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Effects of somatostatin/octreotide treatment in neonates with congenital chylothorax

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Abstract

The influence of somatostatin/octreotide treatment on outcomes of neonates with congenital chylothorax remains controversial. We retrospectively reviewed our experience with somatostatin/octreotide therapy in neonates with this very rare disease.

Fourteen neonates with congenital chylothorax who were treated with somatostatin (3.5–7 μg/kg/h, before 2016) or octreotide (1–6 μg/kg/h, after January 2016), along with traditional management between 2013 and 2016, were retrospectively reviewed in this observational study. Their daily volumes of pleural drainage and parameters of respiratory support were recorded, and the potential side effects of somatostatin/octreotide were screened.

Four patients (28.6%) had a unilateral presentation of pleural effusion, whereas 10 patients (71.4%) had a bilateral presentation. Twelve patients (85.7%) survived until discharge without later recurrence or death, whereas 2 patients (14.3%) died within the first 3 days after birth. Somatostatin/octreotide treatment was maintained for a median period of 6 days (range 1–16 days). The chest tube was removed after a median duration of 14 days (range 2–51 days), and no patient needed pleurodesis or thoracic duct ligation surgery. The average daily drain output within 3 days post-treatment (median 62 mL, range 10–651 mL) was significantly lower than that before treatment (median 133 mL, range 70–620 mL) (P = .002). The need for ventilation support was reduced in most patients (85.7%) after the initiation of somatostatin/octreotide therapy. No serious side effects were identified.

Somatostatin/octreotide treatment reduced pleural drainage and respiratory support without significant side effects. Further randomized controlled studies with more patients are necessary to ascertain the benefits of somatostatin/octreotide in neonates with congenital chylothorax.

Abbreviation: MCT = median chain triglyceride.

Keywords: congenital chylothorax, neonates, octreotide, somatostatin

1. Introduction

Chylothorax is occasionally found after complicated heart surgery in neonates; more rarely, it can be detected as an idiopathic lesion called congenital chylothorax. The reported incidence of congenital chylothorax is about 1:5800 to 1:24000[1,2] in live-born neonates. Once the diagnosis is confirmed, the first-line management is dietary modification, which ranges from aggressive fasting with total parenteral nutrition to median chain triglyceride (MCT)-enriched formula, and eventually normal feeding. Supplementation of lost electrolytes and proteins is frequently needed during the hospitalization. Most patients suffer from respiratory distress due to pleural effusion, and require chest drainage and respiratory support. If

the drainage persists for several weeks, pleurodesis with OK-432 (Picibanil), erythromycin, or povidone-iodine[3] is recommended. Surgical methods are used as the last option when all above-mentioned treatments fail, and include ligation/embolization of the thoracic duct.[4]

In addition to the aforementioned management options, pharmacological therapy with somatostatin/octreotide has emerged in the recent years.[1,5–13] Somatostatin is a polypeptide with inhibitory effects on the release of growth hormone and insulin, and lymph fluid excretion. It is known to reduce both the splanchnic blood flow and the intestinal secretion of electrolytes and water.[14] Because of this mechanism of action, somatostatin can reduce the amount of chyle production. Therefore, it has been used by neonatologists as an additional treatment in congenital chylothorax. More recently, octreotide—a synthetic analog of somatostatin—has been more widely used because it has a longer half-life period and does not require continuous administration.[7] However, most studies on congenital chylothorax are case reports.[6,10,12] Moreover, even large case series only included less than 10 patients.[1,8,9] Currently, no consistent conclusion regarding congenital chylothorax treatment has been reached.[1,8,9,13] This fact may be related to the small number of cases and the variable timing and dosages of somatostatin/ octreotide treatment in different studies. Here, we report our experience with 14 neonates managed in a single center based on a care protocol elaborated and used in our unit.

