Propranolol for the Treatment of Lymphatic Malformations in a Neonate – A Case Report and Review of Literature

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Lymphatic malformations in neonates often manifest as a chylothorax, and although rare, morbidity and mortality can be significant. First-line treatment with medium-chain triglyceride–enriched formulas, or enteric rest with total parenteral nutrition, are not always successful. We describe the case of a premature neonate with trisomy 21 who presented with bilateral pleural effusions and a pericardial effusion that worsened with the initiation of enteral nutrition. Clinical improvement was not seen until the initiation of treatment with oral propranolol at a maximum dosage of 0.5 mg/kg/day divided every 8 hours with extubation 8 days after propranolol initiation. Two case reports have described the use of propranolol in similar patients receiving 2 mg/kg/day; however, our experience is the first to report treatment success at a much lower dose. A review of the literature for alternative medication treatments uncovered numerous case reports and series documenting variable results with incongruent definitions of treatment success in a diverse patient population. The rarity of this disease state makes accrual of patients difficult and more robust treatment data unlikely. Therefore, selection of the optimal adjunctive treatment must be based on individual patient and disease state characteristics as well as safety and efficacy profile of the medication.

ABBREVIATIONS DOL, day of life; MCT, medium chain triglyceride; mTOR, mammalian target of rapamycin; TPN, total parenteral nutrition; VEGF, vascular endothelial growth factor

KEYWORDS chylothorax; chylous effusion; lymphangiogenesis; newborn; propranolol

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Introduction

Lymphatic malformations in neonates often manifest as a chylothorax, an accumulation of lymphatic fluid in the pleural space. The lymphatic system is a distributed network of vessels that serve as an accessory pathway for the return of blood to the heart. Much of the lymphatic fluid volume is derived from interstitial fluid, but the abdominal lymphatic system also contains emulsified fats called chyle, produced by the digestion of food. Initiation of fatty meals increases lymph flow up to 10 times and transitions chyle from clear to milky.^{1,2} The biochemical composition of enteric-derived lymph includes high triglyceride levels, low cholesterol levels, lymphocyte abundance, and protein and electrolyte profiles similar to those of plasma. Long-chain fatty acids pass into lymph and reach the venous system via the thoracic duct.³

Neonatal chylothoraces are rare, but they represent the most common cause of pleural effusions in the neonatal period.¹ A primary chylothorax can be spontaneous or due to congenital and/or chromosomal abnormalities. In congenital cases, syndromes such as trisomy 21, Noonan syndrome, Turner syndrome, and hydrops fetalis can be involved.^{1,3} Secondary chylothorax is more common, due to disruption of the

thoracic duct from postoperative complications, trauma, or infection. Lymphatic malformations can be characterized by complex lymphangiogenesis (generalized lymphangiomatosis) and/or dilatation of lymphatic vessels (generalized lymphangiectasia). The mediastinum, lung, intestine, liver, and subcutaneous soft tissue can all be involved.⁴

Left untreated, chylothoraces can result in significant respiratory morbidity, malnutrition, and immunodeficiency. First-line treatments include drainage of the pleural fluid and conservative management with medium-chain triglyceride–enriched (MCT) formulas or cessation of enteral feeds and initiation of total parenteral nutrition (TPN).^{4,5} Use of conservative management over an extended period of time (2–6 weeks) may reduce the need for surgical intervention; however, it can also extend the hospitalization, increase the risk of central line infections with prolonged use of TPN, and result in complications secondary to nutritional and immune losses in refractory cases, making alternative treatment strategies warranted.^{3–5} Medical management with adjunctive medications, such as α -interferon, octreotide, sildenafil, sirolimus, and propranolol, has resulted in variable success in uncontrolled case reports in neonatal and pediatric patients. Treatment options have variable adverse effect profiles that must be taken into

consideration before use.⁶⁻⁹ A lack of consensus on preferred treatment options or protocols in different patient populations and limited data make treatment in neonates difficult. We encountered a challenging case of chylothorax in a premature neonate, prompting intense review of the available literature on adjunctive medications. We chose to use low-dose propranolol in this case.

