Use of Octreotide for the Management of Chyle Fistula Following Neck Dissection

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IMPORTANCE Chyle fistula is an uncommon complication of neck surgery. A variety of management strategies have been described, including diet restriction, parenteral nutrition, use of pressure dressings, and revision surgery. Octreotide has been used with success in patients with neck and thoracic chyle fistulas, but data regarding efficacy in neck chyle fistulas are lacking.

OBJECTIVE To evaluate the efficacy of octreotide for use in patients with postoperative chyle fistulas.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review of 12 patients who received octreotide for neck chylous fistula after neck dissection was performed during the period 2004 through 2014 at 2 tertiary care academic hospitals.

EXPOSURES Patients with postoperative neck chyle fistulas were given a restricted diet and subcutaneous octreotide.

MAIN OUTCOMES AND MEASURES The main outcome was fistula closure rate, defined as fistula resolution without surgical intervention. Secondary outcomes of fistula duration (days from detection until resolution), length of hospital stay (surgery to discharge), and treatment complications were also examined.

RESULTS All 12 patients had resolution of their neck chyle fistula with octreotide therapy without need for revision surgery. Mean (SD) hospital stay was 8.7 (4.76) days, with a range of 3 to 18 days. The chyle fistula resolved after a mean (range) 5.5 (2-11) days. Self-resolving nausea was encountered in 1 patient from octreotide use, and 1 patient developed a salivary fistula as a result of the chylous fistula.

CONCLUSIONS AND RELEVANCE In these patients, octreotide was safe and effective in resolving neck chylous fistulas. Octreotide therapy appears superior to traditional conservative measures of diet restriction and pressure dressings when compared with literature rates. A prospective study is needed to confirm results, but octreotide therapy should be considered as first-line conservative management for neck chyle fistulas that occur after neck surgery.
Chyle leak, although rare, is a well-documented complication following surgical dissection of the neck. To date, reports of the rate of this complication have ranged between 1% and 2.5% of cases, with a higher rate for radical neck dissections than selective neck dissections. Patients who received radiation therapy prior to neck dissection had a higher incidence of chyle fistula, but the difference was not statistically significant. Because of the location of the thoracic duct in the left side of the neck, there is a risk of chyle leak in lateral and central neck procedures, but injury can also occur in penetrating trauma. The duct terminates at the junction of the left internal jugular and subclavian veins and typically has a complex branching pattern into multiple smaller channels. Although the left side of the neck is the most common site, chyle fistulas have been reported in the right side of the neck as well because of the variability in the lymphatic system, with the possibility of a thoracic duct outlet on the right side. Although it occurs infrequently, it is a serious complication with substantial risk that can ultimately be life threatening. Left untreated, patients can experience hypovolemia; metabolic imbalances such as hyponatremia, hypochloremia, and nutritional deficiencies; and immunological complications. Patients may require total parenteral nutrition (TPN), with associated risks of liver failure and thrombosis and sepsis associated with central venous access. In addition, prolongation of a chyle leak can lead to longer hospital stays, delayed healing, and necrosis of skin flaps. In refractory cases, a return to the operating room may be required, causing a substantial increase in cost for the hospitalization.

Historically, chyle leaks have been difficult to manage. Traditional treatments for a chyle leak of the neck involve diet modification, closed drainage, and use of pressure dressings. Diet modification includes the use of a medium-chain fatty acid (MCT) diet, TPN, or no oral intake and aims to decrease thoracic duct flow by bypassing absorption through the lymphatic system and directly absorbing through the portal system. However, in many cases, chyle leaks continue despite conservative measures and operative interventions are required.

In the literature to date, octreotide has been well documented for the treatment of chylothorax as an effective means to resolve fistulas. Fewer studies have looked at chyle leaks in the neck following surgical dissection, with evidence of octreotide treatment success in these instances limited to case reports. Octreotide therapy has been shown to be successful in high-volume leaks, with reported success in a 2300-mL chyle leak that persisted after 8 days of MCT diet then resolved 6 days after initiation of octreotide therapy with no adverse events. We aimed to present our findings with the use of octreotide as a safe and effective means for prompt resolution of chyle leaks of the neck.

Methods
The institutional review board of University of Southern California approved this study, and informed consent was waived due to the retrospective nature of the study. Records of patients with a chyle leak after neck dissection performed at Los Angeles County Hospital or Keck Medical Center of the University of Southern California were retrospectively reviewed. The inpatient pharmacy databases were queried for patients who received subcutaneous octreotide from 2004 to 2014. The list was reduced by limiting the search to patients on the otolaryngology service. These patients’ medical records were retrospectively reviewed and were included in the study if they indicated a neck chylous fistula following a neck dissection. During this period, all chyle fistulas were treated with octreotide and diet modification. If surgical drains were in place, they were maintained without application of a pressure dressing until the chyle fistula resolved.

