Use of Octeriotide in the Management of Neonatal Chylothorax Secondary to Repair of Congenital Diaphragmatic Hernia: A Report of Two Cases and Review of Literature

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ABSTRACT

Chylothorax, a known complication of surgery for Congenital Diaphragmatic hernia, can sometimes be resistant to treat. Octeriotide (Somatostatin analogue) can be useful in this situation. However, the dose and schedule of Octeriotide therapy in neonates is not well established. We report two cases of resistant chylothorax following surgery for congenital diaphragmatic hernia which were successfully managed by using an escalating infusion of octeriotide. The literature on the subject is also reviewed.

Key words:
Chylothorax, congenital diaphragmatic hernia, octeriotide

INTRODUCTION

Chylothorax is a known complication of surgery for congenital diaphragmatic hernia. It is usually the result of leakage from the thoracic duct or one of its main draining lymphatic vessels.[1] The most common causes of chylothorax in children are lymphoma and trauma caused by thoracic surgery. The effusion can be identified by its white and milky appearance which is due to its high levels of triglycerides and lymphocytes. Postoperative chylothorax occurs in less than 1% of thoracic procedures with a prevalence ranging from 0.5% to 2%. Postoperative chylothorax is a serious complication with a high mortality, which can approach 50% in untreated patients. It causes nutritional deficiencies, respiratory dysfunction, dehydration, immunosuppression, and increased vulnerability to infections.[1] The initial management consists of indwelling pleural drainage and feeding with a milk formula rich in medium chain triglyceride (MCT) along with total parenteral nutrition if required. In resistant cases, ligation of thoracic duct or placement of pleuroperitoneal shunts may be considered.[2]

Somatostatin, or its analog octeriotide, has recently been used with success in a number of pediatric cases of postoperative and iatrogenic chylothorax.[1] In pediatric patients the reported effective doses of intravenous Somatostatin ranges from 3.5 to 12 mcg/kg/h[1]. However, the dose and regimen in newborn babies are not well established. We report two cases of successful management of postoperative chylothorax, following surgery for congenital diaphragmatic hernia, both in full-term newborn babies, using an escalating regimen of octeriotide infusion. A review of the literature on the subject is also presented.

CASE REPORTS

Case 1

A term female 3.5-kg infant, diagnosed with left diaphragmatic hernia on antenatal ultrasound scan done at 19 week of gestation, was born by spontaneous vaginal delivery in a very good condition. She was electively intubated and stabilized for surgical repair of diaphragmatic hernia which was done uneventfully on third day of life [Figures 1 and 2]. During surgery left diaphragm was found to be very vascular, which is a known risk factor for postoperative chylothorax. There were no other associated congenital anomalies. The 2-D echocardiography did not show any evidence of persistent pulmonary hypertension. She developed left pleural effusion on third postoperative

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Access this article online	
Quick Response Code:	Website: www.jcnonweb.com
	DOI: 10.4103/2249-4847.96767

day requiring ongoing ventilation and an indwelling chest drain. The amount of fluid drained was high (130 ml/day). The initial pleural fluid was serosanguinous with a protein content of 26 g/dl and normal triglyceride level (during this time the baby was only on TPN with no oral feeds). The oral feeds were gradually built up over the next 8 days. By the age of 13 days the pleural fluid developed classic consistency of Chylothorax: milky appearance with high lymphocyte and triglyceride (Protein 28 g/dl and WBC 8000 with 98% lymphocyte). The condition was initially managed with enteral feeding with medium chain triglyceride formula (Monogen) and total parenteral nutrition. There was no reduction in the amount of chylothorax drainage over a period of 1 week (day 20 of life) [Figure 3]. On day 21 of life Intravenous octeriotide infusion was started at a dose of 3 mcg/kg/hr. The enteral feeds were stopped because of reports of high risk of necrotizing enterocolitis with Octeriotide infusion. The TPN without any intralipids was continued. The patient was also supported by fresh frozen plasma; albumin and intravenous immunoglobulin. The dose of Octeriotide was gradually increased by 1 mcg/kg/hr everyday till we reached a dose of 9 mcg/kg/hour after 8 days. There was a sudden drop in the chylothorax output once the dose Octeriotide dose reached 9 mcg/kg/hr. The infusion was maintained at the same level (9 mcg/kg/hr) for 11 days. During this period, the chyle drainage per 24 hours reduced gradually to a minimal amount with significant response noted 2 days after reaching 216 mcg/kg/day (9 mcg/kg/hr). The infant was extubated successfully to nasal cannula and then to room air within 3 days after administration of octeriotide infusion (day 20 postsurgical repair). The enteral feeding was resumed with a medium chain trigyceride formula (Monogen). This resulted in transient increase in chylothorax drain which resolved spontaneously [Figure 4]. The octeriotide infusion was weaned over 5 days by decreasing the dose at a rate of 2 mcg/kg/hr everyday till the infusion was discontinued. During octeriotide therapy the baby was monitored closely, on daily basis, for any evidence of glucose intolerance, liver and renal impairment. No side effects were noted.