Case

We present the case of a 1910-g female neonate with antenatal diagnosis of trisomy 21 and concern for hydrops fetalis born via cesarean delivery at 34 and 4/7 weeks' gestation. Delivery room resuscitation with blow-by oxygen was provided, and she was transitioned to continuous positive airway pressure 5 cm H₂O with 30% FiO₂ at 5 minutes of life. Apgar scores were 7 and 7 at 1 and 5 minutes of life, respectively. Trisomy 21 was confirmed with karyotype 47,XX,+21. Maternal serologies revealed no infectious source of hydrops, and initial echocardiogram showed normal segmental anatomy with appropriate biventricular function. Non-invasive positive pressure respiratory support was weaned to nasal cannula during the first few days of life, and trophic feeds of 20 mL/kg/day were started on day of life (DOL) 2 with expressed breast milk. On DOL 4, respiratory distress and acidosis developed requiring intubation and mechanical ventilation. Serial chest x-rays and echocardiograms demonstrated growing bilateral pleural effusions (Figure 1A) and a large pericardial effusion. A chest and abdominal ultrasound showed subpulmonic pleural effusions and a small amount of ascites. Thoracentesis was unsuccessful, yet because of concern for tamponade, the patient underwent pericardiocentesis and pericardial drain placement. Pericardial fluid analysis showed: triglyceride level 66 mg/dL; protein >600 mg/dL; LDH 784 units/L; cholesterol 83 mg/dL; cell count 1457 cells/ μ L. Subsequent serum measurements showed hypoproteinemia (plasma total protein 3.1 g/dL) and hypoalbuminemia (albumin 1.8 g/dL). Trophic feedings were discontinued at this time and the patient was placed on TPN. Repeat pericardial fluid triglycerides the following day were 57 mg/dL with a serum triglyceride level of 62 mg/dL.

Pericardial drain output decreased and the drain was removed on DOL 6. Despite decreased drain output, the patient continued to have anasarca and an invasive ventilation requirement. Enteral feeding was reinitiated on DOL 9, with subsequent reaccumulation of effusions with increasing enteral nutrition. Enteral nutrition was discontinued and the patient was continued on TPN. Nutritional deficits were persistent on DOL 12 (total plasma protein 3.6 g/dL and albumin 2 g/dL) requiring replacement with 1 g/kg of 25% albumin. On DOL 16 because of concern for progressive lymphatic dysfunction, oral propranolol was started at 0.3 mg/kg/day divided every 8 hours. Ventilator settings on day of initiation

of propranolol were a rate of 45 breaths per minute, peak end expiratory pressure of 7, pressure control of 16, and FiO₂ 40%.

During the next few days, ventilator settings and clinical status improved. A repeat chest x-ray 4 days after propranolol initiation demonstrated a significant reduction in pleural effusions with a small left and trace right pleural effusion. Repeat echocardiogram showed continued evidence of pericardial effusion, although small. Serum glucoses and blood pressures were frequently monitored during treatment initiation, and no adverse effects were noted (Figure 2). Given improved, persistent effusions and good tolerance to the medication, the dosage was increased to 0.5 mg/kg/day divided every 8 hours.

With continued clinical and respiratory improvement, she was started on a trial of MCT-enriched formula (EnfaPort) on DOL 20. Enteral nutrition was slowly advanced without reaccumulation of chyle. Extubation occurred on DOL 23, 8 days after initiation of propranolol and in the setting of continued feeding advancement. Ten days after propranolol initiation, the patient had complete radiographic resolution of her bilateral pleural effusions (Figure 1B), and echocardiogram demonstrated a tiny pericardial effusion. She tolerated full-volume feeds and was then transitioned back to breast milk. Twenty days after initiation of propranolol, she had transitioned to full breast milk feeds, required no respiratory support, and had continued improvement on chest x-rays (Figure 1C). The propranolol therapy was discontinued, yet surveillance chest x-rays and echocardiograms continued through 2 months of life without reappearance of effusions (Figure 1D). No adverse effects were observed throughout the propranolol treatment course (Figure 2).

Discussion

We report the case of a premature neonate with a presumed lymphatic malformation and chylothorax successfully treated with low-dose propranolol. In our case, conservative management failed to produce resolution. Given our patient's worsening clinical status and the concern for long-term implications of continued invasive respiratory requirements in a premature patient, we opted to assess additional methods of medical management with the goal of decreasing lymphangiogenesis and lymphatic flow. We undertook a review of the published literature for available medication options to evaluate for potential use in our patient. Medications were considered based on efficacy, adverse effects, and use in clinical scenarios with similarities to that of our patient. A review of octreotide, sildenafil, sirolimus, and propranolol was performed.

