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Chylothorax in Children After Congenital Heart Surgery

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Background. A definitive management strategy for postoperative chylothorax remains elusive. We reviewed our experience in the management of chylothorax in children after congenital heart surgery.

Methods. The case records of 51 patients, with a median age of 11 months (range, 4 days to 19.6 years), diagnosed to have postoperative chylothorax between 1981 and 2004 were reviewed. The responses of patients to nutritional modifications, octreotide therapy, and surgical interventions were noted.

Results. The prevalence of postoperative chylothorax, which developed at a median of 9 days after operation (range, 0 to 24 days), was 0.85% (51 of 5,995). Four patients died, and among the 47 survivors the median duration and total volume of chylous drainage was 15 days (range, 1 to 89 days) and 156 mL/kg (range, 3 to 6,476), respectively. The duration of chyle output was significantly longer after the Fontan-type procedures ($p = 0.0006$). Twenty-one patients were diagnosed between 1981 and 1999 and managed by nutritional modifications, 2 of whom required further surgical interventions. Of the 30 patients diagnosed between 2000 and 2004, 12 responded to nutritional modifications alone while 18 were started on octreotide therapy at a median of 19.5 days (range, 7 to 35 days) after the onset of chylothorax. Fifteen of the 18 (83%) patients responded to octreotide therapy at 15.3 ± 5.5 days after starting octreotide, while 3 required further surgical interventions. None developed side effects from octreotide therapy.

Conclusions. Octreotide has been incorporated into the management algorithm of postoperative chylothorax and appears to be a useful adjunctive therapy.

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Chylothorax in children occurs most commonly after cardiothoracic procedures [1]. Damage to the thoracic duct, disruption of accessory lymphatics, and an increased pressure in the systemic vein exceeding that in the thoracic duct have been proposed as possible causes of chylothorax after surgery for congenital heart disease [2–4]. Recent studies suggest an increase in the prevalence of postoperative chylothorax from the previously reported 1% or less [3–6] to 2.5% to 4.7% [4, 7, 8], which has been attributed to the increased complexity of the surgery being performed and possibly earlier reintroduction of feeding after surgery [7, 8].

Whereas the morbidity and mortality relating to excessive loss of chyle are well-documented [5, 6, 9], a definitive management strategy for postoperative chylothorax remains elusive [10]. A commonly adopted management strategy is a period of conservative management with the use of medium-chain triglycerides or total parenteral nutrition, followed by surgical interventions as pleurodesis, ligation of the lymphatic ducts, and pleuroperitoneal shunting for nonresponders [1, 4, 7, 11]. We reported the first successful use of octreotide, a long-acting synthetic analogue of somatostatin, in the management of postoperative chylothorax [12]. Over the past few years, octreotide has increasingly been incorporated into the management algorithm of postoperative chylothorax [7]. Notwithstanding the evolution of the management strategy, the experience of octreotide is limited to case reports and small case series [13]. Indeed, to date, only 21 reports on the use of octreotide in 33 children have been published [12–32]. In the present study, we reviewed our experience in the management of chylothorax that occurred after congenital heart surgery in a relatively large cohort of 51 patients, 18 of whom had received octreotide therapy.

Patients and Methods

Patients

Fifty-one patients who developed chylothorax after surgery for their underlying congenital heart disease between 1981 and 2004 were identified from the hospital database. The diagnosis of chylothorax was made based on one or more of the following abnormalities of the milky fluid draining from the chest tube: (1) positive Sudan staining of fat globules; (2) elevated triglyceride (>1.1 mmol/L); and (3) lymphocyte predominance (>80%) [6, 12, 33]. Their case records were reviewed with the following data collected: demographic information, cardiac

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diagnoses, types of surgical procedures, the onset, duration and management of chylothorax, the daily chyle output volume, laboratory investigation findings including total white cell counts and serum albumin levels, and postoperative complications and outcomes. To define the overall prevalence of chylothorax, the total number of operations performed during the same period was retrieved from the hospital database. The Institutional Review Board approved the study and waived the need for patient consent.