The infant was discharged home self-ventilating in room air after 1 week on Monogen formula. Medium chain triglyceride (MCT) oil and oral polycose were added to the feed to increase her caloric intake and promote weight gain. On postdischarge follow-up in neonatal and dietetic clinics she had symptomatic of massive gastroesophageal reflux which required antireflux medication.

Case 2

A term male 3.5 kg infant was born by spontaneous vaginal delivery in a good condition. He developed respiratory distress soon after birth requiring intubation and ventilation. The chest X-ray confirmed left diaphragmatic hernia. There were no other associated congenital anomalies. The surgery for diaphragmatic hernia was done uneventfully on second day of life. The chest drain placed during surgery-drained blood-stained fluid which decreased gradually and chest

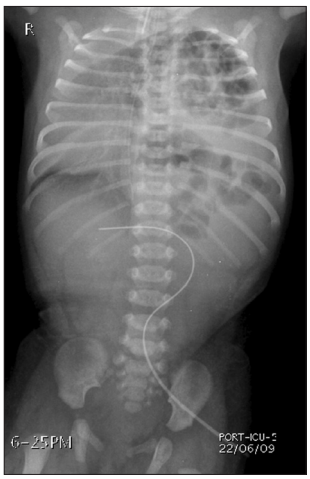

Figure 1: Left diaphragmatic hernia before surgery

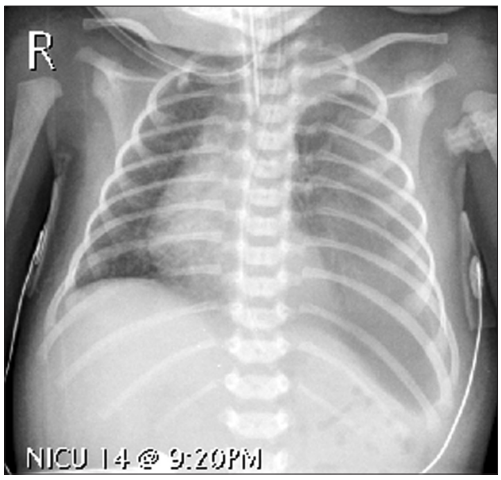

Figure 2: Chest X-ray of our patient immediately after surgery

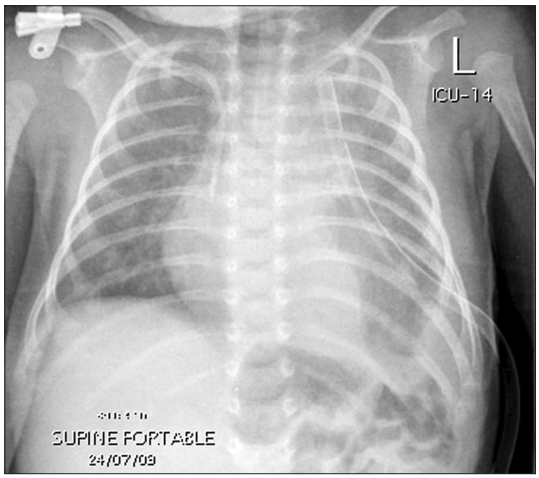

Figure 3: Left chylothorax with chest tube drainage

tube was removed on 7th post-op day. The baby was extubated to room air the same day. Oral feeding with breast milk was started on 9th post-op day. The next day baby developed respiratory distress requiring reintubation and ventilation. The chest X-ray confirmed left pleural effusion. A new chest drain was placed in. The amount of fluid drained was high (95 ml/day). The initial pleural fluid was serosanguinous with a protein of 26 g/dl and normal triglyceride level. During this time the baby was only on TPN with expressed breast milk feeds. Over the next few days the contents became