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Title: Octreotide in the treatment of neonatal postoperative chylothorax: report of three cases and literature review.

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Abstract: Chylothorax is a well recognized complication after neonatal cardiothoracic surgery. Diagnosis is established by needle aspiration or at chest tube insertion. The "milky" pleural aspirate with raised triglycerides and predominance of lymphocytes confirms chylothorax. Although exact etiology of chylothorax following surgery remains unknown, various theories have been proposed, including disruption of lymphatics, injury to the thoracic duct, and back pressure phenomenon of the visceral lymphatics leading to small breaks in the thoracic duct. Management strategies include cessation of enteral feedings, repeated aspiration, chest drainage, and total parenteral nutrition. Ligation of the thoracic duct, pleurodesis of pleuroperitoneal shunting is reserved for refractory cases. Somatostatin and its analogue, octreotide, have been used in treating chylothorax after various cardiothoracic procedures with promising results. The authors present three cases of neonatal postoperative chylothorax in which octreotide was used.

Dear Sirs,

Thank you for your valuable comments on our article “Octreotide in the treatment of neonatal postoperative chylothorax: report of three cases and literature review” (PSI-D-10-00398). It is true that our manuscript does not add significantly to the existing literature. Even though it is the first review focusing on neonates submitted to surgical procedures.

We revised the manuscript according to your suggestions:

1. Figure legends were incomplete. We added the color code.
2. We added the titles in English for references 13, 14, 15, and 17.
3. We took the columns you suggested out.

We hope hearing from you soon.

Sincerely,

João Moreira-Pinto

(moreirapinto@gmail.com)

Title: Octreotide in the treatment of neonatal postoperative chylothorax: report of three cases and literature review.

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Abstract

Chylothorax is a well recognized complication after neonatal cardiothoracic surgery. Management strategies include cessation of enteral feedings, repeated aspiration, chest drainage, and total parenteral nutrition. Somatostatin and its analogue, octreotide, have been used with promising results. The authors present three cases of neonatal postoperative chylothorax in which octreotide was used. After literature review, we can say that octreotide is relatively safe, and may reduce clinical course and complications associated with neonatal postoperative chylothorax. One should be aware of possible association between octreotide and necrotizing enterocolitis. Prospective controlled trials supporting octreotide use are lacking.

Octreotide in the treatment of neonatal postoperative chylothorax: report of three cases and literature review.

Chylothorax is a well recognized complication after neonatal cardiothoracic surgery. Diagnosis is established by needle aspiration or at chest tube insertion. The "milky" pleural aspirate with raised triglycerides and predominance of lymphocytes confirms chylothorax. Although exact etiology of chylothorax following surgery remains unknown, various theories have been proposed, including disruption of lymphatics, injury to the thoracic duct, and back pressure phenomenon of the visceral lymphatics leading to small breaks in the thoracic duct.[1] Management strategies include cessation of enteral feedings, repeated aspiration, chest drainage, and total parenteral nutrition. Ligation of the thoracic duct, pleurodesis of pleuroperitoneal shunting is reserved for refractory cases.[2] Somatostatin and its analogue, octreotide, have been used in treating chylothorax after various cardiothoracic procedures with promising results. The authors present three cases of neonatal postoperative chylothorax in which octreotide was used.

Case Reports

Patient 1

A 36-week gestation, 2.46-kg girl was submitted to laparotomy for right diaphragmatic hernia repair in day two of life. On eighth postoperative day respiratory distress developed. Chest x-ray showed a moderate right pleural effusion. A 10F chest tube was inserted, draining 54ml of chylous and another 63 ml during the following 24h. Oral feeding was discontinued, and parenteral nutrition started. There was initial decrease in pleural drainage, but on 14th postoperative day there was considerable raise in thoracic tube output and octreotide infusion was started. We used initial dose of 2 µg/kg/h and progressively raised it to maximum dose of 10 µg/kg/h. Chylothorax resolved on 13th day of treatment and thoracic tube was removed (Figure 1.). On 33rd postoperative (day 19th of octreotide treatment), patient was extubated. Control chest x-ray revealed small pleural effusion that resolved in the following 48h without

need for aspiration. Tapering for octreotide was initiated on 22nd of treatment. No side effects of octreotide therapy were noted. Medium chain triglyceride (MCT) feeds were introduced on 24th day of treatment and maternal milk was initiated six days after that.

