

Original Research Article

Conservative management of chylothorax in infants using octreotide

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ABSTRACT

Background: Chylothorax is defined as abnormal accumulation of lymphatic fluid in the pleural space and is a rare condition in neonates and infants. Chylothorax causes respiratory and nutritional problems and has a significant mortality rate. Octreotide is a long-acting somatostatin analogue that can reduce lymphatic fluid production and has been used as a new strategy in the treatment of chylothorax.

Methods: Infants with spontaneous chylothorax over a period of 3 years were included in this study. A prospective, observational study was done. All patients were nil per oral initially. Oral feeds were resumed once the ICD output declined. Octreotide was given subcutaneously for all patients at a dose of 40 microgram/kg/day in 3 divided doses. Octreotide was stopped once the ICD output was less than 70-80 ml/day. ICD was inserted in all patients and removed once drainage was below 50 ml/day.

Results: Five patients were diagnosed with chylothorax over a period of 3 years out of which 3 were male and 2 were females. 1 patient had right sided and 4 patients had left sided chylothorax. The average age of presentation was 5.6 months. Octreotide was administered for an average of 14.4 days (8-22 days). The average duration of ICD was 18.2 days. All patients recovered well and were discharged.

Conclusions: Spontaneous chylothorax is rare in infants. Conservative management is usually successful. Early institution of oral feeds with octreotide preserves the child's nutrition and avoids invasive procedures, such as reinsertion of chest tubes or surgery.

Keywords: Congenital chylothorax, Octreotide, Somatostatin

INTRODUCTION

Chylothorax is defined as abnormal accumulation of lymphatic fluid in the pleural space and is a rare condition in neonates and infants. There are several causes of chylothorax. It may result from congenital abnormalities of the lymphatics, which may not present in the neonatal period. Pulmonary lymphangiomas and lymphangiectasia, absence or atresia of the thoracic duct are the major lymphatic abnormalities associated with chylothorax.¹ It is associated with various syndromes such as Down syndrome, Turner syndrome, Noonan syndrome, Gorham-Stout syndrome, X-linked myotubular myopathy, Missense mutation in integrin $\alpha 9b1$, Hydrops fetalis and

Yellow nail syndrome. Rupture or laceration of the thoracic duct can be caused by trauma leading to chylothorax. It occurs as a postoperative complication after various surgeries involving structures in the neck and thorax such as treatment of scoliosis, vascular rings, diaphragmatic hernia; cardiothoracic surgery and catheterization of the subclavian vein. Trauma such as blunt force or penetrating trauma to the chest, severe coughing or vomiting, the force of child birth, child abuse can lead to the development of chylothorax. Venous thrombus or obstruction in the superior vena cava or subclavian vein may lead to rupture of the thoracic duct. Chylothorax can be associated with various tumors and malignancies (neurogenic, lymphoma, teratoma, Wilms,

ovarian, and Kaposi sarcoma) or granulomatous infections such as tuberculosis, histoplasmosis, and sarcoidosis. The etiology of the chylothorax may be uncertain in many cases and is thought to be caused by abnormality of thoracic or pulmonary lymphatic system. This is termed idiopathic congenital chylothorax.

Congenital chylothorax presenting antenatally can act as a space-occupying lesion and restrict normal development of the lungs. Chylothorax causes respiratory problems, muscle wasting, weight loss, malnutrition and immunological complications because of lymphocyte depletion and hypogammaglobulinemia and is associated with a significant mortality rate.

A chest radiograph can reveal pleural fluid and assess the size and location of the effusion. Thoracentesis yields is white, odorless, and milky chyle. The triglyceride level of chyle is above 110 mg/dL and lipoprotein analysis shows the ratio of the pleural fluid to serum cholesterol is 1.0 chylomicron. Octreotide is a long-acting somatostatin analog that acts on somatostatin receptors in the splanchnic vessels to inhibit lymphatic fluid production. Octreotide has been used in the treatment of postoperative or spontaneous chylothorax in infants and older children.² It has also been used for the treatment of congenital chylothorax in term neonates. The objective of this study was to evaluate the role of octreotide in the management of spontaneous chylothorax in infants.

METHODS

All infants who presented at the Department of Pediatric Surgery at Niloufer institute of Women and Child Health, Hyderabad, India with spontaneous chylothorax over a period of 3 years from January 2016 to December 2018 were included in this study. A prospective, observational study of these patients was done. All infants with spontaneous chylothorax were included in the study, those patients who had chylothorax due to any other pathology or post operatively were excluded from the study. Institutional ethical committee clearance was taken prior to starting the study. All patients were nil per oral initially. ICD (intercostal drain) was inserted in all patients. Octreotide was given subcutaneously for all patients at a dose of 40 microgram/kg/day in 3 divided doses. Total parenteral nutrition was administered. Octreotide was stopped once the ICD output was less than 70-80 ml/day. ICD was removed once drainage was below 50 ml/ day. Oral feeds were resumed once the ICD output declined. Statistical analysis was done using SPSS software.