Institutional Management Strategy

Conservative management with nutritional modifications followed by surgical interventions for nonresponders was the mainstay of management before 2000. Since 2000, octreotide therapy was introduced to our unit for the management of chylothorax refractory to conservative management. The indications for octreotide therapy were persistent chyle leak for more than 2 weeks and significant drainage that exceeded 10 mL/kg/day, in which case octreotide would be started even after 1 week of conservative treatment. Subcutaneous octreotide (Norvatis, Basle, Switzerland) was given at a starting dose of 10 μg/kg/day in 3 divided doses. The stepwise increase in the dosage was by 5 to 10 μg/kg/day every 72 to 96 hours to a maximum of 40 μg/kg/day. Weaning of octreotide would be commenced after 3 days of insignificant chyle output (<10 mL/day). The dose was decreased by 10 μg/kg/day daily and was so withdrawn rapidly over 3 to 4 days [12]. The patients were monitored for potential complications of octreotide therapy, including hyperglycemia or hypoglycemia, cardiopulmonary side effects, and gastrointestinal disturbance.

Statistical Analysis

The data are expressed as median (range) unless otherwise specified. The differences in duration of chylothorax and total volume of chyle loss among different types of cardiac operations were compared using one way analysis of variance with posthoc comparison using the Tukey test. The demographic and clinical variables of patients who received octreotide therapy were compared with those of contemporary patients (2000 to 2004 period) who did not require octreotide therapy and those in the earlier period (1981 to 1999) using the Wilcoxon rank sum test and the Fisher's exact test where appropriate. The Pearson correlation analyses were performed to determine potential relationships between age, time of onset of chylothorax, time of starting octreotide, and duration and volume of chyle output in the survivors. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS Version 8.02 (SAS, Cary, NC).

Results

Patients

The 51 patients (26 males), with a median age of 11 months (range, 4 days to 19.6 years), were identified from a total of 5,995 congenital heart patients who had undergone operations over the 24-year period, giving an overall prevalence of 0.85% (95% confidence interval 0.63% to

Table 1. Cardiac Diagnoses and Operations of the 51 Patients

Cardiac Diagnoses	No.	Cardiac Operations	No.
Left-to-right shunts		Repair of left-to-right shunts (VSD, AVSD, ASD, PDA)	10
VSD	3		
VSD + PDA	1		
AVSD + PDA	2		
VSD + ASD + PDA	1		
ASD	1		
PDA	2		
Aortic lesions		Aortic reparative surgery	4
Coarctation of the arota	3		
Double aortic arch	1		
RVOT obstructive lesions			
PAVSD	8	Systemic-to-pulmonary arterial shunt insertion	13
PAIVS	3		
TOF	9	Right ventricular outflow reconstructive surgery	16
Isolated PS	2		
PS with left-to-right shunts	2		
Univentricular hearts	9	Fontan-type operation	4
TGA with VSD	3	Miscellaneous procedures (arterial switch operation, pulmonary venous repair, ligation of aortopulmonary collaterals)	4
TAPVD	1		

ASD = atrial septal defect; AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; PAIVS = pulmonary atresia with intact ventricular septum; PAVSD = pulmonary atresia with ventricular septal defect; PDA = patent ductus arteriosus; PS = pulmonary stenosis; RVOT = right ventricular outflow tract; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

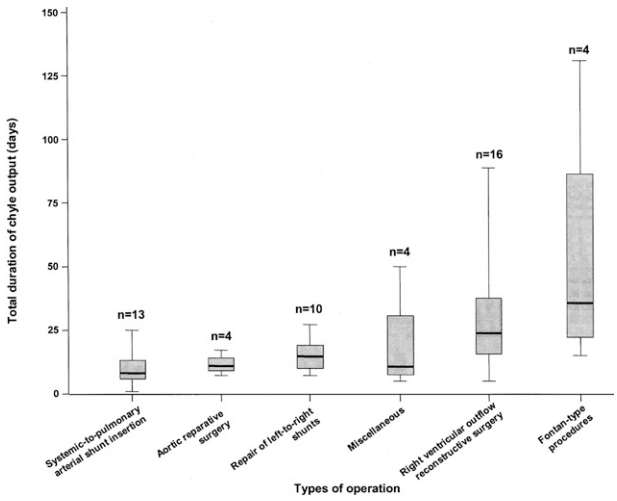

Fig 1. Box-plots of duration of chyle output after different types of operations. The line within each box represents the median in each group.

