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SYSTEMATIC REVIEW

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Somatostatin or octreotide as treatment options for chylothorax in young children: a systematic review

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Abstract *Objective:* Chylothorax is a rare but life-threatening condition in children. To date, there is no commonly accepted treatment protocol. Somatostatin and octreotide have recently been used for treating chylothorax in children. We set out to summarise the evidence on the efficacy and safety of somatostatin and octreotide in treating young children with chylothorax. *Design:* Systematic review: literature search (Cochrane Library, EMBASE and PubMed databases) and literature hand search of peer reviewed articles on the use of somatostatin and octreotide in childhood chylothorax. *Patients:* Thirty-five children treated for primary or secondary chylothorax (10/somatostatin, 25/octreotide) were found. *Results:* Ten of the 35 children had been given somatostatin, as i.v. infusion at a median dose of 204 μg/kg/day, for a median duration of 9.5 days. The remaining 25 children had received octreotide, either as an i.v. infusion at a median dose of 68 μg/kg/day over a median 7 days, or s.c. at a median dose of 40 μg/kg/day and a median duration of 17 days. Side effects such as cutaneous flush, nausea, loose stools, transient hypothyroidism, elevated liver function tests and strangulation-ileus (in a child with asplenia syndrome) were reported for somatostatin; transient abdominal distension, temporary hyperglycaemia and necrotising enterocolitis (in a child with aortic coarctation) for octreotide. *Conclusions:* A positive treatment effect was evident for both somatostatin and octreotide in the majority of reports. Minor side effects have been reported, however caution should be exercised in patients with an increased risk of vascular compromise as to avoid serious side effects. Systematic clinical research is needed to establish treatment efficacy and to develop a safe treatment protocol.

Keywords Chylothorax · Infant · Somatostatin · Octreotide · Pleural effusion

Abbreviations *AVC:* atrioventricular canal · *CHD:* congenital heart disease · *GA:* gestational age · *i.v.:* intravenous · *NEC:* necrotising enterocolitis · *OCT:* octreotide · *POD:* postoperative day · *s.c.:* subcutaneous · *SST:* somatostatin · *TAPVC:* total anomalous pulmonary venous connection

Introduction

Chylothorax in children is a rare but life-threatening condition. It is defined as the accumulation of lymphatic fluid in the pleural space (triglyceride content > 1.1 mmol/l, total cell count > 1000 cells/ μl, lymphocyte predominance > 80%) [1]. Primary chylothorax (< 10% of all chylothoraces) occurs either congenitally, in association with chro-

mosomal abnormalities [2] or as spontaneous chylothorax [3]. Secondary chylothorax may result from the disruption of the lymphatic system due to trauma, cardio-thoracic surgery obstruction or raised pressure in the superior vena cava [1, 2, 3, 4, 5, 6, 7]. The incidence of chylothorax in infants and children following surgery has been reported as 2.5% [5].

The clinical course of chylothorax is usually prolonged, with several weeks of significant thoracic effusions. Most cases require intermittent or semi-permanent drainage by repeated thoracocentesis or thoracostomy drains [4, 5, 8, 9]. Respiratory failure due to lung compression, hypoproteinaemia and cachexia from excessive protein and lipid loss, as well as nosocomial infections due to hypogammaglobulinaemia and lymphopenia complicate the clinical course and prolong the treatment [4, 5, 8, 10, 11, 12, 13]. There is no standard regime for treating chylothorax. Medical therapy includes pharmacologic agents [4], dietary modifications such as total parenteral nutrition (TPN), or medium-chain triglycerides (MCT) [4, 14, 15, 16], replacement of protein and immunoglobulins [4, 17], infection control [4] and pleurodesis [18]. Surgical treatment, like the ligation of the thoracic duct, is associated with a high failure rate [19]. As an addition to the current therapeutic options, somatostatin [20] (SST) and its synthetic analogue octreotide [21] (OCT) have recently been successfully used for treating patients with chylothorax.

The aim of this review was to assess the efficacy and safety of both SST and OCT in the treatment of primary and secondary chylothorax in infants and young children in the context of the current literature.