Patient 2

A 37-week gestation, 2.37-kg boy was submitted to laparotomy for left diaphragmatic hernia repair in day two of life. He also had bilateral undescended testis. On second postoperative day a moderate left pleural effusion was noted on chest x-ray. A 10F chest tube was inserted and fluid analysis revealed chylothorax. Enteral feeding had not been initiated yet. 24H drainage started at 60ml and rose to 218ml within three days (Figure 2.). On forth postoperative day we started 1 μg/kg/h octreotide infusion. Octreotide dose was progressively increased until maximum dose of 8 μg/kg/h, on 9th day. By that time, drainage suddenly decreased. MCT diet was introduced in that same day. Complete resolution of chylothorax was achieved on 12th day of treatment. No side effects were noted. Chest tube was removed and the patient was extubated. Regular milk formula was initiated thirteen days after that without pleural effusion recurrence.

Patient 3

A 37-week gestation, 3.02-kg boy was submitted to left thoracotomy for esophageal atresia type C repair on first day of life. He also had a small patent foramen ovale not requiring any intervention. On 11th postoperative day respiratory distress obliged reintubation. Chest x-ray revealed bilateral pleural effusion. 81Ml of chylous was aspirated on the right side. On 12th postoperative day another 14mL was aspirated and a chest tube was left in place (Figure 3.). Oral feeding had not been initiated yet. Octreotide was promptly initiated at a starting dose of 0.5 μg/kg/h and progressively increased until 10 μg/kg/h. There was temporarily decrease of thoracic output when maximum dose was achieved, but it started increasing by the 25th day of treatment. On 30th day of treatment pleurodesis was performed using povidone-iodine solution. Chylothorax resolved within six days. Thoracic tube was removed eight days after pleurodesis. Octreotide was stopped on the tenth day. The patient was extubated and started on regular milk formula.

Discussion

Chylothorax after neonatal surgery is usually a transient disorder that will resolve after a period of diminished flow through the thoracic lymphatics. Diminished lymphatic flow can be accomplished by minimizing chyle production, through the use of MCT diet, or (as is usually required) by the discontinuation of enteral feedings altogether. Conservative approach usually entails prolonged pleural drainage, mechanical ventilation, and total parental nutrition. Reported complications of such management include hypoproteinemia, coagulopathy, lymphopenia, hypogammaglobulinemia, line sepsis, and ventilator-associated ling injury. Surgical intervention is recommended if chylous drainage persists after 2-5 weeks of conservative management. Surgical options include thoracic duct ligation, pleuroperitoneal shunting, pleurectomy, or pleurodesis.[3] Pleurodesis is one way to obtain pleural adhesion, obliterating chylous leaks. Available agents include talc, bleomycin, tetracycline, OK-432, and povidone-iodine.[4,5]

The use of somatostatin to treat chylothorax was first reported in an adult in 1990[6] and in a neonate in 2001[7]. Octreotide is a synthetic somatostatin analog that has been used in the management of persistent hyperinsulinemic states, in newborn infants[8]. Somatostatin and octreotide cause mild vasoconstriction of splanchnic vessels and reduces gastric, pancreatic and intestinal secretions as well as intestinal absorption and hepatic venous flow, which collectively may act in concert to reduce chyle flow.[9] Reported side-effects include transient loose stools, nausea, flatulence, hypoglycemia and liver dysfunction. Two cases of necrotizing enterocolitis due to octreotide have been reported in neonates. The first case reported was a newborn with a chylothorax after gastroschisis correction.[10] The other case was a 22-day-old boy with refractory hypoglycemia. [11]

Since the first two cases of reported use of octreotide in postoperative neonatal chylothorax,[7] 26 other cases have been reported in the literature[1, 2, 3, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20] (Table 1). There is significant heterogeneity in dosing regimens, therapeutic durations, and time to star octreotide. All the authors used octreotide as second line treatment. Octreotide was initiated when total parenteral nutrition (TPN) or MCT feeds alone failed in resolving chylothorax. Days to

octreotide therapy initiation ranged from 4 to 31. Therapy duration ranged from 3 to 49 days. Intravenous infusion has been the most used mode of administration, although subcutaneous and intravenous bolus have been used. Intravenous infusion dosing ranged from 0.3 to 10 μg/kg/h (7-240 μg/kg/day). Most authors began treatment with a lower dose and progressively raised it, but the dose to elicit significant reduction in lymphorrhea was quite variable. There was no apparent consensus about how long therapy should be continued after chylothorax resolution. Tapering of octreotide was longer if chylous effusion recurred.

There is no consensus about enteral feeding while on octreotide therapy either. Most of patients were on TPN until resolution of chylothorax. Some were on MCT feeds from the beginning and other started them before finishing octreotide therapy. Reported side-effects included loose stools, transient rash, and the case of necrotizing enterocolitis reported earlier. Gonzalez et al.[1] reported that one of their patients died of sepsis while on octreotide therapy, but point of origin was not specified.

