Octreotide in a Critically Ill Extremely Preterm Infant With Perforated Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) is the most severe gastrointestinal complication of prematurity. Surgery, either peritoneal drainage placement or laparotomy with resection of the intestinal necrotic tracts, is the definitive treatment of perforated NEC; however, when clinical conditions contraindicate surgical approaches, little is known about medical treatments adjuvant or alternative to surgery. Octreotide is a synthetic somatostatin analog that inhibits pancreatic secretion and leads to splanchnic vasoconstriction. In preterm neonates, it is mainly used off-label for chylothorax and congenital hyperinsulinism, whereas gastrointestinal indications are limited. We describe the case of a critically ill extremely low birth weight infant with perforated NEC, who had unsuccessfully undergone peritoneal drainage placement and laparotomy. Her unstable condition contraindicated a further laparotomy, thus off-label treatment with octreotide was attempted. No adverse events occurred. The infant’s condition gradually improved and progressive reduction of peritoneal outputs and successful resolution of pneumoperitoneum were achieved, with no relapse after octreotide discontinuation.

The substantial improvement in neonatal care achieved over the past decades has led to a significant increase in the survival of extremely preterm infants.1 Necrotizing enterocolitis (NEC) represents the most severe gastrointestinal complication of prematurity, with very high rates of morbidity and mortality.2 Medical approach (ie, abdominal decompression, bowel rest, total parenteral nutrition, and broad-spectrum intravenous [IV] antibiotics) is the initial treatment of nonperforated NEC, whereas the presence of intestinal perforation requires surgical intervention, either peritoneal drainage (PD) placement or laparotomy with resection of the intestinal necrotic tracts and eventual stoma formation.2 Laparotomy allows the definitive resection of the necrotic and perforated bowel segments but, in the presence of hemodynamic instability, there is a significant risk of severe intra- and postoperative complications.3 On the other hand, PD placement aims at removing blood, gas, and pus from the abdominal cavity in critical infants, to stabilize clinical conditions before attempting laparotomy.4 Failure to improve after PD placement often leads to an emergency laparotomy, which has been associated with an even worse outcome.5 To date, little is known about medical strategies adjuvant or alternative to surgery in critically ill preterm infants with perforated NEC.

Octreotide is a somatostatin analog, which exerts multiple effects on the gastrointestinal (GI) tract; among these, it reduces GI secretions and decreases mesenteric blood flow.6

abstract

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Octreotide is a somatostatin analog, which exerts multiple effects on the gastrointestinal (GI) tract; among these, it reduces GI secretions and decreases mesenteric blood flow.6

Although its off-label use in critically ill infants is increasing, the effect of octreotide on perforated NEC has not been described yet. Moreover, there are very few data about its use in infants <1 kg body weight.

We report the case of an extremely low birth weight (ELBW) infant with perforated NEC, who was successfully treated with octreotide before definitive surgery could be performed.