2. Patients and methods

This retrospective study was approved by our institutional research ethics board, and the need for patient consent was
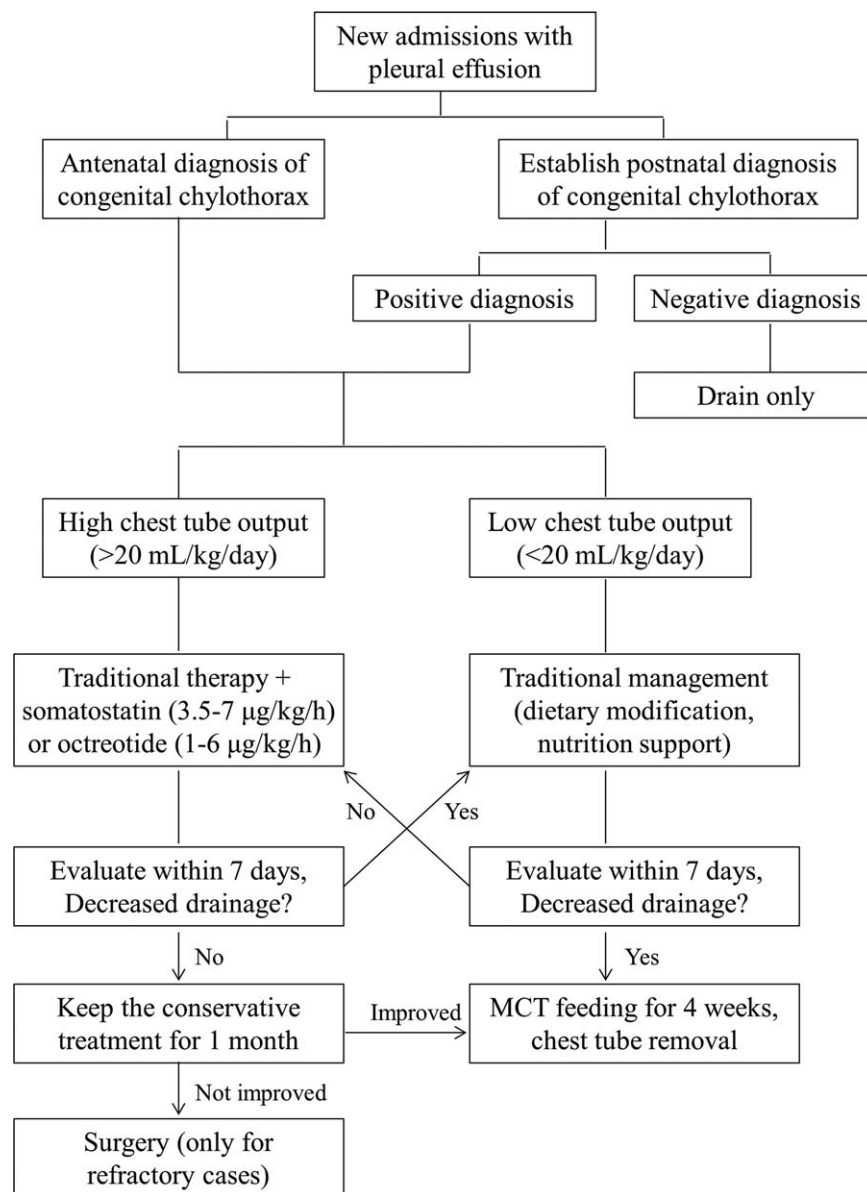
Figure 1. Algorithm of the care protocol for neonates with congenital chylothorax in our department. MCT = medium chain triglyceride.

waived. All neonates diagnosed with chylothorax admitted between January 2013 and December 2016 were identified from the electronic database of Children's Hospital of Fudan University. The diagnosis of chylothorax was made according to widely used criteria.[15] Briefly, pleural effusion in children was considered a chyle when it contained >1.1 mmol/L triglycerides (with oral fat intake), and a total cell count >1000 cells/mL or a lymphocyte fraction >80%. A lymphocyte fraction >80% in pleural effusion is essential to diagnose congenital chylothorax antenatally. Only neonates with congenital chylothorax were included in this study. Patients with other known causes of chylothorax, such as trauma and surgery, were excluded. Because the purpose of this study was to evaluate the efficacy and safety of somatostatin/octreotide treatment, patients with congenital chylothorax were further refined, and only those who received treatment of somatostatin/octreotide (n = 14) were finally included.

