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Octreotide for chylous effusions in congenital diaphragmatic hernia

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Abstract

Background/Purpose—Chylothorax is a frequent complication in congenital diaphragmatic hernia (CDH) infants and is associated with significant morbidity. The optimal treatment strategy remains unclear. We hypothesize that octreotide decreases chylous effusions in infants with CDH.

Methods—This is a retrospective study of all infants with CDH admitted to our institution from October 2006 to October 2011.

Results—Eleven (12%) infants developed a chylothorax. Five infants were managed conservatively with thoracostomy and total parenteral nutrition. Six infants were started on octreotide therapy. None of the infants required surgical intervention to stop the effusion. There was no significant difference in survival to discharge, length of stay, or average daily chest tube output between groups. There appeared to be a temporally associated drop in chest tube output upon initiation of octreotide in two infants; however, the overall rate of decline in chest tube drainage was unchanged. In addition, there were infants in the conservative group who demonstrated a similar drop in daily chest tube output despite the absence of octreotide.

Conclusions—Our data suggest that the majority of chylous effusions in CDH infants resolve with conservative therapy alone.

Keywords

Congenital diaphragmatic hernia; Chylothorax; Octreotide

Chylothorax is reported in 6%–27% of infants with CDH [1–6]. This complication contributes significantly to the morbidity already associated with CDH, adding problems such as nutritional deficiency, hypoproteinemia, electrolyte abnormalities and a compromised immune system [2,5]. Effective management remains a challenge and many treatment strategies are controversial. Initial approaches to management include tube

thoracostomy, withholding of enteral feeds and administration of total parenteral nutrition [1,2,4,6,7]. In cases that are refractory to this conservative management, surgical interventions such as pleurodesis, thoracic duct ligation or pleurectomy, are considered [2,5].

Octreotide, a somatostatin analogue, has been used in patients with refractory chylothorax that do not respond to conservative management; however, no randomized studies in the neonatal population are available [7]. The exact mechanism of this therapy is uncertain, but is thought to cause vasoconstriction of splanchnic vessels, thereby reducing gastrointestinal secretions and intestinal absorption, which ultimately reduces the flow of chyle. Reported adverse effects of this medication include transient impairment of liver function, transient hypothyroidism, abnormal glucose homeostasis, and necrotizing enterocolitis [8].

Octreotide is used frequently as second-line treatment in patients who develop chylothorax following congenital heart surgery [9–11]. While there are no published controlled clinical trials regarding its use in this population, multiple large case series report success [7–13]. In one of the larger studies, 19 patients with congenital heart disease who developed postoperative chylothorax were treated with octreotide after failed conservative management [9]. Sixty-three percent of those patients demonstrated complete resolution of the chylothorax at an average of about 11 days after starting octreotide.

Use of octreotide for chylothorax in infants with CDH has been reported in only 11 cases with variable success [2,6,14,15]. Four of these cases were reported to have a dramatic reduction in chest tube drainage after initiation of octreotide with resolution of the effusion after 5–13 days of treatment [6,14,15]. In the remaining seven cases, octreotide failed to decrease chest tube output [2,6]. Most of those cases came from a single retrospective series of six patients in which octreotide did not consistently reduce chest tube drainage in any of the infants [2]. Our institution has used octreotide frequently in this population. The aim of this retrospective study was to determine if octreotide decreases chylous effusions in infants with CDH.

1. Methods

A retrospective analysis of infants with a diagnosis of CDH admitted to Cincinnati Children's Hospital Neonatal Intensive Care Unit from October 2006 through October 2011 was performed. Eighty-nine infants were identified for review. Infants with a diagnosis of pleural effusion with chest tube output >15 mL per kg per day were then identified. Chylothorax was diagnosed based on pleural fluid that was documented to be sterile and that had a lymphocyte count of more than 70%. Data on sidedness of the diaphragmatic defect, severity of the defect (based on prenatal total lung volume (TLV) or observed to expected lung area to head circumference ratio (O:E) where mild equals TLV > 40 mL or O:E > 45, moderate equals TLV = 20–40 mL or O:E = 25–45, severe equals TLV < 20 mL or O:E < 25) and need for extracorporeal membrane oxygenation were collected. Those infants with chylous effusions who received octreotide were compared to those who did not receive this therapy. The primary outcome measured was duration of effusion. Secondary outcomes measured were survival to discharge, length of stay, total chest tube output, average daily chest tube output, and culture positive sepsis. Since the duration of chest tube output was variable in the six patients treated with octreotide, some days included data from only one to two patients. To insure that our analysis was not overly weighted toward a single patient, we only included days that represented three or more patients in our results in Fig. 2. Statistical analysis was conducted using Microsoft Excel. Comparison between the two groups was made using a Student's *t*-test and chi-squared analysis. $P < 0.05$ was considered statistically significant.

2. Results

During the 5-year study period, 89 infants with CDH were identified (78 left sided, 11 right sided). Thirty (34%) infants developed a pleural effusion requiring chest tube drainage, of which, 11 were confirmed chylous by pleural fluid analysis. The remaining 19 infants with a pleural effusion were excluded from this study because 10 of the effusions were not chylous and 9 were indeterminate as no pleural fluid was sent for analysis. All of the infants with a chylothorax had a left-sided diaphragmatic defect. Seven of these infants developed a chylothorax after CDH repair, four developed a chylothorax prior to repair. The average survival rate for infants with chylothorax, nonchylous effusions, and no pleural effusions was 64%, 50%, and 70%, respectively, while the average length of stay for these three groups was 82, 105, and 64 days, respectively.