CASE REPORT

A white female infant was born at 25 weeks’ gestation by spontaneous vaginal delivery (birth weight 734 g, Apgar scores: 2-3-6). At 6 hours of life she developed hypotension, hypoperfusion, and hemodynamic instability, thus an echocardiogram was performed, revealing a hemodynamically significant patent ductus arteriosus (PDA), inadequate cardiac output, and severe pulmonary hypertension. Inotropes and inhaled nitric oxide were thus undertaken, with subsequent improvement of pulmonary hypertension and shunt inversion through the PDA. Thus, on day of life (DOL) 2, PDA closure was attempted and achieved after a single dose of ibuprofen. After that, the infant’s clinical condition gradually improved. However, on DOL 6, a sudden deterioration of her clinical status occurred, with progressive abdominal distension, bilious gastric residuals, and the appearance of a bluish abdominal discoloration. Abdominal radiograph showed the presence of free intraperitoneal air and edema of the bowel wall. IV antibiotic treatment with piperacillin/tazobactam, vancomycin, and metronidazole was started and a PD was placed by the surgeon, with subsequent leakage of air and meconium. The abdominal radiographs performed in the next 72 hours documented the gradual resolution of pneumoperitoneum. After an initial improvement, however, on DOL 14, bilious vomiting, worsening of abdominal distension, and gradual enlargement of the bluish abdominal discoloration occurred, with a concomitant decrease of PD outputs and radiologic recurrence of intraperitoneal free air. Due to the progressive deterioration of the infant’s condition, on DOL 20, a salvage laparotomy was attempted. At surgery, the infant weighed 754 g, was on mechanical ventilation, and was receiving inotropes for cardiac support. Direct gut inspection revealed a significant amount of meconium within the peritoneum and at least 3 intestinal perforations, of which 1 in the duodenum, surrounded by hemorrhagic necrosis. During surgery, the infant developed acute hemodynamic instability with desaturation, bradycardia, and hypotension, finally resulting in cardiac arrest, which was responsive to cardiopulmonary resuscitation. Surgery was thus limited to a peritoneal lavage, the creation of a gastric stoma proximal to the duodenal perforation, and, finally, the insertion of a new PD. In the postoperative period, however, there was a further worsening of the abdominal distension with evidence of residual free air at the abdominal radiograph (Fig 1A). The PD proved to be ineffective, but at the same time the infant’s clinical condition contraindicated a new laparotomy. Taking into account its GI effects, and in view of previous evidence of its use in other conditions characterized by intestinal perforation, such as enterocutaneous fistula (EF), treatment with octreotide was attempted. After obtaining parental consent, IV continuous infusion of 1 µg/kg per day of octreotide was started on DOL 24; the dosage was increased to 2 µg/kg per day on DOL 26 and maintained at 2.75 µg/kg per day from DOL 28 on. Outputs from the PD gradually decreased during the first week of treatment, and stopped since DOL 36. No radiologic evidence of abdominal free air was documented (Fig 1B), and the PD was removed on DOL 38. To prevent possible complications related to surgery, such as the occurrence of EF, octreotide was maintained at the same dosage until DOL 45, after which it was halved to 1.5 µg/kg per day without any clinical or radiologic relapse. Hence, from DOL 84 the dosage was gradually tapered and the drug was discontinued on DOL 89 (overall treatment duration: 65 days). During treatment, a daily monitoring of blood pressure, diuresis, and blood sugar, and a periodic evaluation of complete blood count, renal and liver function tests, serum electrolytes, and electrocardiography were performed, with no evidence of octreotide-related adverse events (AEs). Treatment with vancomycin, piperacillin/tazobactam, and metronidazole were maintained until DOL 36, 66, and 85, respectively; no occurrence of infectious complications related to the multiple intestinal perforations was observed.

Given the stability of the infant’s condition, definitive laparotomy with extensive bowel resection (length of residual small bowel: 25 cm) and primary anastomosis was performed on DOL 139 and followed by successful recanalization. Enteral
feeding was thus introduced and slowly increased until full enteral feeding was achieved. The infant was discharged on full oral feeding and in good clinical status on DOL 218.

**DISCUSSION**

We report the case of an ELBW infant with perforated NEC who was treated successfully with octreotide until her severe clinical conditions contraindicated definitive surgery. Perforated NEC is a mandatory indication for surgical treatment; however, the specific approach is guided by the infant’s characteristics and clinical conditions. In the present case, repeated attempts to manage intestinal perforation by placing a PD were unsuccessful. An open laparotomy was thus attempted, but the occurrence of life-threatening complications during the procedure did not allow a definitive resection of the necrotic and perforated bowel segments, leading to postoperative recurrence of pneumoperitoneum, abdominal fluid leakage, and subsequent worsening of the infant’s condition.

