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Evaluating the Use of Octreotide for Acquired Chylothorax in Pediatric Critically Ill Patients Following Cardiac Surgery

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OBJECTIVES To evaluate the impact of octreotide on time to resolution of chylothorax compared with conventional therapy. Secondary outcomes include the following: time to reduction of chest tube output by 20%, additional surgeries for chylothorax, hospital length of stay, in-hospital mortality, and adverse drug reactions.

METHODS We retrospectively evaluated the efficacy of octreotide vs conventional therapy for treatment postoperative chylothorax in pediatric patients in the cardiac ICU following surgery for congenital heart disease between October 2008 and June 2017.

RESULTS Final analysis included 32 patients with chylothorax who met inclusion criteria. Patients who received octreotide had a longer duration of chest tube drainage than those who received conventional therapy (24 vs 9 days, $p < 0.001$). Resolution of chylothorax was achieved in 13 of 16 (81.3%) octreotide patients and 16 of 16 (100%) conventional patients ($p = 0.178$). There was a comparable time to reduction by 20% in drainage (6 vs 8 days, $p = 0.337$). There was no significant correlation between time after starting conventional management and reduction chylous output in either the octreotide or conventional therapy group ($p = 0.809$, $p = 0.107$, respectively). However, there was a significant and moderate correlation between octreotide and reduction in a chylous output following initiation of octreotide ($R^2 = 0.464$, $p = 0.021$).

CONCLUSIONS Octreotide is potentially a safe and effective therapy for treatment in pediatric patients with refractory chylothorax following surgery for congenital heart disease.

ABBREVIATIONS AST, aspartate aminotransferase; EGA, estimated gestational age; IQR, interquartile range; MCT, medium chain triglycerides; NEC, necrotizing enterocolitis; TPN, total parenteral nutrition

KEYWORDS acquired chylothorax; chylothorax; congential heart disease; octreotide; pediatric; refractory chylothorax

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Introduction

Acquired chylothorax is a rare but serious postoperative condition in pediatric critically ill patients following cardiac surgery. Chylothorax is pleural effusion from fluid rich in triglycerides and chylomicrons. The incidence of chylothorax following cardiothoracic surgery varies between 0.25% and 9.2%.[1–4] Chylothorax is the result of a ruptured thoracic duct, a thin-walled lymphatic vessel, channeling the chyle from the upper and lower body include gastrointestinal tract to the left subclavian vein post cardiovascular surgery. In addition, chylothorax can also occur secondary to shearing forces from increased systemic venous pressure or blockage from central vein thrombosis.[3] Chylothorax is most frequently associated with cavopulmonary anastomoses such as with Glenn and Fontan procedures, as well as operations that can cause right ventricular dysfunction include repair of tetralogy of Fallot, due to increased systemic venous pressure or venous thrombosis.[5] The diagnosis of chylothorax is made clinically based on the milky appearance of the drained fluid from the pleural spaces following the reintroduction of oral feedings, and also based on the presence of high levels of triglycerides and lymphocytes in the drained fluid.[6] The clinical course of chylothorax can be lengthy. Conventional therapy is generally accepted as a first step, either with a low-fat diet supplemented by medium chain triglycerides (MCT) or soy oil, or with total parenteral nutrition (TPN) use. Intermittent or continuous pleural drainage may be required for several weeks and is often complicated by respiratory failure, hypoproteinemia, and cachexia due to protein and lipid loss, as well as nosocomial infection resulting from hypogammaglobulinemia and lymphopenia.[7] If such measures fail and the condition lasts for more

than 3 to 4 weeks, or drainage remains over 10 mL/kg/day, surgical intervention should be considered. Surgical procedures that may resolve chylothorax refractory to medical treatments include thoracic duct ligation, pleurodesis, pleuroperitoneal shunts, or percutaneous lymphangiography and embolization.[8]

In recent years, octreotide, a synthetic analog of somatostatin, has been used in the management of acquired chylothorax. The proposed mechanism of octreotide and somatostatin for chylothorax is that they block lymph flow in the thoracic duct through exerting effects on both splanchnic circulation and gastrointestinal motility. In addition, octreotide reduces hepatic venous pressure, intestinal lipid absorption, chyle concentrations in the thoracic duct, and splanchnic blood flow.[4] In comparison to somatostatin, octreotide has a longer half-life, greater potency, and the option of subcutaneous administration.[5,9] Either drug can be given as a continuous intravenous infusion or as an intravenous bolus twice daily.