Methods

Selection of studies and levels of evidence

We systematically reviewed the peer reviewed literature by searching the Cochrane Library [22], EMBASE [23] and PubMed [24] databases. For PubMed, we defined limits for age: 0–18 years. Search terms included chylothorax, somatostatin, octreotide, pa(e)diatric, child, neonate, treatment, side effect and adverse event. Further reports were found through cross-reading and personal communication. Efforts were made to translate non-English papers. If a report could not be ordered through our library, attempts were made to contact the authors. The available reports were independently read by two reviewers, both paediatricians (C.C.R. and A.J.) and classified according to the levels of evidence published by the UK Centre of Evidence-based Medicine [25]. The format of the review was structured according to the MOOSE guidelines (Meta-analysis Of Observational Studies in Epidemiology) [26].

Results

Studies identified

The literature search was performed between December 2003 and August 2005, the last extensive search being conducted on 18 August 2005. Searching the Cochrane Library database, no reviews or registered clinical trials on the medical treatment of chylothorax in children were found. Systematic literature search of PubMed and EMBASE retrieved no controlled trials. In total, 25 publications, describing 35 cases of chylothorax treated with either SST (5 reports on 10 children) [20, 27, 28, 29, 30] or OCT (20 reports on 25 children) [21, 32–50] were retrieved. A Spanish article was translated into German [41]; another article [51] could not be obtained through our library service. In this latter article, no subject age had been stated in the abstract; however, attempts to contact the author failed.

Current evidence

All cases were either reported as single case reports (less than level 4 evidence) or case series (level 4 evidence). No controlled clinical trial on the use of SST or OCT on patients with chylothorax was found.

Diagnosis and treatment regimes

Secondary chylothorax due to cardio-thoracic surgery was by far the most common diagnosis ($n = 26$; age range 19 days to 4 years). Primary chylothorax was less often reported ($n = 9$; 6 congenital, 3 spontaneous; age range 22 days to 3.5 months) (Tables 1, 2). SST was employed for treating cases of postoperative chylothorax only, whereas OCT was used for postoperative, congenital and spontaneous chylothorax. Cases of congenital or spontaneous chylothorax were treated solely with OCT.

Marked variations were found regarding the therapeutic regimes: SST was given either as continuous i.v. infusion or as i.v. bolus. Octreotide, despite its much longer half-life, was also predominantly given as continuous i.v. infusion, but also as i.v. bolus or s.c. SST was given as i.v. infusion at a median dose of 204 μg/kg/day (range 10–288 μg/kg/day) for a median duration of 9.5 (range 3–15 days). Octreotide was given either as i.v. infusion at a median dose of 68 μg/kg/day (range 7.2–240 μg/kg/day) over a median 7 days (range 3–34 days) or subcutaneously at a median dose of 40 μg/kg/day (range 2–68 μg/kg/day) and a median duration of 17 days (range 8–43 days) (Tables 1, 2).