1.12%). Between 2000 and 2004, the prevalence of chylothorax was 2.27% (31 of 1,364), which was significantly greater that the 0.45% (21 of 4,631) between 1981 and 1999 ($p < 0.001$). The mortality was 7.8% (4 of 51). Four patients died at a median of 53 days (range, 24 to 103) after the operations, the causes of death being uncontrolled sepsis in 2, heart failure in 1, and pulmonary hypertensive crisis in 1. For the 47 survivors, the median duration of hospital stay was 32 days (range, 13 to 135).

Table 1 summarizes the cardiac diagnoses and operations. The most frequent cardiac lesions were those with right ventricular outflow obstruction, including tetralogy of Fallot and pulmonary atresia with or without ventricular septal defect. The most frequently performed operations are those involving repair or reconstruction of the right ventricular outflow tract.

Chylothorax

Chylothorax developed at a median of 9 days after operation (range, 0 to 24). It was left-sided in 16, right-sided in 17, and bilateral in 18 patients. For the 47 survivors, the median duration for chylous drainage was 15 days (range, 1 to 89), and the median total volume of chyle output was 156 mL/kg (range, 3 to 6,476). The duration of chyle output was significantly longer after the Fontan-type procedures when compared with that after systemic-to-pulmonary arterial shunt insertion, aortic reparative surgery, and repair of left-to-right shunts ($p = 0.0006$) (Fig 1). The total volume of chyle output, however, did not differ among the different types of operations. The duration and total volume of chyle output correlated with duration of hospital stay ($r = 0.70$, $p < 0.001$ and $r = 0.34$, $p = 0.019$, respectively), but not with age and onset of chylothorax after operation. For the four deaths, the median duration and total volume of chylous drainage were, respectively, 11.5 days (range, 5 to 89) and 744 mL/kg (range, 119 to 6,476).

Evolution of Management Strategy

Twenty-one patients were identified between 1981 and 1999 before octreotide was available to our institution (Fig 2A). All but one of the patients received a medium-chain triglyceride diet, while the remaining patients had complete enteric rest with total parenteral nutrition. Two patients required surgical interventions to achieve complete cessation of chyle leak. One of the patients had pleural cauterization on day 33 of chyle leak with complete resolution achieved in 5 days, while the other required ligation of the right lymphatic duct on day 15 and the left thoracic duct on day 19 of chylothorax. The latter patient, however, eventually died of uncontrolled sepsis 3 weeks after complete cessation of chyle leak. Another death occurred in a patient who died of heart failure after insertion of a right modified Blalock-Taussig shunt, although his chyle leak lasted for only 7 days and resolved with medium-chain triglycerides.

Thirty patients were identified between 2000 and 2004 (Fig 2B). In 12 of the 30 patients, chylothorax resolved completely at a median of 10 days (range, 3 to 16) after institution of a medium-chain triglyceride diet, but one died of pulmonary hypertensive crisis on day 24 after correction of total anomalous pulmonary venous drainage. Four patients required surgical interventions, 3 after and 1 before the institution of octreotide treatment. The latter patient, suspected to have lymphatic injury at the time of operation, underwent ligation of the thoracic duct on day 1 postoperation. The persistent chyle leak, despite surgery, responded to 17 days of octreotide treatment. In 2 patients, respective ligation of the thoracic duct and resection of a large seroma that complicated a left modified Blalock-Taussig shunt insertion resulted in complete resolution of chylothorax. The remaining patient had intractable chyle leak despite surgical interventions and eventually died of uncontrolled sepsis and multiorgan failure 3 months after operation.

Octreotide Therapy

A total of 18 patients received octreotide treatment, which was started at a median of 19.5 days (range, 7 to 35) after the onset of chylothorax. Eighty-three per cent (15 of 18) of patients responded with complete resolution of their chylothorax and none developed side effects from octreotide therapy.