2.1. Protocol of the management of congenital chylothorax in our department

Since 2013, our department follows an institutional management protocol for congenital chylothorax. The algorithm is shown in Fig. 1. After the diagnosis of congenital chylothorax is established, either antenatally or postnatally, the traditional conservative treatment is initiated. The traditional therapy includes nil by mouth, total parenteral nutrition, pleural drainage, and ventilation support, when necessary. MCT-enriched formula is used when the child is ready to restart feeding. If the chest tube output is more than >20 mL/kg/d, an additional treatment with either somatostatin (3.5–7 µg/kg/h) or octreotide (1–6 µg/kg/h) is initiated. Somatostatin was used before 2016, whereas octreotide was used after January 2016 due to the advantage of longer half-time life. The dosages of both medications were decided based on previous studies.[9,13,14] The

medication was started from a low dosage and then gradually increased; we avoided using very high dosages to prevent potential side effects. The drain volume was monitored and evaluated within 1-week treatment; subsequently, a decision was made whether to continue somatostatin/octreotide administration or not. Thoracic duct ligation surgery was only performed when all aforementioned treatments failed after 1 month. Ultrasonography was performed periodically to rule out any residual pleural effusions.

2.2. Data collection

Electronic charts of the patients were reviewed. Prenatal and postnatal characteristics of the neonates and associated anomalies were collected. The results of karyotype test—a routine examination of each neonate—were documented. Clinical course, somatostatin/octreotide administration plan, nutrition support, chest drainages, and respiratory support information were recorded. Laboratory data of the pleural effusion were double-checked to confirm the diagnosis. The outcomes included changes in pleural drainage, respiratory support, mortality, and treatment side effects, according to the suggestions of Das and Shah.[13] The potential reported side effects, including new onset of pulmonary hypertension, necrotizing enterocolitis, transient hypothyroidism, bradycardia, hypoxemia, cholelithiasis, intestinal perforation, hypoglycemia, and hyperglycemia, were carefully reviewed for each patient. Hospital survivors were followed up for chylothorax recurrence every 2 months in the first 6 months after the discharge, and then every year. Chest radiography and ultrasound imaging were performed during the follow-up. Those patients who were unable to come to our clinic were followed up at their local hospitals, and the results of chest radiography and ultrasound imaging were obtained over the phone. All survivors were followed up at a median time of 19 months (3–45 months).

2.3. Statistical analysis

Data were presented as frequencies (percentages), medians (ranges), or means ± standard deviations, as appropriate. Differences between the groups were tested with the chi-square test or Fisher exact test for discrete variables. The Mann–Whitney U test was used for comparison of continuous variables between the groups. The volumes of pleural drainage before and after initiation of somatostatin/octreotide were compared by a paired t test. We were unable to perform a detailed analysis of the risk factors due to the relatively small number of cases. P values <0.05 were considered statistically significant. Data analysis was performed using STATA 14.0 software (StataCorp LLC, College Station, TX).

3. Results

3.1. Demographics and general outcomes

Fourteen neonates with congenital chylothorax underwent somatostatin/octreotide therapy in addition to traditional management. Their demographic data and clinical outcomes are summarized in Table 1. In this cohort, 11 patients (78.6%) were male and 3 patients (21.4%) were female. The median gestational age was 34.7 weeks (range 30.7–38.6 weeks), and the median birth weight was 3.3 kg (range 2.4–4.7 kg). Twelve patients (85.7%) had antenatal diagnosis of pleural effusion, and 5 of them (41.7%) underwent antenatal drainage. Eleven patients (78.6%) had hydrops fetalis. Pleural effusion was unilateral in 4 patients (28.6%, 2 left, 2 right) and bilateral in the remaining 10 patients (71.4%). Chromosomal abnormalities were found in 2 patients (14.3%). The karyotype test of case 1 revealed increased heterochromatin length on the long arm of chromosome 1 (46, XY, 1qh+). In case 6, the karyotype was normal, but 11q deletion (23.3–24.1) was detected when genomic copy number variants were screened. Polydactyly was identified as associated anomaly in one patient (7.1%). MCT feeding was initiated in 12 neonates; however, the other 2 patients (case 2 and case 14) died early (both on day 2 of life) without feeding. The median length of hospital stay is 32.5 days (range 2–77 days), and 12 patients (85.7%) survived to discharge. During the follow-up, no recurrent chylothorax or late death was reported. All patients were in good condition.