Table 1 Reports on children with chylothorax treated with octreotide

Citation	*n*	Study group details	Cause	Age treatment commenced	Duration of treatment (days)	Maximum Dose (μg/kg/day)	Route	Treatment effect	Complications
Maayan-Metzger et al. 2005	1	Preterm infant	Congenital	Day 33	10	60	i.v.	Resolution within 48 h. after initiation of OCT	Transient hypothyroidism
Roehr et al. 2005	1	Preterm infant	Congenital	Day 53	21	40	s.c.	Resolution of chylothorax	None
Mohseni-Bod et al. 2004	1	Term infant with aortic coarctation	Postoperative	POD 16	3	96	i.v.	Prompt resolution with initiation of OCT administration	Onset of NEC while on OCT
Hamdan et al. 2004	1	Three-month-old with congenital cyanotic heart disease	Postoperative	POD 28	21	48	i.v.	Resolution under OCT, reaccumulation 10 days after discontinuing OCT.	None
Tibballs et al. 2004	1	GA 36 weeks, congenital heart , disease (TAPVC) lymphangiectasia	Postoperative	POD 8	4	120	i.v.	Resolution of chylothorax	None
Lam et al. 2001	1	Two months, interrupted aortic arch, cardiac surgery	Postoperative	POD 5	7	100	i.v.	Resolution of chylothorax within 5 days	None
Al-Zubairy et al. 2003	1	Five months, Down syndrome, AVC, cardiac surgery	Postoperative	POD 5	4	84	i.v.	Prompt reduction of chyle drainage, no recurrence at 1 year follow-up	None
Goyal et al. 2003	1	GA 41 weeks, congenital diaphragmatic hernia	Postoperative	POD 16	9	10	TDS s.c.	Chyle drainage stopped on 2nd day of treatment, no recurrence	None
Aleo Lujan et al. 2003	1	Three years, Down syndrome, AVC, cardiac surgery	Postoperative	POD 22	61	68	i.v. and s.c.	No obvious effect. Thoracic duct ligation prior to treatment without effect; starting dose 4 μg/kg/day s.c. for 8 days, changed to 24 μg/kg/day IV for 34 days	None
Au et al. 2003	1	GA 36 weeks, gastroschisis, karyotype 46, XY	Postoperative	POD 33	7	84	i.v.	Resolution of chylothorax within 5 days	None
Lauterbach et al. 2004	1	GA 24 weeks	Spontaneous	Day 103	4	7.2	i.v.	Resolution of chylothorax, no recurrence at 1 year follow-up	None
Coulter et al. 2004	1	GA 26 weeks	Spontaneous	Day 103	42 days	4 μg/kg/day s.c. and 24 μg/kg/day i.v.	1st i.v., then s.c.	Resolution of chylothorax over first 6 days of treatment	None

Table 1 Continued

Citation	*n*	Study group details	Cause	Age treatment commenced	Duration of treatment (days)	Maximum Dose (μg/kg/day)	Route	Treatment effect	Complications
Goto et al. 2003	1	GA 26 weeks	Spontaneous	Day 36	3	7.2	i.v.	Resolution of chylothorax on day 2 of treatment	None
Rasiah et al. 2004	1	GA 34 weeks, hydrops fetalis, normal chromosomes	Congenital	Day 32	10	240	i.v.	Prompt respiratory improvement on commencement of OCT. Thoracic effusions cleared within 10 days of treatment	Transient abdominal distension
Sivasli et al. 2004	1	GA 34 weeks, dysmorphic features, karyotype 46, XY	Congenital	Day 22	10	84	i.v.	Resolution of chylothorax after 3 days of treatment	None
Young et al. 2004	1	GA 40 weeks, dysmorphic features, normal karyotype	Congenital	Day 2	17	70	via s.c. port	No obvious effect. Chyle still aspirated after discontinuation of treatment	None
Ottinger et al. 2002	1	Twelve-year-old male	Lymphoma	Age 12	11	8,4	i.v.	Resolution of chylothorax	Hypoglycaemia, resolved after dose reduction
Rosti et al. 2002 (case series)	2	No details provided other than cardiac surgery	Postoperative	Not mentioned	7	24	i.v.	Resolution of chylothorax	None
Cheung et al. 2001, 2002 (case series)	2	Three months TGA Fifteen months TOF	Postoperative	POD 37 POD 47	26 16	40 20	Both TDS s.c.	Prolonged resolution	None
Pratap U et al. 2001, 2002 (case series)	4	Three years AVSD Two years AVSD Four years TGA Three years TOF	Postoperative	POD 33 POD 26 POD 6 POD 5	5 8 9 8	48 96 96 24	i.v.	Resolution of chylothorax, no reoccurrence	None