RESULTS

5 patients were diagnosed with chylothorax over a period of 3 years out of which 3 were male and 2 were females. All 5 patients presented with respiratory distress. Radiograph of the chest was done in all, which showed a left sided massive pleural effusion in 4 patients and right sided effusion in one patient. Aspiration of the fluid

revealed a milky white fluid which was sent for biochemical analysis. The fluid showed the presence of triglycerides and chylomicrons which are pathognomonic of chylothorax. A chest drain was placed to relieve the respiratory distress and the patients were given supplemental oxygen. The chest drain output was measured each day. The patients were kept nil orally and total parenteral nutrition was administered for the caloric requirements. Octreotide was given to all patients once the diagnosis was made. 40 microgram/kg/day of octreotide was given subcutaneously in 3 divided doses. The octreotide was continued till the chest drain output decreased to below 70 ml/day. Oral feeds were then started and the response noted. There was no rebound increase in chyle production. The chest drains were removed once the drain output was less than 50 ml/day. All the patients recovered well and were discharged.

Table 1: Details of the individual patients.

Age (months)	Sex	Side of chylothorax	Number of days octreotide was administered	Number of days chest drain was in situ
3	Male	Left	12	17
1	Female	Left	9	12
4	Male	Left	22	26
8	Female	Right	8	11
12	Male	Left	21	25

The details of the individual patients are mentioned in Table 1. The average age of presentation was 5.6 months. Average number of days a patient was kept nil per oral was 11.4 days. Octreotide was administered for an average of 14.4 days (8-22 days). The average duration of ICD was 18.2 days.

DISCUSSION

Management of chylothorax includes relief of respiratory distress by drainage of the pleural fluid, treatment of the underlying cause to prevent recurrence, and prevention and treatment of malnutrition and immunodeficiency.¹

The initial step is aspiration of the pleural fluid for diagnostic purposes. A chest tube should be inserted for large effusions, causing respiratory distress, for continuous drainage of the pleural space. Quantification of drainage is useful to guide treatment of fluid imbalances and as a guide for clinical improvement or failure. In severely ill patients, assisted ventilation may be necessary. The use of positive end expiratory pressure ventilation may tamponade the injured duct, helping to decrease chyle flow.³ There are several nonsurgical methods (dietary modifications and/or adjunctive medications) that can be used to prevent or treat chylothorax if the leak does not spontaneously resolve. Most studies performed in

children recommend up to a two- to four-week trial of conservative management before surgery is considered. To reduce the flow of chyle through the thoracic duct while waiting for spontaneous healing to occur, a fat-free diet with the addition of medium-chain triglycerides is instituted. Medium-chain triglycerides with saturated fatty acids of 8 to 12 carbon chain lengths are absorbed directly into the portal venous system, bypassing lymphatic drainage. Medium-chain triglyceride formulas do not contain essential fatty acids, so those will need to be supplemented if these formulas are used for 3 weeks.⁴ A more aggressive option is complete enteric rest by using total parenteral nutrition.⁵ Somatostatin is a polypeptide secreted from the paraventricular nucleus of the hypothalamus. It has an inhibitory effect on the secretion of growth hormone, glucagon, and insulin. Octreotide is a synthetic, long-acting somatostatin analog. These agents have been used in the management of chylothorax with varying results. They cause vasoconstriction of the splanchnic circulation leading to a reduction in intestinal blood flow and consequently reduction of lymphatic fluid production. Somatostatin receptors are also present in lymphatic vessels, and their stimulation results in decreased lymphatic flow. These agents also decrease gastrointestinal motility, and decrease the volume of gastric, pancreatic, and biliary secretions, which in turn decreases lymphatic flow. In comparison with somatostatin, octreotide has a longer half-life, greater potency, and the option of subcutaneous administration. Somatostatin and octreotide have been used to treat a variety of diseases, including acromegaly, carcinoid syndrome, secretory diarrhea, severe gastrointestinal bleeding, postgastrectomy dumping syndrome, chemotherapy-induced diarrhea, and persistent hyperinsulinemic hypoglycemia. Either drug can be given as a continuous intravenous infusion or as an intravenous bolus twice daily. The starting dose of somatostatin is 3.5 mg/kg per hour, which can be increased to 10 mg/kg per hour.⁶ The dose for octreotide in children has ranged from 0.3 to 1.0 mg/kg per hour. Side effects of somatostatin and octreotide include hyperglycemia, hypothyroidism, cramps, nausea, diarrhea, renal impairment, necrotizing enterocolitis, and liver dysfunction. Shah and Sinn reported 6 patients with congenital chylothorax treated with octreotide in a dose range of 0.5 to 10 mg/kg per hour. Five of the 6 patients had resolution of their chylothoraces with this therapy.⁷ Roehr et al performed a systematic literature review of the use of somatostatin and octreotide in 35 children with primary or secondary chylothorax.⁸ Most studies reported a significant decrease in chylous drainage within 5 to 6 days of starting octreotide or somatostatin. The use of octreotide in 20 neonates with chylothorax was described in a 2010 Cochrane report. Fourteen of the case reports described successful resolution of chylothorax, reported no resolution, and 1 reported equivocal results.⁴ No practice recommendation was made based on this evidence.⁹ Horvers et al reported on the use of octreotide in 7 patients with congenital chylothorax. Administration of 5 to 6 mg octreotide/kg per minute lead to a decrease in pleural effusions in all