Table 1

Characteristics of the neonates with congenital chylothorax.

Case	Sex	Gestational age, wks	Birth weight, kg	Antenatal diagnosis of pleural effusion	Antenatal drainage	Hydrops fetalis	Site of pleural effusion	Chromosomal anomalies	Other associated clinical anomalies	MCT feeds	Chest drainage, d	Ventilation time, d	Length of stay, d	Outcomes
1	Male	33.6	3.4	Y	Y	Y	Bilateral	Y[*]	N	Y	11	29	59	Discharge
2	Male	33.9	3.3	Y	Y	Y	Bilateral	N	N	N	2	2	2	Death
3	Female	37.3	4.7	Y	N	Y	Bilateral	N	N	Y	51	25	77	Discharge
4	Male	38.1	3.7	Y	N	Y	Right	N	N	Y	20	7	26	Discharge
5	Male	38.1	3.9	N	N	Y	Right	N	N	Y	23	23	26	Discharge
6	Female	32	3.1	Y	Y	Y	Bilateral	Y[†]	Y[‡]	Y	25	24	58	Discharge
7	Male	35.9	3.4	Y	N	Y	Bilateral	N	N	Y	14	15	25	Discharge
8	Male	37.7	3.3	Y	N	Y	Bilateral	N	N	Y	10	8	20	Discharge
9	Male	33.1	3.2	Y	N	N	Bilateral	N	N	Y	9	24	30	Discharge
10	Male	38.6	3.8	N	N	N	Left	N	N	Y	10	0	35	Discharge
11	Male	32	3.0	Y	Y	Y	Bilateral	N	N	Y	17	25	62	Discharge
12	Male	35.6	3.3	Y	N	N	Left	N	N	Y	17	6	38	Discharge
13	Male	30.7	2.5	Y	N	Y	Bilateral	N	N	Y	11	5	42	Discharge
14	Female	32.6	2.4	Y	Y	Y	Bilateral	N	N	N	2	2	2	Death

MCT = median chain triglycerides, N = no, Y = yes.

[*] Increased heterochromatin length on the long arm of chromosome 1 (46, XY, 1qh+).

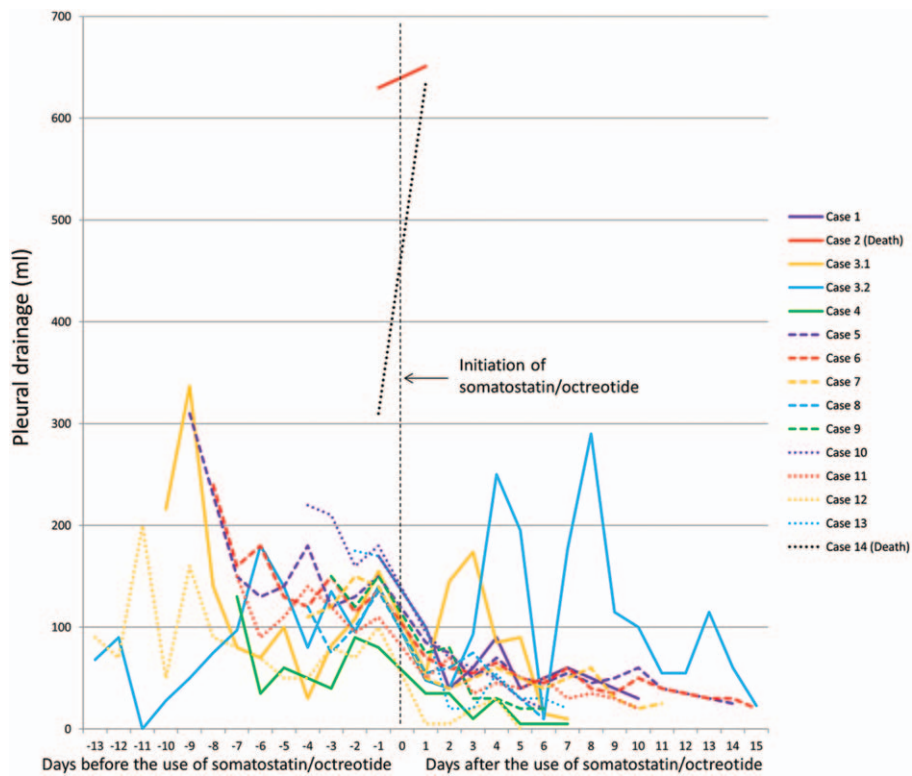[†] 11q deletion (23.3–24.1).