The demographic and clinical variables of these patients, those of contemporary patients (2000 to 2004 period) who did not require octreotide treatment, and those in the earlier period (1981 to 1999) are summarized in Table 2. The chyle leak in patients requiring octreotide therapy was more severe than the other two cohorts as evidenced by the significantly greater total volume and longer duration of chyle leak and prevalence of hypoalbuminemia and septicemia (all $p < 0.05$). Nonetheless, the duration of hospital stay, the mortality, and the duration of chyle leak after the start of octreotide therapy of these patients were similar to those of the earlier 1981 to 1999 cohort.

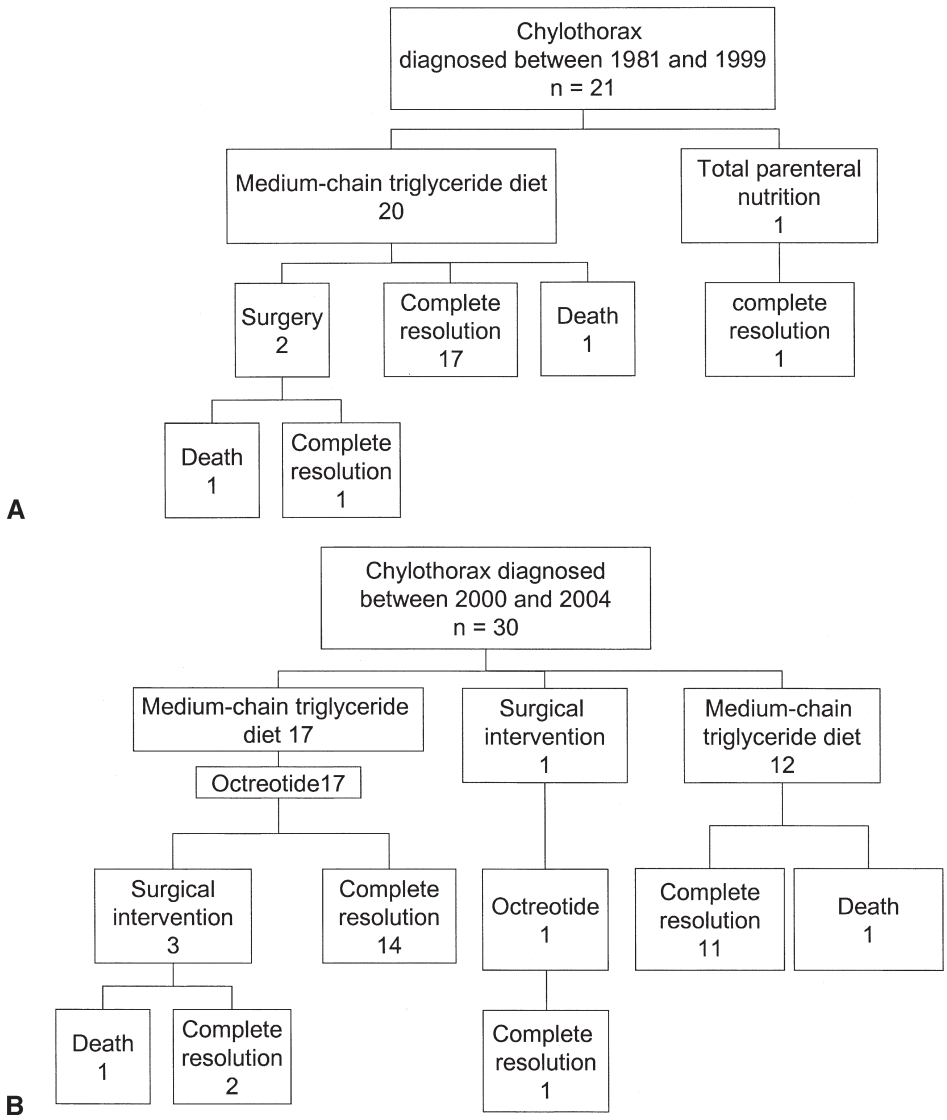

Fig 2. Flowchart showing the management strategies and outcomes in patients diagnosed to have postoperative chylothorax (A) between 1981 and 1999, and (B) between 2000 and 2004.

