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European Journal of Cardio-thoracic Surgery 30 (2006) 49—53

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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The role of somatostatin in the treatment of persistent chylothorax in children

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Received 19 January 2006; accepted 20 March 2006

Abstract

Objective: To analyze the success rate of somatostatin in children with persistent chylothorax who failed dietary treatment options (fat-free nutrition, total parenteral nutrition) and to work out predictive factors for a successful therapy with somatostatin. **Methods:** Retrospective cohort study over a 5-year period (2000—2004) in a neonatal and pediatric intensive care unit of a tertiary university hospital. We analyzed the data of 85 neonatal and pediatric patients. Treatment of chylothorax occurred according to a multistage protocol with progressing invasiveness: (1) fat-free enteral nutrition, (2) total parenteral nutrition, (3) somatostatin infusion, (4) surgery. The percentages of patients successfully treated at the progressing steps were recorded. The somatostatin group was analyzed regarding to physiologic, diagnostic, treatment and outcome parameters. Somatostatin-responders were compared with non-responders. **Results:** Seventy-six of the 85 patients had chylothorax after cardiac surgery. Sixty-six percent could be treated with fat-free nutrition alone, 19% needed treatment with total parenteral nutrition and in 15% somatostatin was added. Of the whole sample, 4.7% required a surgical intervention. Of the 13 patients treated with somatostatin, all had bilateral chylothorax. Six patients (46%) responded to somatostatin. Responders and non-responders did not differ significantly regarding age, day of postoperative diagnosis of chylothorax, amount of chylous effusion before somatostatin infusion, triglyceride concentration and lymphocyte percentage in chylous, and central venous pressure ($p = 0.066$). **Conclusions:** Somatostatin, integrated in a treatment algorithm, was successful in resolving persistent chylothorax in around 50% of patients. With this strategy, some children may be prevented from undergoing an operation. However, factors predicting successful therapy with somatostatin could not be elicited.

Keywords: Chylothorax; Somatostatin; Infants; Pleural effusion

1. Introduction

Chylothorax, an accumulation of lymphatic fluid in the pleural space, is still a severe disease after cardiac or thoracic surgery and an important factor for length of stay in pediatric intensive care units [1]. The incidence of post-operative chylothorax is between 0.25% and 5.3% [1—3]. The congenital form of chylothorax is uncommon, but the most frequent reason for pleural effusion in the neonatal period and often associated with other malformations [4,5]. Other reasons for chylothorax are thrombosis of the subclavian vein, congenital anomalies, lymphangiectasis, injuries of the thoracic duct and tumors. Increased central venous pressure and, rarely, lymphatic vessel malformation in patients with dysmorphic syndromes may aggravate the pleural effusion.

The standard treatment of chylothorax in pediatric and neonatal intensive care includes conservative therapy with fat-free or medium chain triglyceride nutrition (MCT), total parenteral nutrition and, if this is not successful, surgical interventions (pleurodesis, ligation of the duct, pleuro-peritoneal shunt).

In the last years several case studies reported on a new conservative treatment option with somatostatin or somatostatin analog with a high success rate [6—9]. Only two publications reported on side effects and unsuccessful treatment [8,9].

The acting mechanism of somatostatin in the therapy of chylothorax is still not completely known. Recent published data showed an effect on the splanchnic and liver blood flow as well as a reduced lymphatic flow mediated by somatostatin receptor subtypes 2, 3 and 5 [10].

However, there are still no data about the success rate of somatostatin or analog in the treatment of chylothorax. We analyzed the data of the patients with chylothorax during the last 5 years treated by a predefined algorithm. We focused on the group treated with somatostatin in order to establish factors predictive for successful therapy.

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doi:10.1016/j.ejcts.2006.03.039