Initial conservative treatment includes termination of enteral feedings and provision of nutrition via TPN. Use of conservative management is generally accepted as the first-line treatment strategy and has been reported

Figure 1. Serial chest x-rays of preterm patient with trisomy 21.

(A) Chest x-ray on day of respiratory decompensation with bilateral chylothous pleural and pericardial effusions after pericardial drain. (B) Resolved effusions 10 days after propranolol initiation. (C) Resolved effusions after 20 days of oral propranolol therapy with full breast milk feeds. (D) Normal chest x-ray 1 month after oral propranolol therapy was discontinued.

to reduce or stabilize drain output in 71% to 84% of patients treated.^{4,10–13} Conservative management may decrease thoracic lymph flow, allowing for spontaneous healing of the damaged thoracic duct. Medium-chain triglycerides bypass the thoracic duct and lymphatic drainage via direct absorption into the portal venous system. However, introduction of any enteral nutrition has the potential to stimulate gastric output and increase flow through the lymphatic system, potentially worsening chylothorax output. A more aggressive approach is complete enteric rest and TPN, circumventing enteral absorption and providing fat intravenously, which does not travel through the lymphatic system and therefore does not contribute to chyle production.^{4,14} There are currently no prospective or randomized controlled trials that have evaluated the use of MCT-enriched formulas compared with TPN in pediatric and neonatal patients.

Several retrospective studies have shown no difference in clinical outcomes, including duration or volume of chest tube output, calorie and protein provision, and requirement of surgical intervention between patients receiving MCT-enriched enteral nutrition or those on complete enteric rest and TPN.^{5,12,14,15} Management with MCT-enriched formula is preferred in most patients to protect gut barrier function and avoid complications related to TPN administration, but enteral nutrition may not always be tolerated.⁵ Total parenteral nutrition may be preferred initially in severe cases of chyle accumulation and clinical instability. Evaluation of this treatment has mostly been for postoperatively acquired chylothorax, not in the setting of lymphatic malformations. Regardless of the modality, goals of nutritional therapy should be to reduce chyle production, replace fluid and electrolytes, and maintain or replete nutritional status.^{4,14}

Figure 2. Blood glucose (mg/dL) and systolic blood pressure (mmHg) monitoring during oral propranolol therapy.

● Blood Glucose; ■ Systolic Blood Pressure

Although the pericardial drain was able to be removed in our patient with conservative management, the general clinical status of the patient did not improve, and reinitiation of feedings resulted in reaccumulation of pleural and pericardial effusions. The case was further compounded by nutritional deficiencies and continued respiratory complications.

Octreotide has the most robust evidence describing use for chylothorax and lymphatic malformations. Somatostatin is an endogenous hormone with a variety of inhibitory activities, including effects on the gastrointestinal tract. Octreotide is a synthetic somatostatin analog with a longer duration of action given intravenously or subcutaneously. Octreotide likely exerts its effects by decreasing gastrointestinal blood flow through mild vasoconstriction of splanchnic vessels, resulting in decreased gastric, pancreatic, and intestinal secretions. Additional potential mechanisms include decreased absorption of triglycerides and reduced lymph production by direct stimulation of somatostatin receptors on lymphatic vessels. Overall, these effects lead to decreased lymphatic drainage, allowing for healing of the thoracic duct leak.^{4,5,16,17}

Octreotide is administered as either intermittent subcutaneous doses, a continuous subcutaneous infusion, or an intravenous continuous infusion. Dosing varies dramatically (1.7–2.9 mcg/kg/hr subcutaneous continuous infusion, 10–117 mcg/kg/day subcutaneous in 2 or 3 divided doses or 0.3–20 mcg/kg/hr intravenously), with most cases using a starting dose of 1 mcg/kg/hr with

a titration to 10 mcg/kg/hr as an intravenous continuous infusion.^{17–25} There is no consensus on the utility or the method of weaning the infusion after resolution of a chylothorax, although reports have described dose reduction daily by 2 to 3 mcg/kg/hr.^{26,27} In those patients who responded to octreotide, response was usually seen early (24–48 hours), and chest tube output was significantly decreased.^{23,27–34} However, a recent systematic review reported efficacy of only 47%, with a slightly higher efficacy in congenital (53.3%) versus acquired (33.3%) chylothorax.²⁰ Furthermore, octreotide treatment may correlate with a longer duration of pleural drainage, higher use of antithrombin, longer length of stay, longer respiratory support, higher incidence of sepsis, and no change in mortality compared with conservative management.³⁵