As alluded to earlier, of the 18 patients who received octreotide therapy, 4 required surgical interventions. Figure 3 shows the clinical response of the remaining 14 patients after starting of octreotide. The median daily output, in terms of the percentage of baseline output just prior to the start of octreotide, reduced to less than 50% at about 6 days of the treatment. The total duration of chyle output in these 14 patients correlated with the interval between onset of chylothorax and time of starting octreotide ($r = 0.89$, $p < 0.0001$). However, regardless of the timing of initiation of octreotide, the duration of chyle leak from the start of octreotide was similar ($p > 0.05$) and lasted for a mean (±SD) duration of 15.3 (±5.5) days (Fig 4).

Comment

The prevalence of chylothorax in our institution has shown a significant increase over the past decades, which concur with the findings of previous reports [4, 7, 8]. The changes in prevalence have been attributed to the increased complexity of the surgery being performed and possibly earlier reintroduction of feeding after surgery [7, 8]. The mortality rate of our patients is similar to that reported previously, which varied from 6% to 21% [1, 4, 6, 8, 9, 34]. The cause of death is likely to be multifactorial, due to unfavorable hemodynamics, sepsis, and multiorgan dysfunction.

While chylothorax may develop in virtually all types of intrathoracic procedures, several congenital heart operations have been shown to be prone to this complication [1, 4, 7]. In particular, bidirectional cavopulmonary shunt operation, Fontan-type procedures, and right ventricular dysfunction after repair of tetralogy of Fallot, which may predispose to increased systemic venous pressure and thus risk of postoperative chylothorax [4, 7]. The present study also showed that the duration of chylothorax after

Table 2. Comparison of Demographic and Clinical Variables Among Different Patient Cohorts

Variables	1981–1999 (a) (n = 21)	2000–2004 Octreotide (b) (n = 18)	2000–2004 No Octreotide (c) (n = 12)	p_1	p_2
Age (months)	6 (0–235)	11 (0.5–60)	15 (0.25–79)	0.788	0.949
Sex (M:F)	12:9	9:9	5:7	0.753	0.722
Onset of chylothorax after operation (days)	10 (0–35)	8.5 (1–15)	9.5 (4–18)	0.788	0.595
Duration of chyle output (days)	12 (1–131)	27 (11–89)	10 (3–16)	0.007[a]	<0.001[a]
Duration of chyle output after starting octreotide therapy (days)	—	14.5 (7–30)	—	0.453[b]	0.006[a,b]
Total volume of chyle (mL/kg)	150 (4–1334)	388 (91–6476)	78 (3–179)	0.003[a]	<0.001[a]
Length of hospital stay (days)	36 (17–135)	43 (15–103)	26 (13–32)	0.884	0.001[a]
Surgical intervention	2 (9.5%)	4 (22%)	0 (0%)	0.386	0.130
Mortality	2 (9.5%)	1 (5.5%)	1 (8%)	1.0	1.0
Morbidity					
Hypoalbuminemia	12 (57%)	18 (100%)	8 (67%)	0.002[a]	0.02[a]
Lymphopenia	10 (48%)	13 (72%)	8 (67%)	0.192	1.0
Septicemia	1 (5%)	6 (33%)	0 (0%)	0.035[a]	<0.001[a]
Pneumonia	13 (62%)	6 (33%)	5 (42%)	0.111	0.711
Acute renal failure	5 (24%)	6 (33%)	1 (8%)	0.723	0.193

[a] Statistically significant. [b] Compared with the total duration of chyle output in the 1981 to 1999 cohort and the 2000 to 2004 cohort not requiring octreotide therapy.

Data are expressed as median (range) unless otherwise stated.

p_1: (b) vs (a); p_2: (b) vs (c).

the Fontan-type procedures was significantly longer, which corroborates the findings of Chan and colleagues [7]. Closed heart procedures performed in the vicinity of the thoracic duct, such as systemic-to-pulmonary arterial shunt insertion, repair of aortic coarctation, and ligation of arterial duct, likewise predispose to the development of chylothorax as evidenced in this and previous studies [4, 6].