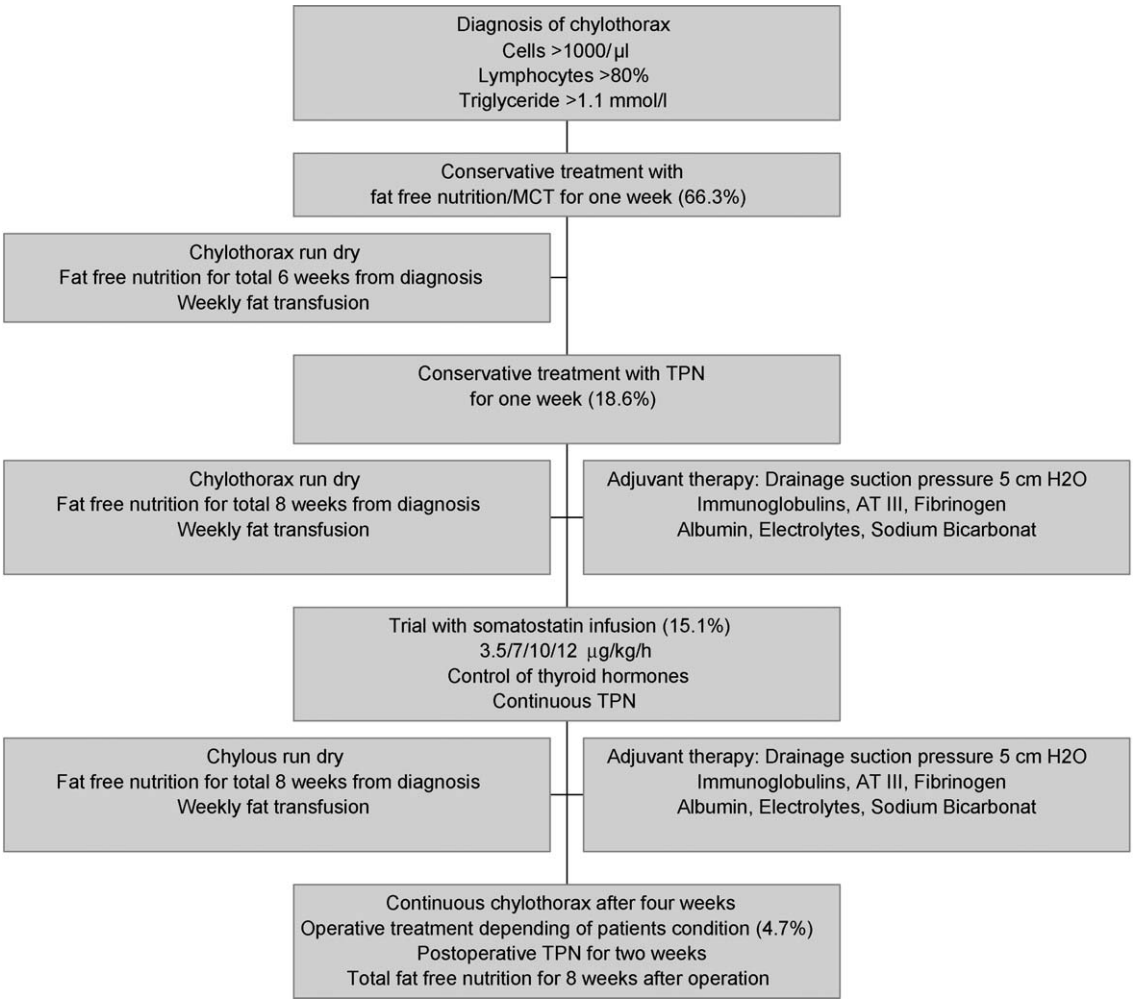

Fig. 1. Treatment algorithm for chylothorax. The percentages of patients reaching the progressing treatment stages are given in parentheses. MCT, median chain triglyceride; TPN, total parenteral nutrition.

2. Materials and methods

We retrospectively studied the data of all patients with the diagnosis of chylothorax in our pediatric and neonatal intensive care database for the years 2000 through 2004. The diagnosis of chylothorax was made according to the definition of Buttiker et al. [5]: concentration of triglyceride in pleural effusion >1.1 mmol/l and total cell count >1000 cells/µl with predominance of $>80\%$ lymphocytes. The patients were treated according to our hospital guideline (Fig. 1), an algorithm with a four-step treatment progression from fat-free nutrition to total parenteral nutrition, somatostatin, and surgery. Somatostatin was started at 3.5 µg/(kg h) and increased every day to a maximal dose of 12 µg/(kg h) (Fig. 1). If somatostatin infusion was not successful after 3 days on the maximal dose, the infusion rate was gradually reduced over the next 3 days to zero. Successful treatment was defined as reduction of chylous amount $>50\%$ on maximal dose. We used a short acting form of somatostatin (Stilamin®, Serono, Switzerland).

For the patients treated with somatostatin, the following parameters were recorded: underlying disease, type of surgical intervention, postoperative incidence of chylothorax, amount of chylous before starting somatostatin, triglyceride level, total white cell count, percentage of lymphocytes in the pleural effusion at the time of diagnosis of chylothorax, duration and success rate of somatostatin infusion. We further looked at physiologic and treatment parameters during somatostatin infusion: central venous pressure (median value, calculated for the days of somatostatin treatment), inotropic support, suction pressure on the pleural drainage and thrombosis. We further focused on expected and described side effects of somatostatin like hypo- or hyperglycemia, thyroid dysfunction, necrotizing enterocolitis, and blood pressure variations.