According to the 1999 Guidelines for Diagnosis and Management of Chylothorax in Children, the recommended treatment strategy is not fully established, and octreotide was not mentioned.[6] However, several proposed treatment algorithms have suggested consideration of octreotide if chylothorax persists despite TPN[10] or with TPN if patients have high volume drainage (>20 mL/kg/day).[4] In a prospective study conducted by Rosti et al,[11] octreotide was found to be more effective than conventional therapy for the treatment of chylothorax in pediatric patients following cardiac surgery. Patients who received octreotide had significantly reduced total fluid losses, duration of chest tube use, and postoperative length of stay. Paramés et al[8] also published a retrospective study that demonstrated similar results for octreotide use in chylothorax. Duration of chylothorax and hospital length of stay were shorter in the octreotide group. However, the study did not meet the power to detect a significant difference between the 2 groups.[8]

A systematic literature review by Helin et al[9] analyzed the use of octreotide for chylothorax in infants and children. The authors concluded that octreotide is relatively safe, even at very high doses and for as long as 3 weeks. In addition, initiating therapy early and using higher initial doses (3.3–4.2 mcg/kg/hr) rather than using a low initial dose with upward titration may reduce fluid and electrolyte complications of chylothorax, and may enable earlier removal of thoracostomy tubes. No consensus has been reached as to the optimal route of administration, dose, duration of therapy, or strategy for discontinuation of therapy.[9]

In contrast to previous findings, the 2002 case report by Mikroulis et al[12] detailed the use of octreotide for chylothorax after left pneumonectomy. They did not observe reduction in drainage, and octreotide was deemed to be ineffective for chylothorax treatment after a week of therapy.[12] Church et al[13] conducted a retrospective study to develop an evidence-based algorithm for chylothorax management. Authors concluded that octreotide has no advantage compared with TPN alone in infants with chylothorax.

From a safety standpoint, side effects of octreotide include hyperglycemia, hypothyroidism, cramps, nausea, diarrhea, renal impairment, and liver dysfunction.[5,9,14] In addition, Mohseni-Bod et al[15] reported a possible link between postoperative chylothorax treated with octreotide and necrotizing enterocolitis (NEC) in an infant following aortic coarctation repair. The authors suggested that octreotide should be limited to patients with stable hemodynamic findings without recent history of compromised splanchnic perfusion.

Chylothorax can cause significant respiratory morbidity, as well as lead to malnutrition and immunodeficiency. Thus, the prompt initiation of chylothorax management could decrease morbidity, mortality, and improve quality of life in cardiac ICU patients. Literatures regarding the use of octreotide in acquired chylothorax after congenital heart surgery are sparse and have shown contradicting results.[11–13]

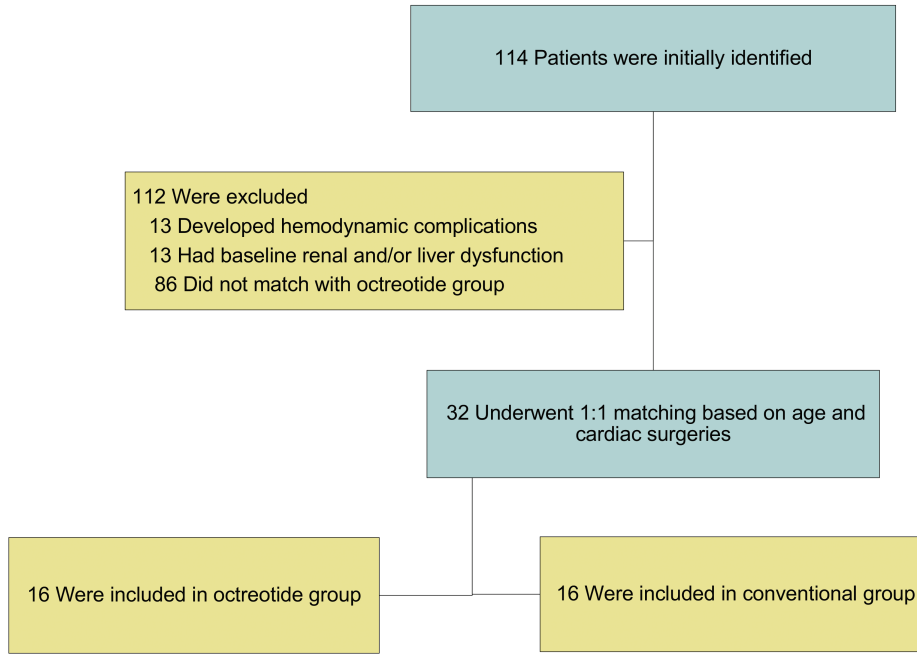
In this current institutional practice, octreotide has been used for acquired chylothorax in cardiac ICU patients based on the medical team's decision post cardiac surgery. Additional understanding of safety and efficacy could help guide prescribers in their selection of treatment options for chylothorax. To that end, the goal was to evaluate the efficacy and safety of chylothorax management at a pediatric medical center.