Although chest tube drainage and nutritional support, albeit nonstandardized in terms of the type of nutritional replacement [8], is probably the general consensus for the initial management of postoperative chylothorax in children, the next steps in the management algorithm for nonresponders remain elusive. Conservative management for several weeks appears justified as resolution of chylothorax has been reported in up to 77% of patients after giving either medium chain triglycerides or total parenteral nutrition for up to 45 days with an average of about 12 days [1, 8, 33]. Previous studies suggested that persistence of chyle output for more than 3 weeks [1] and lesions associated with elevated systemic venous pressure [4, 7] are risk factors for failure of conservative management. While 90% (19 of 21) of our 1981 to 1999

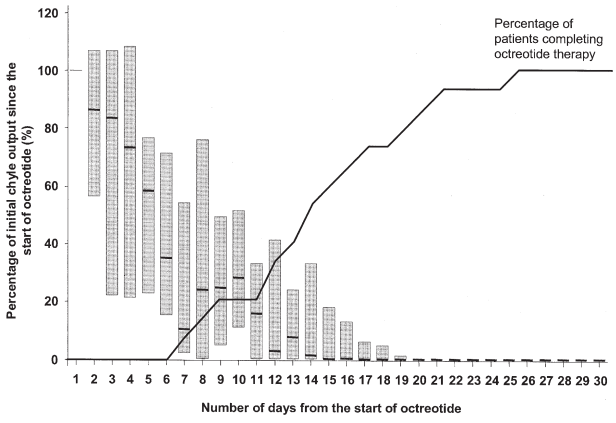

Fig 3. Box-plots showing the clinical response of the 14 patients with complete resolution of chylothorax after given octreotide without the need for surgical interventions. The line within each box represents the median daily output in terms of the percentage of baseline output just prior to the start of octreotide.

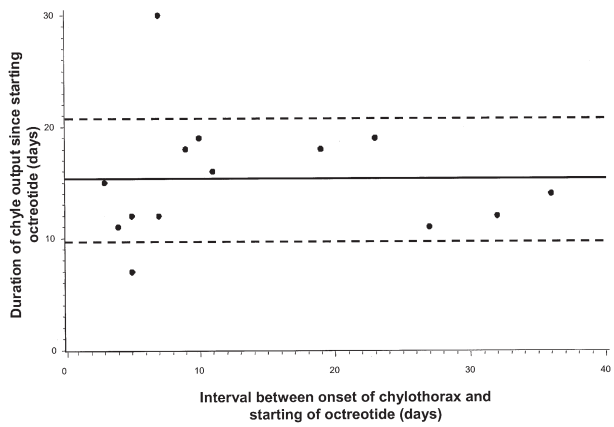

Fig 4. The relation of duration of chyle output since starting octreotide to the interval between the onset of chylothorax and the starting of octreotide. The lines represent the mean ± SD duration of chyle leak of the 14 patients (●) from the start of octreotide.

cohort of patients survived and responded to conservative management, the risk of prolonged chylothorax, the need for prolonged hospital stay, and the need for total parenteral nutrition in some of the patients have to be taken into account in the evaluation of the cost-effectiveness of such an approach. The duration of conservative management varies among institutions, and surgical intervention has been recommended for drainage that lasts for more than 1 to 4 weeks [11, 35, 36]. Nonetheless, surgical interventions are invasive and not always effective [7, 32, 33], which may be due to diffuse chyle leak after extensive surgical dissection or anatomic variations of the thoracic duct. Indeed, one of our patients required further octreotide therapy despite ligation of the thoracic duct.

Our initial success of the use of octreotide [12] has prompted a change in the management strategy of postoperative chylothorax in our institution since 2000 (Fig 2B). Indeed, such change has been included in a recently proposed algorithm, in which a trial of octreotide therapy is suggested prior to surgical interventions for prolonged chylous drainage not responding to conservative management [7]. Octreotide may reduce lymph fluid excretion directly by acting on the vascular somatostatin receptors [37] and indirectly to decrease lymph flow by reducing splanchnic, hepatic, and portal blood flow and inhibiting intestinal motility [38]. A recent systematic review revealed marked variations of the treatment regimens [13], with the octreotide given either subcutaneously at a median of 40 μg/kg/day (range, 2 to 68) or as continuous intravenous infusion at a median of 2.8 μg/kg/hour (range, 0.3 to 10).