[‡] Polydactyly.

Figure 2. Pleural drainage changes before and after the initiation of somatostatin/octreotide treatment 3.1 and 3.2 represent 2 episodes of somatostatin/octreotide use in case 3. The day of initiation of somatostatin/octreotide treatment was set as 0 on the horizontal axis. Somatostatin was used before 2016, whereas octreotide was used after January 2016 (case 12, 13, and 14).

3.2. Pleural effusion and the use of somatostatin/octreotide

A chest tube was inserted in all patients, and the drainage was collected daily. Somatostatin was administered in 11 patients before 2016, and octreotide was administered in the remaining 3 patients (case 12, 13, and 14) since January 2016. In case 3, somatostatin was administered twice during 2 episodes, with an interval of 16 days, because of a recurrent pleural effusion. Therefore, in total, there were 15 episodes of treatment by somatostatin/octreotide in these 14 patients. Somatostatin/octreotide was started at a median of 4 days (range 1–13 days) after chest tube insertion, and maintained

Table 2

Average daily pleural drainage 3 days before and 3 days after somatostatin/octreotide treatment.

Patient no.	Average daily drainage within 3 d pretreatment, mL	Average daily drainage within 3 d post-treatment, mL	Ratio over pretreatment	Outcome
1	170	67	0.39	Alive
2	630	651	1.03	Death
3.1	115	125	1.09	Alive
3.2	124	60	0.48	Alive
4	70	27	0.39	Alive
5	133	73	0.55	Alive
6	133	62	0.47	Alive
7	137	47	0.34	Alive
8	103	63	0.61	Alive
9	140	62	0.44	Alive
10	183	75	0.41	Alive
11	108	52	0.48	Alive
12	83	10	0.12	Alive
13	173	47	0.27	Alive
14	310	635	2.05	Death

3.1 and 3.2 represent the 2 episodes of somatostatin/octreotide use in case 3.
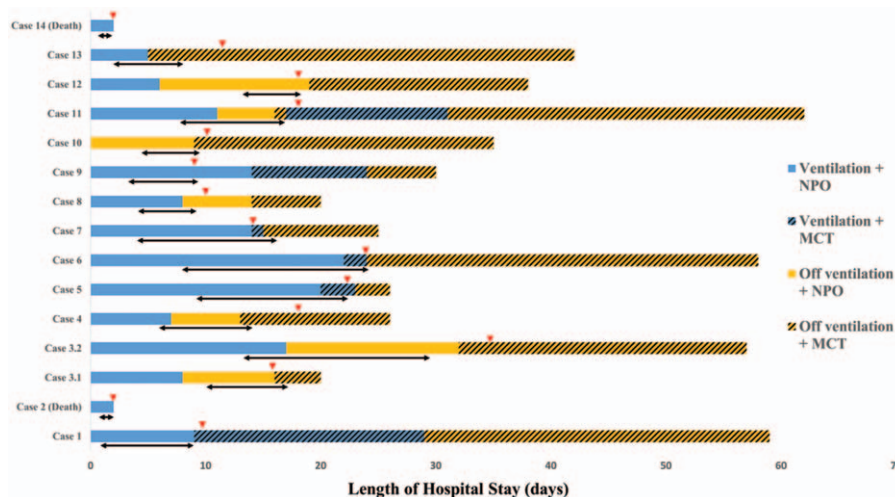
Figure 3. Respiratory support and feeding plan before and after the initiation of somatostatin/octreotide treatment 3.1 and 3.2 represent 2 episodes of somatostatin/octreotide use in case 3. The black arrows below the bars represent the duration of somatostatin/octreotide treatment; the red triangles above the bars represent the timings of chest tube removal. Somatostatin was used before 2016, whereas octreotide was used after January 2016 (case 12, 13, and 14). MCT = medium chain triglyceride, NPO = nil per os.

for a median period of 6 days (range 1–16 days). The chest tube was removed after a median of 14 days (range 2–51 days), and no patient required pleurodesis or thoracic duct ligation surgery.