typical of chylothorax with triglyceride level of 4 mmol/l and lymphocytes count of >91%. Management with formula feed containing medium chain triglycerides (Monogen) and total parenteral nutrition did not reduce the amount of chylothorax drainage. Octeriotide infusion was started at 2 mcg/kg/hr and increased gradually by 1 mcg/kg/hr everyday till we reached 10 mcg/kg/hr on post-op day 24 [Figure 5]. A dramatic response in terms of reduction of pleural drainage was noted once a dose of 10 mcg/kg/hr was reached. The baby was extubated successfully to nasal cannula and then room air within 3 days. The octeriotide infusion was kept at the same dose (10 mcg/kg/hr) for 5 days and then gradually reduced at a rate of 2 mcg/kg/hr every day over the next 5 days. Within three days the baby was discharged home self-ventilating in room air and on full enteral feeding with Monogen formula. During the phase of high pleural drainage the baby was also supported with i.v. immunoglobulin and albumin infusions. During octeriotide therapy the baby was monitored closely for any evidence of glucose intolerance, liver and renal impairment. No side effects were noted.

DISCUSSION

Chylothorax may occur spontaneously in the neonatal population e.g., due to abnormal congenital lymphatic malformations or in the postoperative setting after thoracic duct injury or disruption of lymphatic channels. The incidence of chylothorax following surgery for congenital diaphragmatic hernia ranges from 7 to 28%[3,4]. The

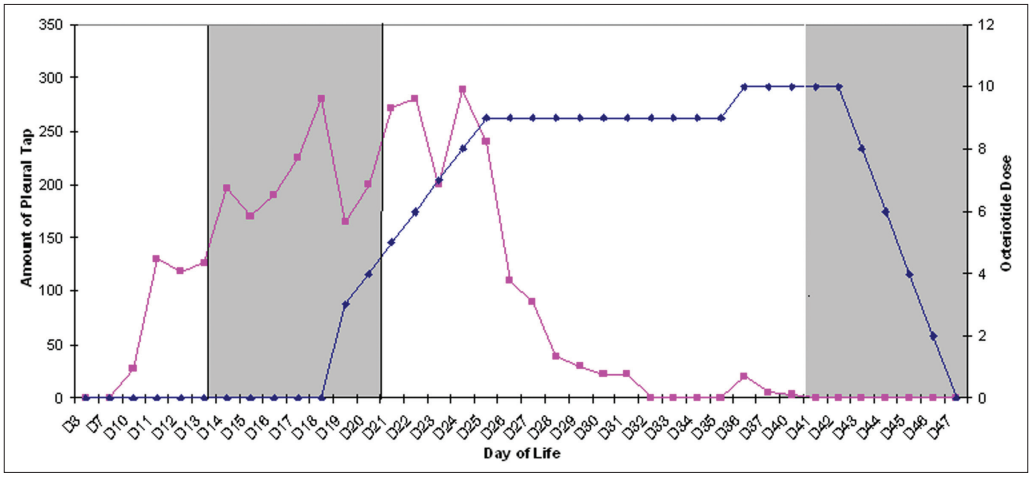

Figure 4: Chylothorax drainage (pink line), octeriotide dose mcg/kg/hr (blue line), gray zone reflect days of enteral feed, white zone reflects days of exclusive TPN with no oral feeds