Initial management consisted of cessation of enteral feeds, total parenteral nutrition and chest tube drainage. Five of the 11 infants with chylothorax were managed successfully with this conservative approach alone and required chest tube drainage for an average of 9 days (range 2–18 days). These infants were all male with an average gestational age of 38 weeks. Three of these infants had a moderate-sized diaphragmatic defect and two had a severe defect. Those two infants with a severe diaphragmatic defect required ECMO. The remaining six infants who did not demonstrate a decrease in chest tube output with conservative management were started on octreotide therapy. This therapy was initiated on average 8 days into the pleural effusion. The octreotide dosing range used in these patients (1–13 $\mu\text{g/kg/h}$) was consistent with previously published octreotide dosing regimens [8]. These infants required chest tube drainage for an average of 29 days (range 10–51 days). Five of the infants in this group were female and one was male, with an average gestational age of 37 weeks. Two of these infants had a severe diaphragmatic defect, three had a moderate defect and one had a mild defect. Those two infants with a severe diaphragmatic defect required ECMO.

Outcome variables for the conservative and octreotide groups are shown in Table 1. The duration of chylous effusion was longer in the group that received octreotide. Survival to discharge in the conservative and octreotide groups was similar (60% vs. 67%) and there was no significant difference in average daily chest tube output observed between groups.

There was a marked amount of variability in the daily chest tube output in both groups (Fig. 1). Although there appeared to be a temporally associated drop in chest tube output upon initiation of octreotide in two infants, the overall rate of decline in chest tube drainage was unchanged. In addition, there were infants in the conservative group who demonstrated a similar drop in daily chest tube output despite the absence of octreotide.

The variability in daily chest tube output limited conclusions regarding the efficacy of octreotide in individual patients. To move past this limitation, the daily chest tube output in each patient treated with octreotide was calculated relative to the output in that patient on the day octreotide was started. The relative daily outputs were then averaged for all six patients with the start day of octreotide designated as day 0 (Fig. 2). A trendline in relative chest tube output was determined for days –7 to 0 which demonstrated that a gradual decline in average relative chest tube output was present prior to the initiation of octreotide. Using the pretreatment trendline, the estimated day of pleural effusion resolution would have been day 12.

3. Discussion

Chylothorax is a common complication in CDH infants. In our study, 12% of infants with CDH developed a chylothorax, consistent with previous reports describing an incidence of

6%–27% [1–6]. Many of the current treatment strategies for chylothorax in CDH infants are controversial and based primarily on anecdotal clinical experience. Use of octreotide for chylothorax in these infants has been reported in only 11 cases in the literature with variable success [2,6,14,15].

In the current study, there appeared to be a transient decrease in chest tube output on the day octreotide was started in some infants; however the overall rate of decline in chest tube drainage in those infants was unchanged. In fact, infants in the conservatively managed group also demonstrated similar drops in daily chest tube output despite the absence of octreotide therapy. This suggests that changes in chest tube output were more caused by the variable course of the effusion than the therapeutic effects of octreotide.

The variability of chest tube output in chylous effusions tends to confound conclusions regarding the efficacy of octreotide therapy that are based on single-patient experiences. To move beyond this limitation the relative chest tube output from multiple patients treated with octreotide was analyzed. When the relative output from these six patients was averaged, the day-to-day variability was minimized and a decreasing trend was apparent even before the initiation of octreotide. The trendline in relative chest tube output (Fig. 2) prior to octreotide predicted that the effusions would have resolved by day 12 on our relative timeline, which was similar to the actual median day of resolution of 15.5 days in these patients. While our trendline is not the standard method for evaluating drug efficacy, within the limits of our study group it does suggest declining chest tube output prior to octreotide. Interestingly, our median day of resolution mirrors the experience in congenital heart disease patients in which the average day of resolution of chylous drainage was 11 days following initiation of octreotide therapy in one series [9].

Although we present one of the largest reported series of chylothorax treated with octreotide in CDH infants, the number of chylothorax cases in this study was small and direct comparisons between the octreotide and conservative groups were not possible because the more severe effusions were selectively placed in the octreotide group. It is unlikely that a randomized trial in this patient population will be possible given the low incidence of CDH and chylothorax. This study is also limited by the variability in timing of initiation and treatment doses in the infants given octreotide.

Chylothorax remains a frequent obstacle in the care of infants with CDH and is associated with significant morbidity. Although our study was small, we did not observe any negative side effects of octreotide therapy. This fact notwithstanding, our data suggest that most cases of chylothorax resolve with conservative therapy alone.

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Fig. 1.

Daily chest tube output in patients receiving octreotide and patients receiving conservative management. In the infants receiving octreotide (A and B), there appeared to be a drop in chest tube output after octreotide, but, the overall rate of decline in chest tube drainage was unchanged. The infants managed conservatively (C and D) demonstrated a similar amount of variability in daily chest tube output. (#) refers to dosage of octreotide in $\mu\text{g/kg/hour}$.

Fig. 2.

Average relative chest tube output of patients receiving octreotide therapy. Daily chest tube output of the octreotide patients is depicted graphically relative to the amount of chest tube output on the start day of octreotide. Start day of octreotide for each patient was set as day 0 on the above graph. As can be seen, there is a gradual decline in chest tube output that is present prior to the initiation of octreotide. Using the pretreatment trendline, the estimated day of pleural effusion resolution prior to the start of octreotide would have been day 12.

Table 1

Outcome comparison between conservative and octreotide groups.

	Conservative management (<i>n</i> = 5)	Octreotide therapy (<i>n</i> = 6)	<i>P</i> value
Survival to discharge (%)	60	67	0.82
Length of stay (days)	86	79	0.81
Duration of effusion (days)	9	29	N/A
Average daily chest tube output (mL)	114	139	0.76
Sepsis (%)	20	33	0.62