Materials and Methods

Study Design. This was a retrospective study to determine the efficacy of octreotide in patients with acquired chylothorax after cardiac surgery at Children's Health Children's Medical Center Dallas between October 2008 and June 2017. All patients 18 years of age or younger who underwent cardiac surgeries were included. Patients were excluded if they had major hemodynamic complications after surgery, had renal and/or liver dysfunction at baseline, or did not match the octreotide group based on age and cardiac surgeries. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board. Because this study is retrospective in nature, written informed consent was not required by the institutional review board.

Primary endpoint was to determine if the use of octreotide reduces time to resolution of chylothorax compared with conventional therapy (low-fat diet with MCT or soy oil, or TPN). The secondary endpoints were to identify time to reduction of chest tube output by 20%, additional surgeries for chylothorax, hospital length of stay, in-hospital mortality, and adverse drug reactions such as NEC, liver, and renal abnormalities. Twenty percent represents the reduction of chest

Figure 1. Study design.



tube output measured by mL/kg/day compared with the baseline chest tube output on day 0. To analyze efficacy, we compared these parameters in patients who received octreotide with those who received conventional therapy. To analyze safety, we compared the adverse drug reactions between both treatments.

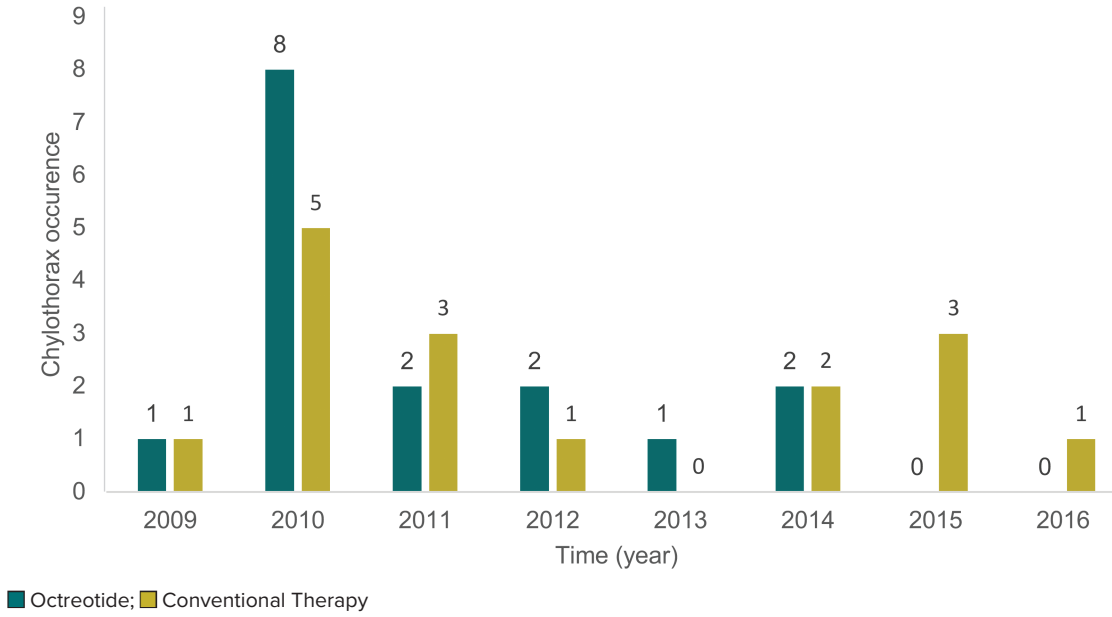
Definition. Chylothorax was diagnosed based on the milky appearance of the drained fluid from the pleural spaces following the reintroduction of oral feedings, and on the presence of high levels of triglycerides (>110 mg/dL) and lymphocytes (>80% of cells) in the drained fluid.[6] Liver abnormalities were defined as total bilirubin > 3 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase > 5 times the upper limit of normal. Renal abnormalities were defined as abnormal renal blood tests with elevated serum creatinine using the Kidney Disease Improving Global Outcomes Guidelines or creatinine clearance < 90 mL/min/1.73 m^2 calculated by Bedside Schwartz in pediatric patients.[16]