The potential efficacy of octreotide must be balanced with the adverse effect profile. A large database review of 490 courses of octreotide in infants being treated for various indications found the most common adverse effects were thrombocytopenia, hyperkalemia, and leukocytosis.³⁶ Although necrotizing enterocolitis, abdominal distension, or bloody stools have been observed in several case reports, this review found necrotizing enterocolitis was only observed in 2% of the overall treated population.^{8,30,35–41} Octreotide also disrupts thyroid function and glucose homeostasis, although both effects occur transiently.^{10,18,29,35,42} Other concerning adverse effects reported include cholelithiasis and pulmonary hypertension.^{41,43–45} These serious adverse

effects outweighed uncertain efficacy in our case, and we decided against the use of octreotide.

One major consideration in our literature evaluation was feasibility if a prolonged treatment course was required. Sirolimus, a commercially manufactured oral solution (1 mg/mL), is an inhibitor of mammalian target of rapamycin (mTOR), a kinase overexpressed in cutaneous vascular malformations. Sirolimus also has antiangiogenic properties through mitigation of vascular endothelial growth factor (VEGF).⁴⁶ This therapy has not specifically been used for treatment of chylothorax in neonates, but it has been shown to elicit response in lymphatic malformations. A single case report of use in a neonate with diffuse lymphangiomatosis documented significant reduction in masses within 5 days after treatment failure with propranolol.⁴⁷ Subsequent case reports and series demonstrate favorable outcomes in pediatric patients treated for a variety of lymphatic and vascular anomalies. Most cases initiated therapy at 0.8 to 1.6 mg/m²/day divided twice daily, with doses titrated to achieve sirolimus concentrations between 5 and 15 ng/mL.^{9,46–52} Elevated sirolimus concentrations have been reported in neonates, and a lower dose may be required in this patient population.^{47,53} A high incidence of adverse effects is reported with sirolimus, including 27% of patients experiencing blood or bone marrow toxicity, 3% gastrointestinal toxicity, and 3% metabolic toxicity.⁹ The risk of sirolimus-related infection and mortality has been described in 2 infant cases.⁵⁴ Given the high incidence of bone marrow suppression, immunoprophylaxis has been used in conjunction with sirolimus.⁴⁶ Because of the lack of data in premature neonates, the need for additional therapeutic drug and laboratory monitoring, and the high incidence of toxicity, sirolimus was not used in our patient.

Sildenafil was strongly considered in our patient, as an oral option available in a commercially manufactured suspension (10 mg/mL). It selectively inhibits phosphodiesterase-5, mitigating the degradation of cyclic guanosine monophosphate, which facilitates lymphatic endothelial cell proliferation and growth of new lymphatic vessels.²¹ The initial report of treatment success with sildenafil for lymphatic malformations was found coincidentally in an infant treated for pulmonary hypertension in the setting of a congenital lymphatic malformation.⁵⁵ Since then, case reports have documented both success and failure using sildenafil in neonates.^{21,56} Pediatric literature is more informative, with 2 prospective open-label studies evaluating use for lymphatic malformations in infant and pediatric patients (N = 28). Dosing was 2 to 4 mg/kg/day divided 3 times daily with a maximum dosage of 30 mg/day for patients <20 kg and 60 mg/day for patients >20 kg. Treatment success occurred in 67% to 86% of patients. Adverse effects were minimal in both studies, with mild gastrointestinal complications most commonly reported. No patients stopped treatment with sildenafil secondary

to adverse effects.^{57,58}

Sildenafil has historically been used in term neonates for persistent pulmonary hypertension of the newborn with a favorable side effect profile.⁵⁹ Safety data in the premature population are limited. Of particular concern, sildenafil may increase the severity of retinopathy of prematurity. In adult patients, accumulation of nitric oxide and cyclic guanosine monophosphate during sildenafil therapy exerts a proliferative effect on retinal postcapillary venules, resulting in exacerbation of retinal disease.⁶⁰ A case report has linked sildenafil to severe retinopathy of prematurity, but larger observational studies have produced equivocal findings.^{61–63} Given this concern, we chose the use of propranolol in our patient rather than sildenafil. However, the side effect profile in patients outside of the premature period makes it an attractive alternative treatment option in neonatal lymphatic malformations.