It is difficult to evaluate octreotide therapy success rate for neonatal chylothorax, especially those due to surgical intervention. Although most of initial reports presented cases where octreotide or somatostatin had been effective, some recent series of patients presented cases where pleurodesis or surgical procedure was needed to cease chylous drainage. On their series of chylothorax post-congenital diaphragmatic hernia repair, Gonzalez et al.[1] reported that none of their four patients on octreotide therapy had their thoracic tube output consistently reduced, despise a maximum dose of 96 μg/kg/day. Copons Férnandez et al.[14] presented a series of 22 neonatal chylothorax of different etiologies. In their series, five of 10 patients who did not respond to TPN were successfully treated with octreotide. Analyzing the postoperative chylothoraxes alone, there was a 50% success rate for a maximum dose of 36 μg/kg/day.

In our experience, two of three patients had their chylothorax resolved within 12 days after initiation of octreotide therapy. Both these patients had a sudden decrease on chylous output when maximum dose was achieved. The case requiring pleurodesis had a bilateral effusion and large amount of chylous drainage. Massive chylous leakage has been appointed as one of the reasons for octreotide failure in older children.[21]

Because there was some concern regarding chylothorax recurrence, octreotide therapy was maintained and even tapered upwards for some days. In either case, we cannot be sure what was the exact role of octreotide on chylothorax resolution or was it due to TPN and bowel rest alone.

Conclusion

Despite the significant heterogeneity of case reports published, one can say that octreotide is relatively safe, and may reduce clinical course and complications associated with neonatal postoperative chylothorax. The association between octreotide and necrotizing enterocolitis should be noted. Prospective controlled trials comparing various octreotide regimens and conventional therapy are needed.

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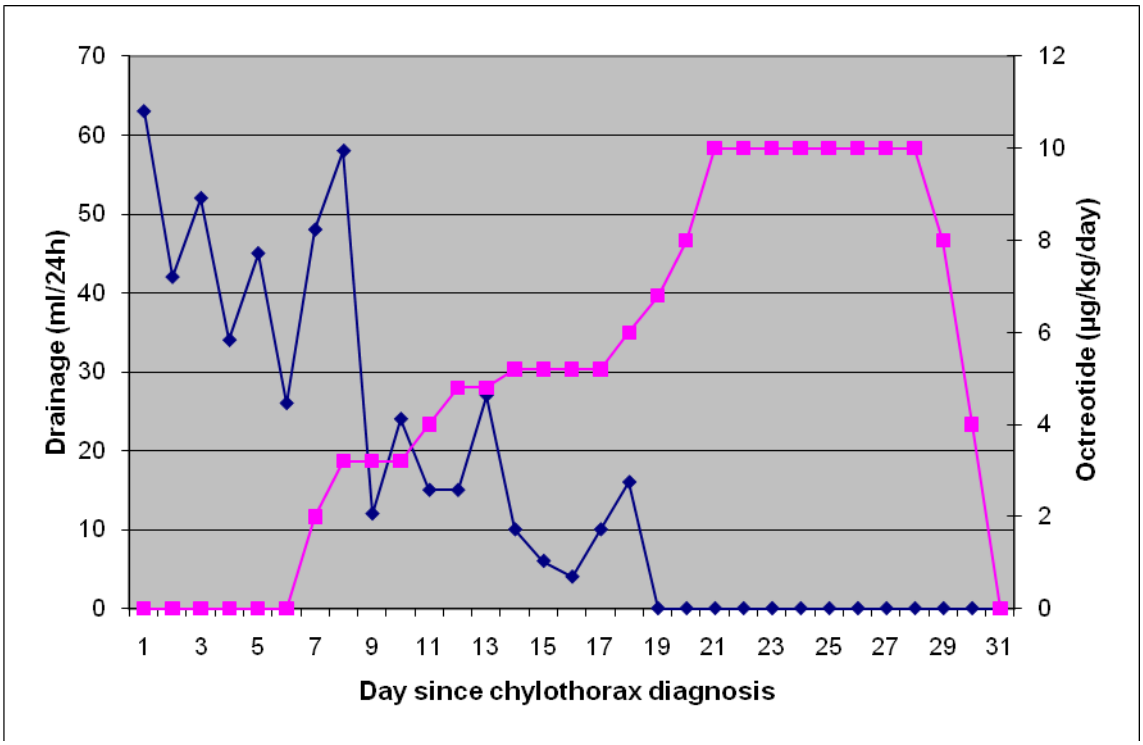

Figure 1 – Drainage of chylothorax (blue line) and octreotide (rose line) dosage in patient 1.