Daily drainage volumes are plotted in Fig. 2. The day of initiation of somatostatin/octreotide treatment was set as 0 on the horizontal axis. The median drainage was 150 mL (range 80–630 mL) in the day before the initiation of somatostatin/octreotide. In the first day after treatment with somatostatin/octreotide, the volume of pleural effusion decreased, except in 2 patients (case 2 and case 14, both of them died) (Fig. 2). The drainage volume in the first day after treatment was significantly lower than that in the day before treatment (median 70 mL, range 5–651 mL vs median 150 mL, range 80–630 mL) ($P=.001$). Subsequently, the drainage was stabilized and gradually decreased in most patients until less than 10 mL/kg/d, which was our cut-off value of removing the chest tube. However, a rebound of the drainage was detected in the 2 episodes of somatostatin/octreotide treatment in case 3 (case 3.1 and case 3.2), as demonstrated by the spikes in Fig. 2. Finally, the drainage decreased in this patient too.

The average pleural drainage volumes during 3 days before treatment and 3 days after treatment are illustrated in Table 2. The average drain output within 3 days after treatment (median 62 mL, range 10–651 mL) was significantly lower than that before treatment (median 133 mL, range 70–620 mL) ($P=.002$). The ratio of post-treatment to pretreatment drain output was lower than 0.5 in 66.7% of cases (10/15). The average drain output was not significantly different between first 3 days and 4 to 6 days of somatostatin/octreotide treatment ($P=.2$).

3.3. Respiratory support

Ventilation support, for example, invasive and noninvasive mechanical ventilation, was used in 13 neonates (92.9%). The median ventilation time was 15 days (range 2–29 days). The need for respiratory support decreased in most patients (85.7%, 12/14) after the initiation of somatostatin/octreotide. Five patients (35.7%) were weaned from ventilator support within 5 days of somatostatin/octreotide administration (Fig. 3).

3.4. Side effects

No serious previously reported side effects were detected in this group of neonates.

4. Discussion

Congenital chylothorax is a rare disease, characterized by primary accumulation of chyle within the pleural cavity without trauma or surgery. During patient screening process of this study, we identified a total of 20 neonates with congenital chylothorax (14 patients with and 6 without somatostatin/octreotide treatment) from about 26,000 new admissions (1:1300) in our department between 2013 and 2016. However, this incidence is not based on general population, but on the number of admissions; therefore, it is reasonable to consider that this incidence is higher than that reported by previous studies (1:5800–1:24000).[1,2] Other possible underlying reasons include different races and referral bias, as our neonatal center is 1 of the biggest territory referral site within China. The incidence of a delivered newborn to be transferred into a neonatal department after birth is around 3% to 5% per year in China.

Somatostatin/octreotide has been proposed for treatment of congenital chylothorax in infants and children in 2000.[14] However, only case reports/series were reported before 2010. Das and Shah[13] conducted a systematic review and found no clinical trial, but only 19 case reports of 20 neonates. Chylothorax resolved in 14 patients (70%). Due to the small number of cases and variable octreotide dose and administration plan, this review did not recommend any practice guidelines about the routine use of octreotide. However, the authors advocated a randomized controlled trial and recommended the use of improvement in the amount of chylous drainage and improvement in respiratory status as primary outcomes, which were used in the current study. Several case reports/series were published after 2010,[1,8–12] and 3 papers had a relatively large number of cases. Downie et al[1] included 10 neonates with congenital chylothorax, but only 3 of them received octreotide therapy and 2 died. Horvers et al[8] from Netherlands reported 7 cases of neonatal congenital chylothorax, but did not identify

clear and consistent effect of octreotide. Shah and Sinn[9] from Sydney reviewed their experience with octreotide in 6 neonates with idiopathic chylothorax. Resolution of chylothorax was found in 5 patients (83%), and the authors recommended early initiation of octreotide therapy in this disease.