Study Population. Patients with acquired chylothorax were retrospectively reviewed through the institution's electronic medical record. Data were record using patient charts in the electronic medical records from October 2008 to June 2017. Based on Figure 1, a total of 144 patients 18 years of age or younger who underwent cardiac surgeries were screened. One hundred twelve patients were excluded for the following reasons: 13 patients developed major hemodynamic complications postsurgery, 13 patients had renal and/or liver dysfunction at baseline, and 86 patients with conventional therapy did not match the octreotide group based on age and cardiac surgery procedures. Thirty-two patients were included in the analysis after matching with 1:1 ratio. Patients who received octreotide were compared with those who did not. Figure 2 represents the distribution of admission dates between the octreotide and conventional therapy groups.

Data Collection. Retrospective collection of patients' clinical and demographic data included: age, gestational age, gender, race, weight, height, date, type of surgeries, octreotide dosing regimens, TPN use, MCT or soy-enriched formula use, central venous pressure, chest tube or pleural drain duration and output, concurrent inotropes, liver function tests (alanine aminotransferase, AST, and total bilirubin), renal function tests (blood urea nitrogen, serum creatinine, and creatinine clearance), hospital length of stay, additional surgeries, in-hospital mortality, and adverse drug reactions.

Statistical Analysis. A total sample size of 28 patients with equal enrollment was needed to achieve 80% power to show a significant difference in duration of chylothorax between octreotide and conventional therapy. Non-normally distributed data were presented as median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. Categorical data were compared using the χ^2 or Fisher exact test, as appropriate. Logistic regression analyses were performed to analyze the correlation between 2 independent variables, and the χ^2 test was applied to compare proportions between both groups. A p value < 0.05 was considered statistically significant.

Figure 2. Distribution of admission dates between the octreotide and conventional therapy groups (n = 32).



Results

Patient Characteristics. Of 32 patients who met inclusion criteria, patients were matched 1:1 based on age and cardiac operations between the octreotide and conventional groups. Table 1 shows baseline characteristics for patients with postoperative chylothorax. The median (IQR) age were 13 (8–32) days in the octreotide group and 18 (7–124) days in the conventional group (p = 0.865). Thirty-eight percent of patients in each group had single ventricle physiology. There was no difference in gestational age, sex, weight, baseline chest tube output, or central venous pressure between groups. Though still within normal limits, patients who received conventional therapy had higher AST at baseline (51 vs 22 units/L, p = 0.018) and more concurrent use of inotropes (93.8% vs 37.5%, p = 0.001). Tables 2 and 3 represent the characteristics of all patients treated with octreotide and conventional therapy, respectively. Pair number represented matched patients in each group. Based on Figure 2, distribution of admission dates was fairly similar between both groups. In addition, majority of chylothorax events occurred in 2010, with 8 of 16 (50%) in the chylothorax group and 5 of 16 (31.3%) in the conventional group.

Primary and Secondary Endpoints. Efficacy outcomes for patients who did and did not receive octreotide are shown in Table 4. All 32 patients with acquired chylothorax were included in the analysis. Patients who received octreotide had a longer duration of chylous drainage than patients who received conventional therapy (24 vs 9 days, p < 0.001), but a comparable reduction of chylous output by 20% or partial resolution (6 vs 8 days, p = 0.337). Resolution of chylothorax was achieved in 13 of 16 (81.3%) octreotide patients and 16 of 16 (100%) conventional patients (p = 0.178). Percentage of recurrent chylothorax was similar between both groups. Patients with octreotide use also had longer median (IQR) days of TPN use (24 [9–41] days vs 6 [4–12] days, p = 0.012). Two patients (12.5%) and 1 patient (6.3%) in octreotide and conventional therapy received pleurodesis, respectively. Overall length of stay and mortality were comparable between both groups.

Because the duration of chylothorax was longer in the octreotide group, regression analyses between median daily chest tube drainage and time after the initiation of conventional management in both groups were analyzed in Figure 3. Day zero represents the first day of new chest tube insertion or operating room date if the chest tube was placed during cardiac surgery. During this period, patients were solely being managed by conventional therapy, prior to the start of octreotide. There was no correlation between time after starting conventional management and chylous output reduction in either the octreotide or conventional therapy group (p = 0.809, p = 0.107, respectively). In contrast to decreasing chest tube output observed in the conventional group, chest tube output tended to be flat in the octreotide group, likely serving as the rationale for starting octreotide as an additional medical management. Regression analysis was again performed for the time after octreotide was started (Figure 4). There was a significant and moderate correlation between reduction in chest tube drainage and time after initiation of octreotide (R^2 = 0.464, p = 0.021).