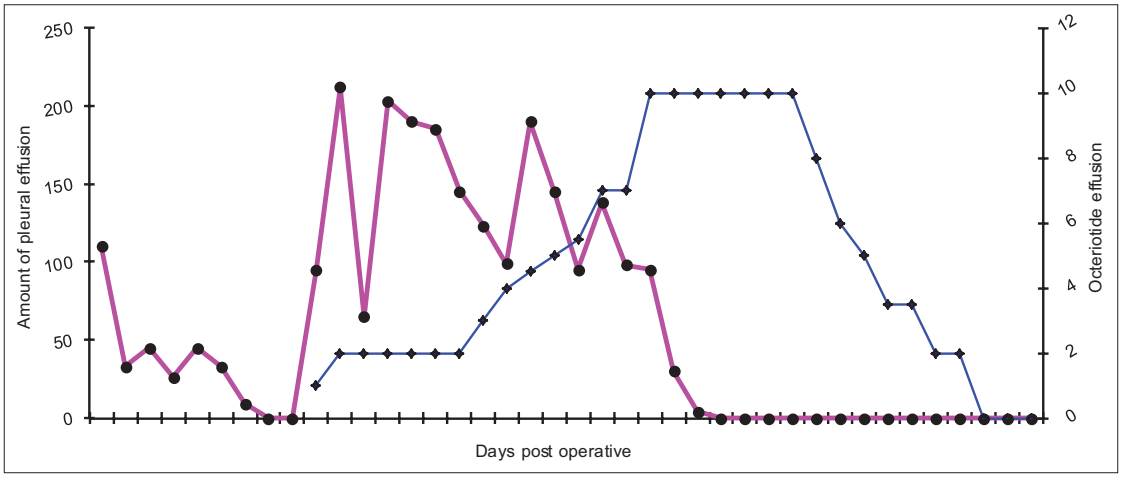

Figure 5: Second patient chylothorax drainage (pink line), octeriotide dose mcg/kg/hr (blue line)

excessive chyle drainage results in nutritional, electrolyte and immunological disturbances. This contributes significantly to the mortality and morbidity due to congenital diaphragmatic hernia.[3,4]

A number of therapeutic interventions have been used to reduce chyle production and promote resolution of chylothorax. Initial management typically includes restriction or temporary cessation of enteral feedings. Milk feeds, high in medium-chain triglycerides (MCT), or parenteral nutrition may be used. MCT is transported directly into the portal system, bypassing the lymphatic pathways, thus diminishing lymphatic flow through the thoracic duct. These strategies alone are not successful in all patients. MCT formulas have been shown to produce resolution of chylothorax in approximately one-third of patients after two weeks, while parenteral nutrition typically results in resolution in 75-80% of cases by that time. In resistant cases, pleurodesis, ligation of thoracic duct, or placement of drains and pleuroperitoneal shunts may be considered.[5,6] However, the failure rate with these options is high and only pleurodesis works in severe cases. Recently, octreotide has emerged as an alternative option for management of patients with chylothorax resistant to conventional therapies. Octeriotide is a long-acting synthetic analog of endogenous somatostatin. Like somatostatin, it is a potent inhibitor of growth hormone, glucagon, insulin and thyroid stimulating hormone. As compared to somatostatin, octeriotide has superior selectivity and longer half-life.[7,8]

Octeriotide acts directly on vascular somatostatin receptors and minimizes lymph fluid excretion. Moreover, by increasing splanchnic arteriolar resistance and decreasing gastrointestinal blood flow, octeriotide indirectly reduces lymphatic duct flow.[7] Some authors have mentioned another mechanism: octeriotide blocks pancreatic and biliary secretion by inhibition of serotonin and other gastrointestinal peptides.[7] Potential adverse effects of octeriotide therapy are bradycardia, stomachache, headache, hypo or hyperglycemia, hypothyroidism, nausea and vomiting.[9] One published report mentions an association between the use of octeriotide and necrotizing enterocolitis in a baby who had postoperative chylothorax.[10] None of these complications occurred in any of our two patients.