The study was approved by the Hospital Ethic Committee.

Summary values are given as medians with their ranges. Differences between groups were analyzed by Mann–Whitney *U*-test or Fischer's exact test. Statistical analysis was done with StatView (SAS, Cary, NC). A p-value of <0.05 was considered statistically significant.

Table 1
Underlying diseases of the patients with chylothorax (n = 85)

Diagnosis	Number of patients
Congenital heart disease	76
Congenital chylothorax	3
Diaphragmatic hernia	2
Cystic adenomatoid malformation	2
Esophageal atresia	1
Lung sequester	1

3. Results

In the 5-year period 2000–2004 we found a total of 85 pediatric and neonatal patients with the diagnosis of chylothorax. Seventy-six of them were post-cardiac surgery patients. Etiology of chylothorax is summarized in Table 1.

During this time a total of 1130 cardiac operations (with and without heart–lung machine) were performed. Chylothorax developed in 6.6% of all patients after cardiac surgery. In this group of patients with post-cardiac surgery chylothorax, 14 had the additional diagnosis of trisomy 21.

Chylothorax was found 31 times on the left side, 25 times on the right side and 29 times bilaterally. Following the hospital guidelines for the treatment of chylothorax, 56 patients (66%) could be treated with fat-free nutrition alone. Sixteen patients (19%) needed treatment with total parenteral nutrition and in 13 children (15%) somatostatin was added (Fig. 1). In the somatostatin group four patients required pleurectomy (4.7% of the whole sample).

Three patients died in the somatostatin group. Two of them died as a result of persistent chylothoraces before pleurectomy could be performed (non-responders). The third patient who died was a responder: 3 weeks after successful therapy he died following sepsis with multiorgan failure.

Table 2 shows some details of the 13 patients treated with somatostatin. The overall success rate of the therapy with somatostatin was 46%. In these six successfully treated patients, the drainage could be removed at a median time of 5.5 days (range 3–13 days) after having reached the maximal dose of 12 μg/(kg h). All of these patients had bilateral chylothoraces.

Median age of the 13 somatostatin-treated patients at the time of diagnosis of the chylothorax was 21 days (range 1–302). All showed very high amounts of chylous before starting somatostatin (median 165, range 80–278 ml/kg per day). Side effects which were possibly related to the treatment with somatostatin were seen in three patients: hyperglycemia, hypoglycemia and transient hypothyroid function. Eight patients were on one or more inotropes during somatostatin infusion (Table 2).

Table 3 shows physiologic, diagnostic, treatment and outcome parameters for responders and non-responders. None of these parameters differed significantly between the two groups.

4. Discussion

In the present study we analyzed the data of children with persistent chylothorax failing dietary treatment options. The objective was to focus on patients who had been treated with somatostatin and to find possible predictive factors for successful therapy in the treatment algorithm for chylothorax.

Table 2
Characteristics of patients treated with somatostatin (n = 13)

Diagnosis	Successful therapy with somatostatin	Age at diagnosis (days)	Postoperative incidence of chylothorax (days)	Maximal effusion before somatostatin (ml/kg per day)	Inotropic support during somatostatin	Chylothorax relevant venous thrombosis
Coarctation	No	22	3	80	Dopamine, milrinone	No
Hypoplastic left heart syndrome	Yes	13	6	80	None	No
Hypoplastic left heart syndrome	No	302	8	38	None	No
Double outlet right ventricle	No	14	13	165	None	Shunt thrombosis
Congenital	Yes	1	0	256	None	No
Atrio-ventricular channel with hypoplastic aortic arch, trisomy 21	No	106	22	220	Adrenaline, dopamine, noradrenaline, milrinone	No
Total anomalous pulmonary venous return with dextrocardia	Yes	21	18	178	Dopamine	Left internal jugular
Esophageal atresia, transposition of the great arteries, VATER association	No	10	3	132	Dopamine	No
d-Transposition of the great arteries	Yes	23	15	278	Dopamine	No
d-Transposition of the great arteries, Holt-Oram syndrome	Yes	24	20	102	None	Superior cava, right internal jugular
Tetralogy of fallot	No	21	15	201	Noradrenaline, dopamine, milrinone	No
Total anomalous pulmonary venous return	Yes	19	15	178	Dopamine	No
Tetralogy of fallot, trisomy 21	No	7	5	115	Noradrenaline, adrenaline, dopamine	No

Table 3
Characteristics of infants with chylothorax responding and not responding to somatostatin treatment