Table 1. Demographic and Baseline Characteristics of Patients Receiving Octreotide Versus Those Receiving Conventional Therapy

Parameters	Octreotide (n = 16)	Conventional Therapy (n = 16)	p value
Age at surgery (days), median [IQR]	13 [8–32]	18 [7–124]	0.865
Gestational age (wk), median [IQR]	38 [33–39]	37 [36–38]	0.471
Sex (male:female)	7:9	9:7	0.48
Weight (kg), median [IQR]	3.4 [2.8–5.8]	3.4 [2.6–4.4]	0.818
Single ventricle, n (%)	6 (37.5)	6 (37.5)	1
Baseline output (mL/kg/day), median [IQR]	47 [16–85]	27 [23–43]	0.226
CVP (mm Hg), median [IQR]	10 [8–12]	11 [10–13]	0.401
Baseline ALT (units/L), median [IQR]	21 [19–34]	30 [23–37]	0.39
Baseline AST (units/L), median [IQR]	22 [16–31]	51 [32–82]	0.018
Baseline SCr (mg/dL), median [IQR]	0.4 [0.3–0.5]	0.5 [0.4–0.7]	0.084
TPN use, n (%)	14 (87.5)	13 (81.3)	0.626
Concurrent inotropes, n (%)	6 (37.5)	15 (93.8)	0.001

ALT, alanine transaminase; AST, aspartate transaminase; CVP, central venous pressure; IQR, interquartile range; SCr, serum creatinine; TPN, total parenteral nutrition

Octreotide Use. Octreotide was administered by continuous intravenous infusion for a median (IQR) duration of 8 (2–13) days post chest tube insertion, with a median (IQR) duration of 15 (6–23) days. Minimum (IQR) dose of octreotide was 2 (1–3) mcg/kg/hr, and maximum (IQR) dose was 4 (1–5) mcg/kg/hr based on therapeutic responses (Table 5).

Adverse Drug Reactions. Liver abnormalities were observed in 18.8% and 6.3% patients who received octreotide and conventional therapy, respectively (p = 0.285). More patients in the conventional group developed renal abnormalities (25% vs 68.8%, p = 0.013). The incidence of NEC appeared to be higher in the octreotide group, though this did not reach statistical significance (12.5% vs 0%, p = 0.287) (Table 6). None of the deaths were attributed to octreotide's adverse

Table 2. Clinical Characteristics of Sixteen Patients With Postoperative Chylothorax Treated With Octreotide

Pair	Age, days	Sex	Cardiac Diagnosis	Surgery
1	8	Male	HLHS	Norwood-Sano procedure
2	6	Female	HLHS	Norwood-Sano procedure
3	5	Female	CoA, aortic stenosis	CoA repair
4	144	Male	HLHS	Glenn procedure
5	29	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
6	8	Female	HLHS	Norwood-Sano procedure
7	216	Male	HLHS	Glenn procedure
8	10	Male	Interrupted aortic arch with transverse arch hypoplasia	Aortic arch reconstruction
9	8	Male	Truncus arteriosus type 1	Truncus repair (RV-PA conduit)
10	4	Female	CoA	CoA repair
11	39	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
12	17	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
13	22	Female	CoA	CoA repair
14	10	Female	HLHS	Norwood-Sano procedure
15	113	Male	TOF, complete balanced AV canal	AV canal repair
16	16	Male	TOF	TOF repair (RV-PA conduit)

ASD, atrial septal defect; AV, atrioventricular; CoA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; RV-PA, right ventricle-pulmonary artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect

Table 3. Clinical Characteristics of Sixteen Patients With Postoperative Chylothorax Treated With Conventional Therapy

Pair	Age (days)	Sex	Cardiac Diagnosis	Surgery
1	7	Female	HLHS	Norwood-Sano procedure
2	8	Male	HLHS	Norwood-Sano procedure
3	5	Female	CoA, aortic stenosis	CoA repair, aortic valvuloplasty
4	137	Female	HLHS	Glenn procedure
5	119	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
6	7	Male	HLHS	Norwood-Sano procedure
7	224	Male	HLHS	Glenn procedure
8	6	Female	CoA	CoA repair
9	5	Male	Truncus arteriosus type 1	Truncus repair (RV-PA conduit)
10	4	Male	CoA	CoA repair
11	156	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
12	265	Female	VSD, ASD, PDA	VSD/ASD repair, PDA ligation
13	77	Male	CoA	CoA repair
14	8	Male	HLHS	Norwood-Sano procedure
15	108	Male	Complete balanced AV canal	AV canal repair
16	28	Male	TOF	TOF repair (RV-PA conduit)

ASD, atrial septal defect; AV, atrioventricular; CoA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; RV-PA, right ventricle-pulmonary artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect

drug reactions; rather they were related to patients' comorbid conditions.