Our current study included 14 patients with congenital chylothorax treated with somatostatin/octreotide, and it might be 1 of the largest case series of congenital chylothorax with such therapy to date. Our experience revealed that this additional treatment is effective. Chylothorax responded to somatostatin/ octreotide therapy, and the amount of pleural drainage and the need for ventilation support significantly decreased in most patients; additionally, none of the patients needed pleurodesis or surgery. Congenital chylothorax resolved in 12 patients (85.7%) who survived to discharge; no recurrent chylothorax was noticed during the follow-up. These results are comparable with those reported by previous reported studies. No severe side effects were found in this cohort.

In addition to congenital chylothorax, somatostatin/octreotide treatment is also used for postcardiac surgery chylothorax. Caverly et al[16] reviewed 19 patients with postcardiac surgery chylothorax treated with octreotide, and found 74% response rate and 63% resolution. Zuluaga[17] reviewed multiple uncontrolled case series of octreotide treatment, and found its usage is increasing around the world for patients nonresponsive to dietary modifications. The use of octreotide was recently included in clinical practice guideline in a children's hospital in Michigan, and this guideline-directed therapy obtained excellent results.[18] Due to its high efficacy, it has been recommended as part of conservative managements of chylothorax in the modern era.[19]

Despite the fact that most of our patients responded well to somatostatin/octreotide therapy, there were 2 deaths (case 2 and case 14) in this study. Both of them had huge amount of pleural drainage in the first day (630 and 310 mL) and died 2 days later. MCT feeding was not possible to use in them, as shown in Table 1, and they died quickly, before the onset of somatostatin/ octreotide action (both medications were started on day 1, but patients died on day 2). Huge amount and rapid production of pleural effusion seems to be a risk factor for these patients, but statistical power is limited due to the small number of cases. We could speculate that somatostatin/octreotide treatment works better in mild congenital chylothorax. Genetic anomalies and other associated malformations were also reported as major risk factors in such patients[1]; the underlying reasons are that some of these anomalies are untreatable and lead to poor outcomes. Two patients in our study had chromosomal abnormalities; however, the abnormalities were only minor and not lethal or associated with severe organ dysfunction. Patient 1 had increased length of the heterochromatin on the long arm of chromosome 1, which had little effect on phenotype.[20] Deletion of 11q (23.3–24.1) in case 6 may be associated with facial dimorphism or heart disease; however, patient did not present such congenital malformations. Both these patients survived. The incidence of genetic disorders in our study is lower than that reported in the previous studies.[1,9] It may be underestimated, because only karyotype analysis was performed in the study participants. Another reason is that only neonates without major anomalies were referred to our department for further treatment, and those who had major malformations were withdrawn by parents in referring maternal hospital, and this leads to patient selection bias in our study.

In the present study, there were 11 patients with hydrops fetalis, and 9 of them (81.2%) survived. This survival is comparable with that previously reported in neonates with nonimmune hydrops (~64.5%).[21] The reasons may be the correct management of chylothorax and the lack of other uncorrectable etiologies of hydrops, such as chromosomal anomalies, metabolic disorder, severe cardiovascular malformation, and syndromic diseases.[22,23]

This study had several limitations. First, it was a retrospective study and included only a small number of patients; however, it might be 1 of the largest available studies performed in neonates with congenital chylothorax. Due to the rarity of congenital chylothorax, patients with both somatostatin and octreotide treatment were included in our study, because these drugs share similar mechanisms. The majority of neonates (n=11) received somatostatin and only a few patients received octreotide (n=3); therefore, we were unable to identify the differences between somatostatin and octreotide effects due to the small number of cases. Second, the selection bias of the patient group could occur and the study lacked a control group. When we screened the neonates, we found several patients with congenital chylothorax treated without somatostatin/octreotide; however, we did not use them as controls, because most patients only had small pleural effusions and responded relatively well to dietary control. Finally, the follow-up data need to be interpreted with caution, because 67% of hospital survivors were unable to come to our clinic, and only the results of chest radiography and ultrasound imaging performed at their local hospitals were obtained over the phone.

5. Conclusions

In this relatively large group of neonates with congenital chylothorax, somatostatin/octreotide treatment reduced the volume of pleural drainage and the need for respiratory support, without significant side effects. The hospital survival was 85.7%, and no late death or late recurrent chylothorax occurred. Further randomized controlled studies with more patients are necessary to ascertain the benefits of somatostatin/octreotide treatment in neonates with congenital chylothorax.

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