Treatment with oral propranolol, a non-selective beta-blocker, was decided upon in this case because of its documented inhibition of VEGF and safe adverse effect profile as documented in extensive investigation for infantile hemangiomas. Propranolol acts on the rapidly accelerated fibrosarcoma mitogen-activated protein kinase signaling pathway, causing reduced expression of VEGF levels and direct induction of apoptosis in capillary endothelial cells.^{64–66} Specific use of propranolol in neonates for congenital or acquired chylothorax is limited to case reports and small case series. Variable degrees of efficacy were seen in a variety of lymphatic anomalies, but most patients had clinical improvement within the first few days to a month of therapy.^{47,64,67–72} Two prior case reports in premature patients presenting with hydrops fetalis and chylothorax due to suspected lymphangiectasia have also shown treatment success with propranolol. Response was seen within the first 1 to 2 weeks, and extubation was facilitated in both patients.^{56,65}

Prospective, open-label use in pediatric patients demonstrated a significant decrease in VEGF levels 24 months after propranolol initiation, with a clinical response in 67% of patients, although half of those responders only saw minimal improvement. A reduction in VEGF levels has also been demonstrated to occur in the premature population, although pediatric data suggest clinical response is not solely linked to VEGF levels.^{64,65,67} We did not obtain VEGF levels in our patient, but instead used clinical and objective markers of improvement to dictate response and need for dose escalation. The utility of routine VEGF monitoring requires further exploration.

Minimal adverse effects have been documented with propranolol use for this indication, including mild headache and bradycardia in pediatric patients. No serious adverse effects have been reported in cases including premature neonates.^{56,64,65} Our patient did not experience any adverse effects during treatment.

Dosing in term neonates, infants, and pediatric patients has ranged from 1 to 4 mg/kg/day, with most patients receiving 1 to 2 mg/kg/day divided.^{47,64,67–72} Case reports in premature neonates used lower starting dosages, 0.1 mg/kg/day and 0.5 mg/kg/day, and both patients were titrated to a max dose of 2 mg/kg/day.^{56,65} We reported an analogous time-coincident clinical improvement in our patient of a similar gestational age and presentation. Our patient had clinical improvement without adverse effects at 0.5 mg/kg/day versus 2 mg/kg/day, potentially supporting efficacy at a lower dose than previously reported. We planned to reproduce the dose titration provided by Porella and colleagues; however, 0.1 mg/kg/day was unable to be measured using our commercially available concentration of propranolol (4 mg/mL, Roxane Laboratories, Columbus, OH). Therefore, we started at the minimal measurable dosage of 0.3 mg/kg/day. After a single-dose titration to 0.5 mg/kg/day, the radiographic and clinical improvement was substantial, and further dose escalation was not performed. Extubation occurred in our patient at 8 days, which was in alignment with the prior 2 case reports (10 and 16 days).^{56,65}

Conclusion

Neonatal chylothorax is a rare disorder, but complications secondary to accumulation of pleural fluid and loss of immune and nutritional components can lead to a high rate of morbidity and mortality. Medical management may be necessary when conservative strategies fail, to avoid surgical procedures. We report the case of a premature neonate with bilateral pleural effusions and a pericardial effusion unresponsive to treatment with TPN and MCT-enriched formulas who had successful treatment with oral propranolol. Two previous case reports have described the use of propranolol in a similar patient presentation; however, our experience is the first to report a response at a much lower dose.^{56,65}

Although our patient responded to propranolol treatment, other medication therapies were considered. A review of the literature uncovered a plethora of case reports, case series, and uncontrolled trials of medications proposed to treat chylothoraces and lymphatic malformations. No randomized trials comparing adjunctive medications currently exist. Given the rarity of this disease state, it is unlikely that more robust data will surface, leaving guidance for treatment reliant on low-level evidence. Further complicating factors include the lack of consistently defined treatment success, variability in dosing regimens, and heterogeneous patient populations. Additionally, the natural progression of chylothoraces includes spontaneous resolution, which cannot be accounted for in uncontrolled publications. Despite these limitations, we feel propranolol was a vital factor in the recovery of our patient. If conservative management is inappropriate or unsuccessful,

adjunctive medications can be evaluated, and medication choice should be based on individual patient and disease state characteristics and medication-specific factors, including route of delivery, risk of adverse effects, and monitoring requirements. Our decision to use propranolol in our patient was highly driven by safety, familiarity of use in infantile hemangiomas, and the adverse effect profiles of the alternative available options. Diligent monitoring for adverse effects should be performed if medication management is deemed appropriate. The use of case reports and small patient reviews helps to assist in the available knowledge on medication treatment efficacy and adverse effects.

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Expedited criterion.

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