Discussion

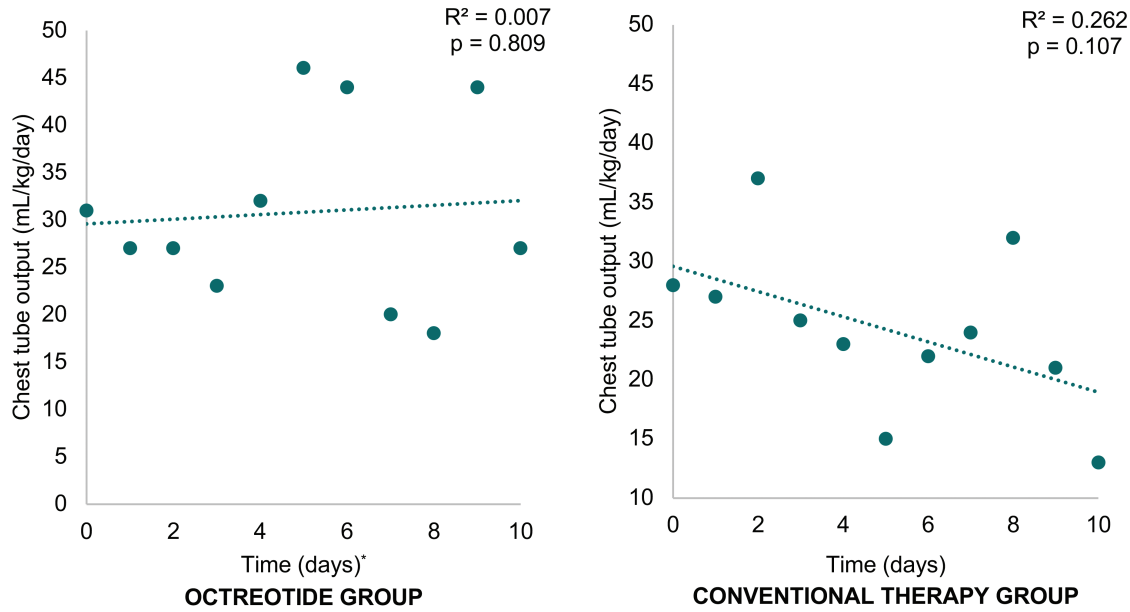
Chylothorax following cardiothoracic surgery is most frequently associated with cavopulmonary anastomosis such as Glenn and Fontan procedures or operations that can cause right ventricular dysfunction such as the repair of tetralogy of Fallot. This institution has developed the management schemes based on existing literature. Treatment begins with supportive care with indwelling chest tubes, diuretic therapy, and placement on a formula or diet low in long-chain fatty acids. If drainage persists, placement on a non-fat diet with intravenous intralipids is trialed followed by nothing orally and TPN if recalcitrant. Octreotide is added to this regimen if high volume chest tube drainage persists before pursuing more invasive interventions. These potentially include chemical pleurodesis, thoracic duct ligation, or percutaneous lymphangiography and embolization. Because there is risk for complications associated with these interventions, octreotide has become popular as an adjunct management of chylothorax.[17] We therefore sought to analyze the outcomes of chylothorax management at this institution.

Table 4. Comparison of the Effects of Octreotide With Conventional Approach

Parameters	Octreotide (n = 16)	Conventional Therapy (n = 16)	p value
Duration of chylothorax (days), median [IQR]	24 [15–36]	9 [6–13]	<0.001
Time to reduction of chest tube output by 20% (days), median [IQR]	6 [3–9]	8 [4–11]	0.337
Chylothorax resolution, n (%)	13 (81.3)	16 (100)	0.178
Recurrent chylothorax, n (%)	6 (37.5)	9 (56.3)	0.288
TPN (days), median [IQR]	24 [9–41]	6 [4–12]	0.012
Required additional surgery, n (%)	2 (12.5)	1 (6.3)	0.544
Overall LOS (days), median [IQR]	81 [60–127]	57 [35–103]	0.165
Overall mortality, n (%)	9 (56.3)	4 (25)	0.072