Pneumoperitoneum is a common finding in both spontaneous intestinal perforation (SIP) and NEC. SIP is a separate clinical entity, associated with lower intestinal inflammation and necrosis compared with NEC. SIP has several risk factors: among them, ELBW, low Apgar score at 5 minutes, PDA and treatment with inotropes in the first week of life were present in the described case. For this reason, SIP was considered as a differential diagnosis: however, the rapid onset of symptoms together with the severe systemic manifestations and the evidence of bowel wall edema at abdominal radiographs led us to a diagnosis of NEC, which was confirmed by the intraoperative findings. At present, there is no evidence of any medical treatment alternative or adjuvant to surgery for the management of perforated NEC in critically ill preterm infants. Octreotide is a synthetic analog of native somatostatin that inhibits the release of glucagon, insulin, and growth hormone. By inhibiting pancreatic secretion, it slows gastrointestinal motility and leads to splanchnic vasoconstriction, with subsequent reduction of mesenteric perfusion. Although the use of octreotide in children is currently off-label, it is being increasingly used in several GI conditions, such as pancreatitis, diarrhea, esophageal varices, and acute and chronic gastrointestinal bleeding. The use of octreotide in newborns has also increased over the past decade. The most common indication is chylothorax as, by decreasing intestinal fat absorption, octreotide contributes to the reduction of lymphatic flow in the thoracic duct. As for GI diseases, there is little evidence about the use of octreotide for GI hemorrhage, bloody stools, and closure of postsurgical EF, but no reports for NEC.

Testoni et al recently described the clinical characteristics of newborns who received octreotide: up to two-thirds of them were preterm and had a median weight >2 kg on the first day of treatment. To the best of our knowledge, the administration of octreotide in ELBW infants is limited to a few reports about newborns with chylothorax who were treated with shorter courses. In the described case, the overall treatment duration was quite long. Such a prolonged course was aimed at avoiding the occurrence of EFs, which are a well-known complication of abdominal surgery on which octreotide is shown to be effective. Furthermore, the dosage was tapered slowly to prevent possible rebound effects. At present, data about the optimal neonatal dosage of octreotide are scarce. Although there is agreement that continuous infusion is the preferred method for octreotide administration, a wide range of the daily dose has been reported. The dosage used in the current study was relatively low, and was chosen taking into account the infant’s critical condition, low weight, and gestational age, all of which could affect drug metabolism. AEs related to octreotide administration have been extensively described in adults, whereas pediatric evidence is limited. Glucose regulation disorders, hyperbilirubinemia, abdominal pain, and diarrhea are the most common AEs; arrhythmias and bradycardia also have been reported. Studies in children receiving long-term courses, such as those treated for congenital hyperinsulinism, have reported transient elevation of liver enzymes and asymptomatic gallbladder pathology as the most frequent AEs. Hypotension is the clinical AE most frequently observed in neonates on octreotide, whereas the more common biochemical alterations are thrombocytopenia, hyperkalemia, and leukocytosis. Although rare, elevated blood urea nitrogen, increased serum markers of cholestasis, and hyperglycemia have been also described. Luckily, none of the AE potentially related to octreotide administration occurred in the infant described in the present case report.

The occurrence of NEC has been reported in full-term infants treated with octreotide for congenital hyperinsulinism; a possible causal role of octreotide-induced splanchnic vasoconstriction was hypothesized. On the other hand, successful closure of EFs thanks to octreotide has been described in a small number of newborns. When evaluating the risk–benefit ratio of treatment with octreotide in the present case, previous literature was reviewed carefully: the treatment...
choice was based on the infant’s critical conditions and the inefficacy of the conventional therapeutic strategies already applied. Following these considerations, octreotide was used as a rescue treatment, aiming at taking advantage of its vasoconstrictor effect on splanchnic circulation to reduce bowel inflammation.

Our experience provides a novel insight into NEC management by reporting the effectiveness of off-label octreotide given as a rescue treatment in a critically ill ELBW preterm infant with perforated NEC, after failure of surgical approaches. Furthermore, the present case provides some evidence on the use of octreotide in extremely preterm infants.

ABBREVIATIONS
AE: adverse events
DOL: day of life
EF: enterocutaneous fistula
ELBW: extremely low birth weight
GI: gastrointestinal
IV: intravenous
NEC: necrotizing enterocolitis
PD: peritoneal drainage
PDA: patent ductus arteriosus
SIP: spontaneous intestinal perforation

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