patients, but that decrease might have been the natural history of congenital chylothorax and, hence, no clear, consistent effect of octreotide was identified. They noted that pulmonary hypertension was a common problem in the patient group.¹⁰ Other agents used in the treatment of chylothorax include nitric oxide and etilefrine. A case report described the use of nitric oxide in a neonate who developed a chylothorax after surgery for congenital heart disease.¹¹ Surgery should be considered when medical management of chylothorax has failed to reduce chyle flow and allow healing of the duct. There is no consensus on the timing of surgery. Surgery is recommended if the effusion persists for more than 2 weeks or if the leak is more than a particular volume, such as 100 mL per year of age in children. However an extended period (3 to 4 weeks) of conservative management may be recommended before proceeding to surgical treatment unless there is a well identified site of chyle leak and high flow which can be managed better with surgery. Successful surgery can shorten hospitalization and reduce the risks of malnutrition and immunosuppression.¹² There are several procedures that can be used for the treatment of chylothorax. If the site of rupture of the thoracic duct can be identified by lymphangiography, direct surgical ligation of the duct represents a definitive treatment of chylothorax. Thoracoscopy has a low rate of complications. Fernandez et al performed thoracic duct ligation via thoracoscopy in 14 children with chylothorax after cardiac surgery and reported that it was successful in 12 (86%).¹³ Nath et al performed duct ligation in 20 pediatric patients with chylothorax after cardiothoracic surgery. They were successful in 16 patients (80%), but noted that patients with thrombus of upper body venous vessels or prolonged chest tube drainage were more likely to fail and/or die. They recommended that duct ligation be done within 2 weeks of recognizing the chylothorax.¹⁴ If needed to visualize the thoracic duct and the site of leakage during surgery, the patient can be given a 200 mL mixture of milk and cream a few hours before surgery, or an intraoperative injection of 1% Evans blue dye.¹⁵ If the site of leakage cannot be identified, a mass ligation of the thoracic duct and its surrounding tissue is done around the aorta, azygos vein, and esophagus, adjacent to the vertebral body, or by ligation of the cisterna chyli. The pleural space may be obliterated using chemicals such as tetracycline, talc, bleomycin, fibrin glue, and povidone-iodine or by surgery. Various agents, such as, have been used. Povidone-iodine 10% dermiquie diluted with saline or povidone-iodine 4% scrub was instilled directly through a chest tube into the pleural space in a group of 4 neonates with chylothoraces. Thyroid function was reported to be normal before and after instillation of povidone-iodine in 3 of the infants; it was not checked in the fourth infant.¹⁶ OK-432 which is an inactive preparation of *Streptococcus pyogenes*, has also been used as an effective sclerosing agent in neonates and in antenatal treatment of patients with nonimmunologic hydrops fetalis with severe chylothorax.¹⁷ Pleurodesis can be performed by instilling the sclerosing agent via a chest tube or by thoracoscopy. Pleurodesis has effectively been used in cases where

medical therapies for chylothorax failed and direct surgical duct ligation was not performed.¹⁸ Another surgical method is the placement of a pleuroperitoneal shunt. This drains chyle from the pleural space without loss of fluid. The shunts are one-way and placed subcutaneously connecting the pleura and the peritoneum. They have been used in children whose chylothoraces have been refractory to other modes of treatment, and are reported to be 75% to 90% effective.¹⁹ After a shunt is implanted, the lymphatic defect closes spontaneously in most cases and the shunt can be removed 30 to 90 days after insertion.

Limitations

The limitation of this study was the small number of cases studied and larger studies were required for better understanding of the effects of octreotide in treatment of spontaneous chylothorax in infants.

CONCLUSION

Chylothorax is a rare cause of pleural effusion in children except during the neonatal period, when it is the most common cause. Diagnosis is made by measurement of the triglyceride level, determination of the pleural fluid to serum cholesterol ratio, and demonstration of chylomicrons in the pleural fluid. There are multiple etiologies of chylothorax in children. Knowledge of the anatomy and physiology of the lymphatic system, particularly the thoracic duct, is vital for assessment and management. Initial treatment involves drainage of the effusion, dietary modifications, and other medical therapies to diminish chyle flow so that the thoracic duct can heal. The prognosis of children who develop chylothorax depends on the etiology of the effusion, its response to therapies, and the complications that result from the chylothorax. Early institution of octreotide limits the chyle production and prevents the nutritional and immunological problems. Octreotide appears to be a safe and effective adjunct therapy in the treatment of congenital chylothorax.

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