IQR; interquartile range; TPN, total parenteral nutrition

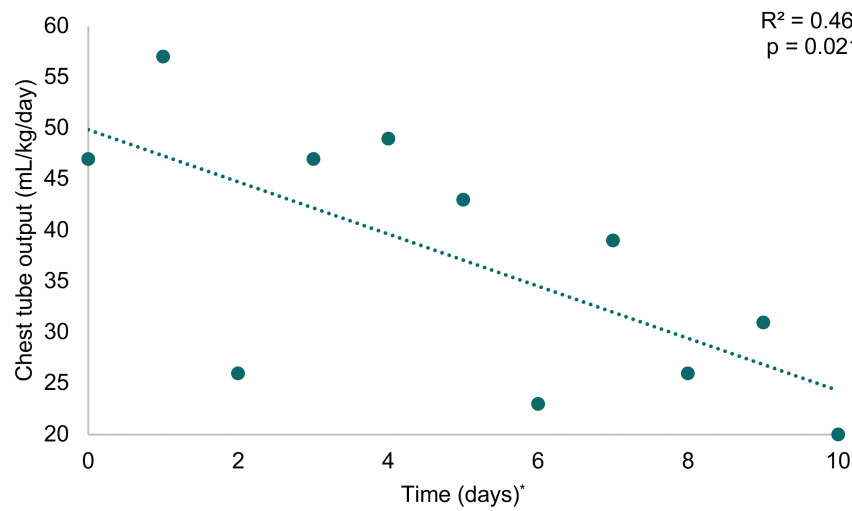
Figure 3. Median daily chest tube drainage of 32 patients after conventional management was started in both the octreotide group (before octreotide was started) and conventional therapy group.



* Time after chest tube insertion and before octreotide was started.
Day zero represents the first day of new chest tube insertion or operating room date if chest tube was placed during cardiac surgery. Regression analyses are represented by the dotted lines.

This study is the first to match and compare pediatric patients using octreotide and conventional therapy for the management of postoperative chylothorax. Because data supporting the role of octreotide in patients with chylothorax are sparse, we aimed to analyze the efficacy and safety outcomes related to the use of octreotide vs conventional therapy. While this analysis (Figure 3) demonstrates that chest tube drainage did not significantly decrease after starting conventional management in either group of patients, decreased chest tube drainage is significantly correlated with the initiation of octreotide (Figure 4). We postulate that

Figure 4. Median daily chest tube drainage of 16 patients after starting octreotide therapy.



* Time after octreotide was started.
Day zero represents initiation of octreotide therapy. Regression analysis is represented by the dotted line.

Table 5. Octreotide Efficacy-Related Parameters

Parameters	Octreotide (n = 16)
Days initiated after chest tube insertion (days), median (IQR)	8 (2–13)
Treatment time (days), median (IQR)	15 (6–23)
Minimum dose (mcg/kg/hr), median (IQR)	2 (1–3)
Maximum dose (mcg/kg/hr), median (IQR)	4 (1–5)

IQR; interquartile range

earlier initiation of octreotide could have potentially shortened the duration of chylothorax. It is also possible that the fall in output after octreotide initiation is due to the natural history and that the volume would have tapered without adding octreotide. Though there are multiple studies with unclear benefits of octreotide,[18–21] multiple case reports and case series[22–25] demonstrated octreotide's effectiveness in treating chylothorax. Some authors even suggested using octreotide as first-line therapy.[26] Chan et al[27] reported high success rate of octreotide therapy in 15/18 (83%) patients with chylothorax after cardiac surgery. However, treatment was initiated at a mean of 19.5 days after onset, which is much later in the course than this study. Statistical analysis provided similar results and suggested a potential benefit of octreotide use in chylothorax. If effective, the addition of octreotide to chylothorax management may potentially avoid more invasive therapies. However, if ineffective it may also potentially prolong the time until more definitive invasive therapies are performed thus potentially prolonging hospital stays. More controlled studies to investigate octreotide's role in chylothorax management are imperative. However, based on this study's analysis, we recommend initiating octreotide if drainage is above 40 mL/kg/day or if it fails to fall below 20 mL/kg/day by day 7.[4]

Because of the retrospective nature of this study, we were unable to control for the timing of initiation, dose, or duration of octreotide therapy. We believe that this reflected a selection bias in which patients were chosen to receive octreotide. The lack of fall in chest tube drainage in the octreotide group confirmed this. In addition, the chest drainage tended to be higher in the octreotide group, though it did not reach significance. Octreotide may have been initiated in more severe, refractory cases. Because of limited efficacy data, some clinicians may be hesitant to use octreotide unless patients have failed all other medical interventions, while others may choose to use it as an initial therapy. In this study, octreotide was added on approximately 8 days after chest tube(s) insertion. This suggests that at this institution most clinicians were hesitant to start octreotide early until other conventional therapies had failed, which likely introduced bias into these results.