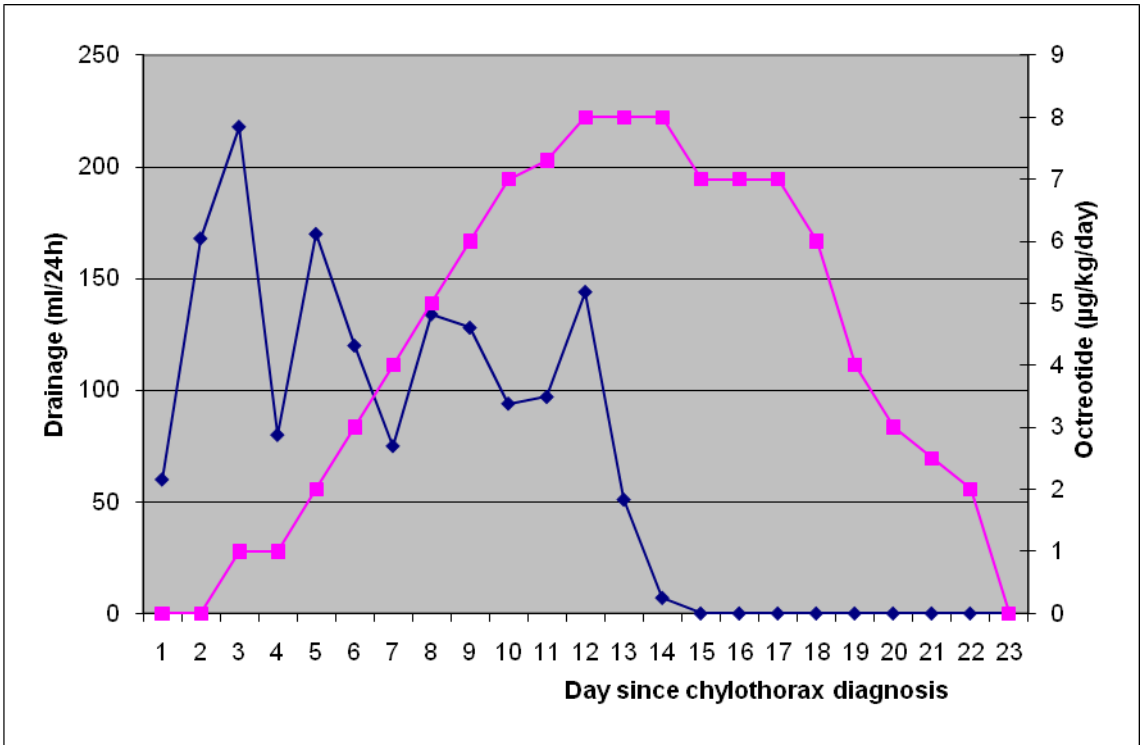

Figure 2 – Drainage of chylothorax (blue line) and octreotide dosage (rose line) in patient 2.