	Patients reacting on somatostatin ($n = 6$)	Patients not reacting on somatostatin ($n = 7$)	p^*
Age (days)	20 (1–24)	21 (7–302)	0.72
Day of diagnosis postoperatively (days)	15 (0–20)	8 (3–22)	0.48
Maximal amount of chylothorax before somatostatin (ml/kg per day)	178 (80–278)	132 (38–220)	0.35
Triglyceride levels in chylous (mmol/l)	3.8 (0.8–5.8)	1.2 (0.4–3.1)	0.06
Central venous pressure (mmHg)	6 (5–9)	8.5 (6–11)	0.066
Inotropic support (%)	50	71	0.59
Pleurectomy (%)	0	57	0.07
Mortality (%)	16	43	0.19

* Mann–Whitney *U*-test and Fisher's exact test.

Most of the patients with postoperative chylothorax could be treated conservatively with fat-free nutrition or total parenteral nutrition (combined 85%). This might be due to our treatment protocol with defined treatment progression steps. The success rate of dietary therapy alone was slightly higher than described in the literature [11,12]. Beghetti et al. [3] published a group of 46 children with chylothorax and a success rate of 80% with conservative treatment. The percentage of patients with chylothorax after cardiac surgery (6.6%) in our study is higher compared to other publications who describe numbers of 1.5–2.3% [3,13]. Finally, 4.6% of the patients underwent surgical pleurectomy. This incidence was higher than that reported by Nguyen et al. [13] for the period of 1984–1993 and may be explained with the more complex procedures done routinely nowadays.

A new approach for conservative management of patients with chylothorax is the treatment with somatostatin. In our study the application of somatostatin was successful in 46%. So far, no data from randomized studies are available to compare our results with. However, we did not find any factors which influence the success of somatostatin or make the success predictable. Only high central venous pressure and low triglyceride level at diagnosis reached nearly statistical significance as factors contributing to somatostatin failure (Table 3). Beghetti et al. [3] mentioned that high venous pressures (between 10 and 16 mmHg) limit the effect of pleuro-peritoneal shunts. Although our non-responders had much lower central venous pressures (median 8.5, range 6–11 mmHg), it is conceivable that high venous pressure may influence the overall treatment success of chylothorax. The lower median triglyceride level at diagnosis in the somatostatin non-responders, might be due to a worse status of enteral nutrition in these patients. Buttiker et al. [5] showed that the triglyceride level in a chylous pleural effusion depends on the nutrition of the patient. The presence of thrombosis did not influence the success rate of somatostatin. This was surprising because thrombosis of the subclavian vein is a known etiologic factor of chylothorax [14–16].

The side effects in our patients might be related to the treatment with somatostatin. Especially, the altered thyroid function is also described in patients undergoing cardiopulmonary bypass operations. The majority of the children treated with somatostatin were post-cardiac surgery patients. Therefore, it is difficult to allocate this side effect to the somatostatin therapy. A severe side effect attributed to somatostatin, namely necrotizing enterocolitis (NEC), has been described by Mohseni-Bod et al. [8]. However, this patient was also suffering from a mild form of coarctation, a well-known risk factor of NEC [17]. One out of three patients with congenital chylothorax went on to somatostatin treatment and he was treated with success. However, this isolated case cannot lead to the conclusion that congenital chylothorax should be first line treated with somatostatin. Most of the congenital cases are resolving with conservative treatment alone after 4–5 weeks [18].

All of our patients who were not treatable by dietary means alone, had bilateral chylothorax. However, no factor could be worked out to explain why some patients with bilateral chylothorax can still be managed with fat-free nutrition or parenteral nutrition alone.

A limitation of our study is its retrospective design. The number of the patients treated with somatostatin is small but nevertheless the biggest number published in the literature so far. We started a randomized, double blind, placebo controlled study of somatostatin treatment 5 years ago. After having included five patients we had to stop the study because of parental refusal. Some parents were not willing to accept the possibility of placebo treatment with normal saline solution in the context of complicated or desperate clinical situations.

In conclusion, somatostatin is an option in the treatment of persistent congenital and postoperative chylothorax. It should be integrated in a treatment algorithm and placed after dietary measures (fat-free nutrition, total parenteral nutrition), but before surgical options. So applied, the success rate of somatostatin in resolving chylothorax may be around 50%. With this treatment regime some children with persistent chylothorax could be prevented from undergoing an operation.

To understand the factors that predict success, to identify the optimal time of application and dosage of somatostatin, and to define the characteristics of possible responders a multicenter randomized controlled trial is required.

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