Mild adverse drug reactions associated with octreotide include transient alterations in blood glucose levels and changes in gastrointestinal transit. Though rare, more serious associated side effects include liver steatosis, nephrolithiasis, and NEC. Side effects and toxicity are likely dose-related but literature in this regard are limited. Despite variability in the literature regarding the starting dose, octreotide was initiated at a median of 2 mcg/kg/hr in this cohort, consistent with the recommended dosing range. Though NEC is the most serious potential complication described, data are limited. A potential mechanism for NEC after use of octreotide is the decrease of splanchnic blood flow contributing to a general lack of adequate gastrointestinal blood flow.[28] Church et al[13] reported that infants ≤ 36 weeks estimated gestational age (EGA) receiving octreotide had a higher incidence of NEC compared with those who did not. Two cases of patients who developed NEC under octreotide therapy in this study for chylothorax were 31 weeks EGA following Norwood-Sano, and 39 weeks EGA after ventricular septal defect/atrial septal defect/pulmonary ductus arteriosus repair procedures. Both patients were receiving TPN and were not receiving enteral nutrition. Both cases were conservatively

Table 6. Adverse Events in Patients Who Received Octreotide and Conventional Therapy For Chylothorax Management

Parameters	Octreotide (n = 16)	Conventional Therapy (n = 16)	p value
Liver abnormalities, n (%)*	3 (18.8)	1 (6.3)	0.285
Renal abnormalities, n (%)†	4 (25)	11 (68.8)	0.013
NEC, n (%)	2 (12.5)	0 (0)	0.287

NEC, necrotizing enterocolitis

* Abnormal liver blood tests with serum alanine aminotransferase and/or aspartate aminotransferase levels > 5 times upper limit of normal and/or total bilirubin level > 3 mg/dL.

† Abnormal renal blood tests with elevated serum creatinine based on Kidney Disease: Improving Global Outcomes Guidelines or creatinine clearance < 90 mL/min/1.73 m^2 calculated by Bedside Schwartz[16] in pediatric patients.

managed with bowel rest, antibiotics, and cessation of the octreotide infusion. This cohort was small and underpowered to detect an association between NEC and octreotide use.

This study had several limitations. It is a single-center, retrospective study with a small sample size. Because this is not a controlled study, there is potential for selection bias. There is also practice variation regarding chylothorax management and octreotide usage. There are biologic reasons that may account for varying responses to therapy such as the etiology of chylothorax.[13] Chylothorax secondary to innominate vein thrombosis, thoracic duct injury, and/or elevated venous pressures would all vary in response to therapies to treat chylothorax. In patients who received octreotide, the median volume on the day of initiation of octreotide was 47 mL/kg/day, despite the use of conventional therapy (Figure 4). Due to a small sample size, we did not stratify patients based on the volume of chylous chest tube drainage or etiology. This may be helpful in identifying high-risk patients who may be candidates for early octreotide initiation.[4] High rates of renal and liver abnormalities may be related to the concomitant use of nephrotoxic and hepatotoxic drugs or drug interactions via cytochrome P450 system. Importantly, there was no difference between the 2 groups in renal injury. Liver abnormalities were higher in the octreotide group, likely due to prolonged TPN and enteral fasting, rather an adverse drug effect. Despite these limitations, this study represents novel findings regarding the efficacy and safety of octreotide for chylothorax management in pediatric patients post congenital heart surgery. Larger data sets and prospective controlled trials will provide more clarity on octreotide's role in the treatment of chylothorax in pediatric patients following surgery for congenital heart disease.

Conclusions

This study demonstrates that octreotide is potentially a safe option to use in pediatric patients with chylothorax following surgery for congenital heart disease and may be an effective adjuvant therapy, particularly in patients with high volume and refractory chylothorax. These data suggest that persistent drainage above 40 mL/kg/day or drainage failure to fall below 20 mL/kg/day by day 7 may benefit from treatment with octreotide. This therapy may help avoid more invasive therapies when effective. Though management with octreotide shows promising benefits, prospective trials are required. In addition, stratifying patients into high-risk categories based on etiology and volume of drainage may provide insight into which patients may benefit from this therapy the most. Until then, octreotide should be considered when patients have failed conventional management before proceeding to more definitive but more invasive therapies.

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