Adverse effects of octreotide in children are infrequent and usually mild [13]. Indeed, none of our patients developed any significant side effects while on octreotide, although transient glucose disturbance [28] and abdominal distension [25] have been reported. Whether octreotide contributes to a higher prevalence of hypoalbuminemia and septicemia (Table 2) is uncertain. While severe chyle leak is probably an important predisposing risk factor, the gastrointestinal side effects and the regulatory, mainly inhibitory role in the immune response of somatostatin are well-documented [39]. Further prospective studies with adequate statistical power are required to clarify this issue. Recently, Mohseni-Bod and colleagues [15] reported a case of necrotizing enterocolitis in a term neonate after repair of aortic coarctation while on octreotide for postoperative chylothorax, although the potential contribution of the complicated preoperative and postoperative course could not completely be excluded.

There has been no randomized control trial on the use of octreotide for the treatment of postoperative chylothorax. To our knowledge, this is the largest single-center experience in the use of this treatment modality and we found that 83% of patients who failed to respond to nutritional modifications had complete resolution of their chylothorax at an average of about 2 weeks after starting octreotide. More importantly, none developed side effects from octreotide therapy. The present study is, however, not designed to compare the efficacy of octreotide therapy to that of conservative management. The apparently slower response of our patients, as compared with the one week or less in previous case reports and small case series [13], might be related to the more gradual increase in octreotide dosage in our institution. Rosti and colleagues [32] recently showed that octreotide therapy might reduce total chyle loss and duration of postoperative stay, although the sample size was small and historic controls were used for comparisons. Given the observed and reported clinical benefits and the absence of significant side effects of the therapy, it appears appropriate to start octreotide as soon as the diagnosis of chylothorax is made. This should probably be the approach in the design of future prospective randomized controlled trials.

The limitations inherent to the retrospective nature of the present study are inevitable. Furthermore, comparisons of patient cohorts in the different eras are likely to be confounded by the differences in the complexity of operations, perioperative management, treatment regimens, and severity of chylothorax. Hence, our data as shown in Table 2 could perhaps only reflect the more severe chyle loss in patients requiring octreotide, rather than used as a means to assess the efficacy of octreotide therapy. It is encouraging though that these patients, albeit having more severe chyle leak, had similar mortality and duration of hospitalization as those of the 1981 to 1999 cohort. Given the small number of patients, we were unable to identify predictors of failure of response to octreotide.

In conclusion, octreotide appears to be a useful adjunctive therapy in the management of postoperative chylothorax. While a period of nutritional modifications may be justified, earlier institution of octreotide therapy in patients at risk of prolonged chyle loss, as those with elevated systemic venous pressure, once chylothorax is diagnosed may be indicated. Prospective randomized controlled trials are nonetheless required to confirm the efficacy of this treatment modality.

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INVITED COMMENTARY

In the past decade chylothorax after heart surgery in children has gained more attention because of a real or perceived rise in its incidence and the emergence of octreotide, the synthetic analogue of somatostatin, as a therapy. Whether postoperative chylothorax is recognized more remains unclear, because as Chan and colleagues [1] suggest, the complexity of congenital heart operations has increased and recovery with the reintroduction of enteral nutrition is expedited. However, this complication can produce significant morbidity from fluid and electrolyte imbalances, protein losses, and immunosuppression, all of which can lead to long hospitalizations and mortality. In several case reports and a small retrospective series including the current study, octreotide use has only been reported in a total of 51 patients with chylous effusions after cardiovascular operations in children. In many reports the results are mixed, but the authors of this study observed resolution of chylothorax in 83% of 18 patients with chylous pleural drainage refractory to dietary modification alone. Although these results are promising, the efficacy and safety of octreotide for treatment of postoperative chylothorax after congenital heart surgery demands a more rigorous evaluation.

Several points are raised by the current study [1]. First, those patients treated with octreotide who responded with resolution of the chylothorax required a mean of 15.3 days for the effect. This interval occurred after a median of 19.5 days from the onset of the chylous pleural effusion, during which time the treatment was a modified diet rich in medium chain triglycerides (MCT) and low in long chain triglycerides (LCT). By comparison, patients

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