The manufacturer does not recommend mixing octreotide and parenteral nutrition solutions. Although infusions of octreotide appear physically stable when mixed with parenteral nutrition solutions, the mixture may result in the formation of a glycosyl octreotide conjugate, resulting in reduced efficacy. Simultaneous Y-site administration is acceptable.[11] Combined TPN and octeriotide increase the speed of chylothorax resolution in children and avoid later surgical intervention, which can have up to 10% perioperative mortality rate.

Octeriotide therapy is relatively safe. It is almost always used as a second line therapy following failure of initial management with no oral feeds, TPN and or MCT feeds. There is significant heterogeneity in dosing regimens, therapeutic duration, and time to start Octeriotide. Most authors began treatment with a lower dose and progressively raised it to achieve a response. The exact maximum dose

Table 1: Previously published studies on the use of Octeriotide in Postoperative Chylothorax following repair of diaphragmatic hernia

Reference	No. of cases	Chylothorax started on (days post op)	TRT started (days post op)	Duration of TRT	Max. dose (mcg/kg/d)	TRT effect	Complication
Moreira –Pinto *et al.* (2010)	2	8	14	24	240	Resolution on day 11	None
		2	4	20	192	Resolution on day 12	None
Hung *et al.*	1	First few days	8	5	24	Resolution in the 2nd day	None
Gonzalez *et al.*	6	Unclear	Unclear	Unclear	96	No effect	One died from sepsis during TRT
Copons Fernandez	8	2-7	Unclear	Unclear	12 in 2 cases 36 → the others	4 resolved 4 failed	None
Gonzalez Santacruz *et al.*	2	Unclear	Unclear	8	84	Resolution on day 8	None
		Unclear	Unclear	10	144	Resolution on day 10	None
Goyal *et al.* (2003)	1	7	16	9	10	Resolution on 2nd day	None
Our first case	1	7	17	23	10 mcg/ kg/hr	Resolution on day 17 (2 days after reaching max dose)	None
Second case	1	10	12	25	10 mcg/kg/hr	Resolution on day 8 (2 days after reaching max dose)	None

at which significant reduction of chylous drainage can be achieved has been variable. In our two cases, we started octeriotide infusion at a rate of 2 mcg/kg/hr which was gradually increased by 1 mcg/kg/hr every day till we reached a maximum dose of 10 mcg/kg/hr. After being at this dose for 48 hours, we observed a dramatic reduction of chylous drainage which kept on decreasing gradually over the next few days. Similarly there is no established protocol for weaning the octeriotide infusion once chylothorax has resolved. In our two cases we weaned octeriotide by reducing the infusion at a rate 2 mcg/kg/hr every day. This gradual weaning process took a minimum of 5 days. We did not observe any side effects of this weaning regime. There was no recurrence of chylothorax once octeriotide was stopped.

We reviewed the literature to find out the most effective dose or regimen of octeriotide infusion in the management of chylothorax following repair of congenital diaphragmatic hernia.[12] The results, as expected, were very variable. Based on these studies we constructed Table 1 which shows a summary of therapeutic regimens of Octeriotide in postoperative chylothorax following surgery for congenital diaphragmatic hernia. The table also includes our two cases being reported in this article. Most of the published studies have used a dose ranging from 3.5 to 12 mcg/kg/hr continuous IV infusion. The chyle drainage was significantly reduced within 48-72 hours once a maximum dose was reached. The total duration of octeriotide therapy ranged from 1 to 3 weeks.

SUMMARY

Octeriotide is a relatively safe second line therapy in the management of chylothorax secondary to surgery for congenital diaphragmatic hernia. A trial of octeriotide therapy can prevent potential permanent surgical procedures like pleurodesis or pleuroperitoneal shunts.

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How to cite this article: Jarir RA, Rahman Su, Bassiouny IE. Use of octeriotide in the management of neonatal Chylothorax secondary to repair of congenital diaphragmatic hernia: A report of two cases and review of literature. J Clin Neonatol 2012;1:91-5.

Source of Support: Nil, **Conflict of Interest:** None declared.