlipressin is 6 hr (the duration of action is 2-10 hr), as opposed to the short half-life of vasopressin, which is only 6 min (the duration of action is 30-60 min). This characteristic allows an intermittent administration of terlipressin, versus the need for continuous infusion of vasopressin [5].

The main clinical advantages and some potential adverse effects of terlipressin are summarized in Tab. 1 and 2.

Several studies have reported a beneficial effect of vasopressin or terlipressin in paediatric patients with septic shock refractory to fluid replacement

<table>
<thead>
<tr>
<th>Advantages of terlipressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced need for catecholamine infusions</td>
</tr>
<tr>
<td>Longer half-life allows for intermittent administration</td>
</tr>
<tr>
<td>Mild or no rebound effects at suspension of the drug</td>
</tr>
<tr>
<td>Available in Europe</td>
</tr>
</tbody>
</table>

Table 1. Terlipressin in septic shock refractory to fluids and catecholamines: advantages.
and catecholamines [6, 7]. Unfortunately, other authors have shown that, despite a transient improvement of mean arterial blood pressure and urine output, vasopressin and terlipressin are ineffective or sometimes even associated with an increase in lactic acidosis and poor outcome, including death [8, 9].

The matter appears to be even more confused in premature and term neonates, in whom hemodynamic response to sepsis is less well characterized compared with children and adults. At present there are very few studies exploring the role of terlipressin in newborns with septic shock, most of them being case reports or small case series [10-12]. Thus, reported results are still inconclusive.

In our case terlipressin did not seem to cause any positive effect, neither in terms of hemodynamics nor in organ function improvement. However, this may have been possibly due to various factors, such as relatively low dosage of terlipressin, too late administration, or both. Indeed, our patient was already very compromised at terlipressin onset, and she received only three doses of the drug. Nonetheless, we never had the clinical impression that terlipressin was somewhat ameliorating her hemodynamics.

**Conclusion**

In conclusion, despite our neonatal case does not support the use of terlipressin as a rescue treatment in refractory vasodilatory septic shock, further clinical, pharmacokinetic, and pharmacodynamic studies are urgently required to better clarify the safety and efficacy profile of terlipressin in term and preterm newborns with septic shock.

**Declaration of interest**

No conflicts of interest exist.

---

**Table 2.** Terlipressin in septic shock refractory to fluids and catecholamines: potential adverse effects.

<table>
<thead>
<tr>
<th>Potential adverse effects of terlipressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive vasoconstriction (e.g., limbs, gut)</td>
</tr>
<tr>
<td>Skin necrosis after extravasation</td>
</tr>
<tr>
<td>Prolonged carry-over effect once suspended</td>
</tr>
</tbody>
</table>

---

**References**


10. Matok I, Leibovitch L, Vardi A, Adam M, Rubinshtein M, Barzilay Z, Paret G. Terlipressin as rescue therapy for...