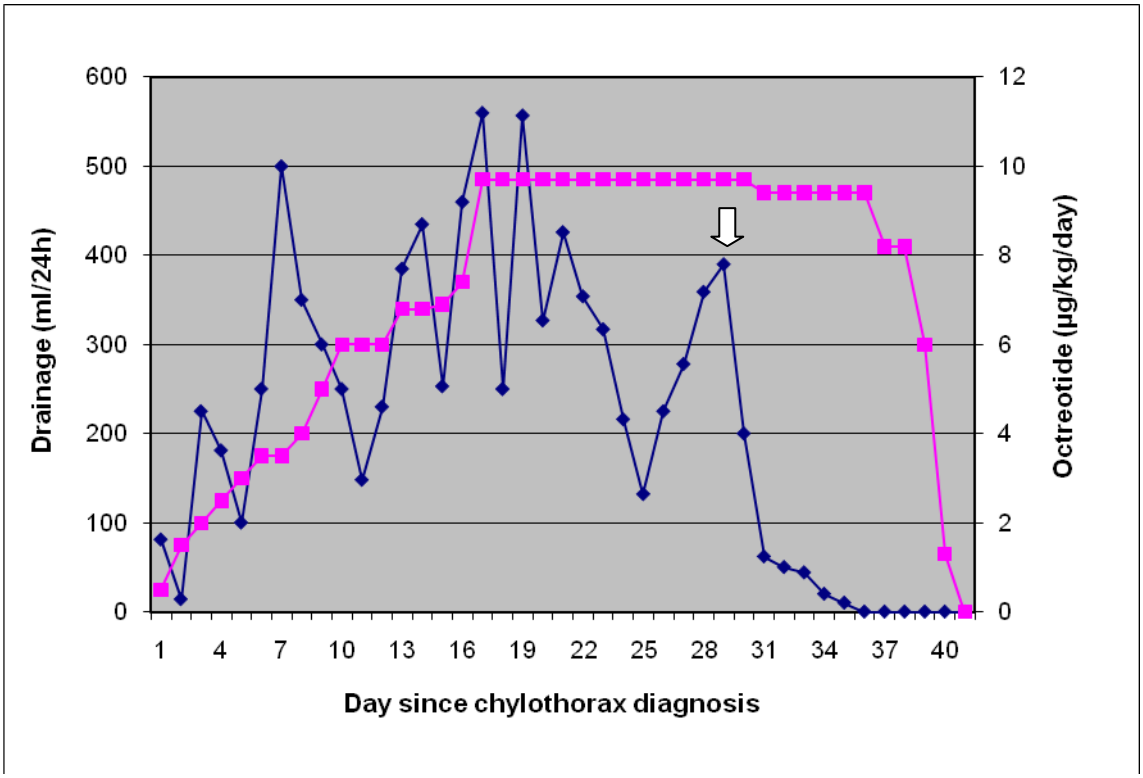

Figure 3 - Drainage of chylothorax (blue line) and octreotide dosage (rose line) in patient 3. Arrow represents povidone-iodine pleurodesis.

Table

Reference	n	Surgical condition	Chylothorax commenced POD	Treatment commenced POD	Duration of treatment (days)	Maximum dose (µg/kg/day)	Treatment effect	Complications
Moreira-Pinto et al. 2010	3	CDH CDH EA	8 2 11	14 4 11	24 20 40	240 192 240	Resolution on 11th day Resolution on 12th day Failed.	None
Hung et al. 2009[12]	1	CDH	First few days	8	5	24	Resolution on 2nd day	None
Gonzalez et al. 2009[1]	6	CDH	Unclear	Unclear	Unclear	96	Did not consistently reduce tube output in any of the patients	One died of sepsis while on octreotide
Prada Arias et al. 2008[13]	1	AE	7	16	49	240	Resolution on 49th day	None
Copons Fernández et al. 2008[14]	8	CDH CHD CHD CHD CHD CHD CHD CHD	6 7 5 5 8 7 2 6	One week after treatment with NPT alone.	Unclear.*	36 12 36 12 36 36 36 36	Resolved Resolved Failed** Resolved Resolved Failed** Failed** Failed**	None
Rocha et al. 2007[15]	1	EA	3	15	13	164	Reslution on 11th day	None
Chan et al 2005[16]	1	CHD***	Unclear	20	8	Unclear	Failed	Unclear
González Santacruz et al 2005[17]	2	CDH CDH	Unclear	Unclear	8 10	84 144	Resolution on 8th day Resolution on 10th day	None
Clarke et al. 2005[19]	1	EA	15	27	14	84	Prompt resolution	None
Mohseni-Bod et al. 2004[10]	1	Iatrogenic cardiac perforation/aortic coarctation	14	16	3	96	Prompt resolution	Onset of NEC while on octreotide
Tibballs et al. 2004[18]	1	CHD lymphangiectasia	4	8	4	120	Prompt resolution	None
Goyal et al. 2003[2]	1	CDH	7	16	9	10	Resolution on 2nd day	None

Au et al. 2003[3]	1	Gastroschisis	1	33	7	84	Resolution on 5th day	None
Pettitt et al. 2002[20]	1	CHD	1	34	3	51	Resolution on 3rd day	Transient cutaneous rash
Buettiker et al. 2001[7]	2	CHD CHD	3 1	17 32	14 15	240 240	Resolution on 12th day Resolution on 11th day	None Loose stools

Table 1 – Neonatal postoperative chylothorax treated with ocreotide/somatostatin reported in the literature.
CDH = congenital diaphragmatic hernia; CHD = congenital heart disease; EA = esophageal atresia; i.v. intravenous; TAPVC = total anomalous pulmonary venous connection, POD = posoperative day; s.c. subcutaneous
* Treatment was suspended when maximum dose was achieved without clear response. For those responding, treatment was maintained during 8-12 days at minimal effective dose.
** Surgical treatment was indicated when chylothorax persisted for more than four weeks after diagnosis.
*** Failed ductal ligation on 15th POD.