Table 2 Reports on children with chylothorax treated with somatostatin

Citation	*n*	Study group details	Cause of chylothorax	Age treatment commenced	Duration of treatment (days)	Maximum Dose (μg/kg/day)	Route	Treatment effect	Complications
Clarke et al. 2005	1	GA 31 weeks	Postoperative	POD 12	14	84	i.v.	Prompt resolution of chylothorax	None
Matsuo et al. 2003	1	Term infant, CHD and asplenia-syndrome	Postoperative	18 months POD 22	5	10	i.v. bolus BD	Chest tube drainage decreased within 3 days of treatment	Strangulation-ileus 6 days after initiation of SST treatment
Rimensberger et al. 1998	1	Four months, TGA, cardiac surgery	Postoperative	POD 17	14	168	i.v.	Resolution of chylous drainage under increasing doses,no recurrence	None
Pettit et al. 2002 (case series)	3	GA 37 weeks, hypoplastic left heart syndrome, cardiac surgery	Postoperative	POD 34	3	51	BD i.v.	Drainage from chest tube stopped within 3 days of therapy	Transient cutaneous flush
		No further details (patients 2, 3)		Not further described	3	No details given	No details given	Treatment electively stopped	Treatment withdrawn because of vomiting, elevated liver function tests and flu-like symptoms
Buettiker. et al. 2001 (case series)	4	Three months TGA	Postoperative	POD 34	9	240	i.v.	Chylothorax ceased under therapy in patients 1, 2 and 4 Patient 3: no response to therapy and died from cardiac failure, still having chylothorax	No side effects
		Fifteen months TOF		POD 17	14	240	i.v.		Died from underlying disease
		7 week AVSD		POD 14	10	288	i.v.		Died from cardiac failure
		Term TAPVC		POD 32	15	240	i.v.		Loose stools reported in one patient

Treatment effect

Treatment effect was evident after 5–6 days of treatment, irrespective of the level of treatment, in all OCT patients and all but one patient treated with SST [30]. For OCT, three children were reported to have had a prolonged period of OCT treatment (17–61 days) [21, 41, 46]; in one of these, chyle was still aspirated after discontinuation of OCT [41]. Chylous effusions reoccurred after discontinuation of the initial course of OCT treatment in three patients [34, 46, 50] (Table 1). One patient did not respond to SST despite 14 days of treatment [30]. For OCT, s.c. administration was associated with a prolonged treatment time. No association was seen for either drug regarding the treatment effect when analysed for dosage, duration of treatment, or cause of chylothorax.

Side effects

Minor side effects such as flu-like symptoms, cutaneous flushing, nausea, loose stools, transient abdominal distension, elevated liver function tests, transient hypothyroidism and hyperglycaemia were reported for both SST and OCT. Of the ten cases treated with SST, four were reported as having potentially serious side effects: Matsuo and co-workers report a case of strangulation-ileus in a neonate with asplenia syndrome, treated with SST for postoperative chylothorax [28]. Pettitt et al. report on two patients with cutaneous flush who also had elevated liver function tests and flu-like symptoms under treatment with SST, leading to the discontinuation of therapy [29]. The majority of children had been treated with OCT; however, fewer side effects were reported for this substance: transient changes in blood glucose levels, transient abdominal distension and emesis were associated with OCT treatment [28, 46]. However, Mohseni-Bod et al. [33] recently reported on a neonate with coarctation of the aorta, who developed NEC on postoperative day 16, whilst on OCT (Table 1).

There was no discernable relationship between dosage or duration of treatment. However, for both substances, the severe side effects observed were seen in patients with a particular vulnerability to vascular insults (asplenia syndrome and aortic coarctation).

Discussion

Chylothorax is a rare but serious and potentially life-threatening condition for children. Over 50% of chylothoraces occur in the neonatal period and are thus considered to be the most common cause of neonatal thoracic fluid collections [5, 10]. Despite this, there is no agreement on an optimal treatment. The primary aim is to stop any thoracic lymph flow and to allow the thoracic duct to heal naturally. The first-line treatment therefore consists of enteric rest with TPN or MCT diet, which may require months of conservative intensive care treatment [8, 52].

The advent of SST/OCT in the treatment of chylothorax promises a potent and effective therapy for chylous pleural effusions [52]. SST is a polypeptide with mainly inhibitory actions on the release of various hormones, for example growth hormone (GH) and insulin, and lymph fluid excretion [53, 54]. In the gut, SST is known to reduce both the splanchnic blood flow and the intestinal secretion of electrolytes and water [53]. Evidence from experimental studies further shows a marked decrease in thoracic lymph flow after administration of SST [31]. In children, it has been used for treating secretory diarrhoea, hypoglycaemia in congenital hyperinsulinism syndrome, and acromegaly [54]. SST was first used for treating infantile chylothorax by Rimensberger and co-workers in 1998 [20]. OCT is a synthetic SST analogue with anti-secretory properties similar to those of SST [53]. In experimental studies, the release of growth hormone and glucagon, respectively, was inhibited 45 and 11 times more effectively than with SST [53]. OCT has the advantage of a much longer half-life (2–6 h) than SST and can be given as s.c. injections [53]. In paediatric medicine, OCT has been employed for similar situations as SST and recently also for treating chylothorax [54]. Acclaimed positive attributes of SST and OCT therapy include a shorter duration of intensive care treatment, a reduction of recurrent thoracocentesis, and fewer fluid and plasma infusions, thereby reducing the risk of infection. Children under OCT therapy were successfully maintained on full fat oral nutrition [32, 34]. Lam and co-workers estimated the cost of therapy with OCT for a standard-size adult at approximately $ 50/day [36]. Given the poor outcome of surgical interventions in children, and when compared with the long-term hospitalisation due to conservative management, medical treatment with SST or OCT may prove to be cost effective.

The current level of evidence for treating young children with chylothorax using SST or OCT is no greater than level 4. Uncontrolled observational reports are always prone to bias towards the treatment effect. In the case of chylothorax, reports of a prolonged treatment period with SST or OCT may have confused treatment effect with the natural history of the disease, where spontaneous closure of the defective thoracic duct usually occurs between 3 weeks and 3 months [8]. Given the relative uncertainty of the duration of chylothorax, the results of any intervention initiated to shorten the disease process need to be interpreted with caution. In the majority of the published reports, treatment effect was evident within 5–6 days of treatment, and was often objectively measured by a significant decrease of the chylous drainage. These findings are in accordance with Markham's experimental studies [31]. However, from the majority of reports, it is not clear which other concomitant forms of treat-

Table 3 Reported side effects of somatostatin and octreotide in children

Organ system	Clinical symptoms
Cardiovascular	Bradycardia, Pulmonary hypertension
Pulmonary	Hypoxemia,
CNS	Headache, Infarction, Cavernous sinus syndrome, Dizziness
Gastrointestinal	Abdominal pain, Nausea, Diarrhoea, Loss of appetite Ileus, Cholelithiasis, Intestinal perforation Necrotising enterocolitis
Endocrine / metabolic	Glucose intolerance (hyper- and hypoglycaemia) Growth retardation, Weight loss, Hypothyroidism
Skin	Injection site pain

ment have been employed while treating with SST or OCT.

For both SST and OCT, we found considerable variations in dosing regimes and modes of drug delivery. Variations in effect between the substances could be explained by their different anti-secretory potency, which is mediated through different effector systems, different SST-receptor distribution in the end-organ system or by the more than 20-fold discrepancy between different dosage regimes used for SST [53]. The route of administration and duration of treatment may also contribute to the effectiveness of treatment, which would also be influenced by the underlying cause and the extent of the thoracic duct leak.

There is only limited experience with either drug in paediatric patients. The safety profile of SST and OCT has only been investigated in a few small clinical trials, and little is known about the long-term treatment sequelae [55]. SST and OCT influence the endocrine system (GH, thyrotropin, insulin and other gastrointestinal peptide hormones). Administration of OCT and SST diminishes the spontaneous secretion of GH, but normal growth has been reported in 51 long-term-treated patients with hyperinsulinism of infancy. The authors found mainly mild and transient gastrointestinal symptoms (vomiting, abdominal distension, steatorrhoea) after the start of therapy, and asymptomatic gallstones in one patient after 1 year of treatment [55]. Arevalo et al. report on OCT-induced hypoxemia and pulmonary hypertension in two premature neonates treated with OCT to enhance resolution of enterocutaneous fistula following NEC [57]. Radetti reports on a newborn treated with OCT for congenital hyperinsulinism who developed cholelithiasis under treatment [58] (Table 3).

In conclusion, growing evidence from uncontrolled case studies suggests a markedly positive treatment effect of SST and in particular OCT in young children with primary and secondary chylothorax. Side effects were predominantly minor and transient, but caution should be exercised in patients with an increased risk of vascular compromise. When treating with OCT or SST, regular monitoring of liver function, blood glucose and thyroid parameters is advisable. In the absence of controlled clinical trials using SST or OCT, the first-line treatment for paediatric chylothorax should include TPN or MCT diet, fluid replacement therapy and infection control. In refractory cases, treatment with OCT and SST should be considered.

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