Demographic information was obtained including age, sex, social history, radiation therapy history, surgical history, and surgical procedure performed. Treatment outcomes were recorded including (1) the amount of drainage from the chyle fistula per 24-hour period, (2) duration of treatment with octreotide, (3) time to resolution of chyle leak, (4) use of any dietary changes in treatment, (5) time to return to normal diet, (6) duration of hospitalization, and (7) need for revision surgery. All patients were treated initially with maintenance of the surgical drains (or repeated aspirations if drain not present), diet restriction, and octreotide.

Results
A total of 12 patients who received postoperative octreotide for a neck chyle fistula between 2006 and 2014 were included in this study. One of these patients was unique in that octreotide was given prophylactically after discovery of a chyle leak intraoperatively, but no leak developed postoperatively. This patient is discussed but excluded from analysis. Of the remaining 11 patients, 6 were from Keck Medical Center and 5 from Los Angeles County Hospital (Table). Of the 11 patients, 6 were male and 5 female with a mean (range) age of 53.3 (25-78) years. Four patients had a preoperative diagnosis of metastatic squamous cell carcinoma, 3 of medullary thyroid cancer, 2 of papillary thyroid cancer, 1 of hyperparathyroidism, and 1 of thyroid goiter. Prior to the chyle leak, 6 patients (55%) had a previous neck surgery, 3 (27%) had prior radiation therapy, and 5 (45%) had no prior treatments. Neck dissection was the most common procedure causing a chyle fistula (9 patients), followed by thyroidectomy (1 patient) and parathyroidectomy (1 patient). The chyle fistula developed in the left side of the neck in 9 patients (82%), central neck in 1 patient (9%), and right side of the neck in 1 patient (9%). The fistula also resulted in chylothorax in 1 patient. The 1 excluded patient who received octreotide prophylactically had a central neck chyle fistula after thyroidectomy and had undergone central neck dissection for papillary thyroid cancer.

The chyle fistula was detected intraoperatively in 4 patients, with attempts at repair using clips and suture ligation (2 patients), or ligation with fibrin sealant (2 patients). The postoperative chyle fistula was detected clinically by the presence of increased drain output and milky fluid in 9 patients (82%), by swelling in the neck after discharge in 1 patient, and dyspnea secondary to pleural fluid in 1 patient. The fistula was
detected a mean (SD) of 17 (3.3) days postoperatively. The mean (SD) drainage output from the chyle fistula over a 24-hour period prior to treatment was 445.5 (392.6) mL, with a range of 28 to 1130 mL (Figure).

Laboratory analysis of drain fluid was performed on 7 patients, with a mean (range) triglyceride concentration of 622.3 (39-1287) mg/dL (to convert to millimoles per liter, multiply by 0.0113). The patient with a triglyceride concentration of 39 mg/dL had chylomicrons detected in the fluid and had 800 mL of milky chylous-appearing fluid aspirated from the pleural space, confirming the diagnosis of chylothorax.

Octreotide therapy was started in all patients after clinical detection of the chyle fistula, except in 1 patient in whom therapy was initiated immediately postoperatively as a prophylactic measure. Dosing of octreotide ranged from 50 mcg subcutaneously twice daily (given prophylactically) to 150 mcg subcutaneously every 6 hours. The most common dosing in this study was 100 mcg subcutaneously every 8 hours, but the drug was also given intravenously in 3 patients. Octreotide therapy was continued at home after hospital discharge in 6 of the patients for a mean (range) of 5.4 (2-15) days.

Diet was managed with either nothing by mouth with progression to normal diet (3 [25%]), MCT diet (8 [67%]), or TPN (1 patient). Patients resumed a normal diet a mean (SD) of 11 (9.2) days after detection of the fistula.

The chyle fistula resolved without operative intervention in all of the patients, with decreased drain output beginning on the first day of octreotide therapy. The chyle fistula resolved after a mean (range) of 5.5 (2-11) days as measured from day of clinical detection to resolution, with inability to determine exact duration of the fistula in 1 patient. The mean (SD) hospital stay was 8.7 (4.76) days, with a range of 3 to 18 days. Octreotide was given for a mean (SD) of 9.4 (6.3) days, with a range of 2 to 20 days. Complications were uncommon; however, 1 patient developed a salivary fistula after total laryngectomy on the side of the chyle leak. Octreotide therapy was well tolerated in all patients, with 1 patient experiencing self-resolving nausea and dizziness that did not require cessation of therapy.

**Table. Patient Demographic Characteristics**

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<th>Patient No./Sex/Age, y</th>
<th>Race/Ethnicity</th>
<th>Smoking</th>
<th>Alcohol Use</th>
<th>Preoperative Diagnosis</th>
<th>Side of Leak</th>
<th>Duration of Fistula, d</th>
<th>Maximum Chyle Output, mL</th>
<th>Hospital Length of Stay, d</th>
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Abbreviations: MTC, medullary thyroid carcinoma; NA, not applicable; PTC, papillary thyroid carcinoma; SCC, squamous cell carcinoma.

* Intraoperative chyle leak detected with octreotide given prophylactically without development of chyle fistula postoperatively.

**Discussion**

Chyle leaks are frequently detected by high or increased drain output postoperatively. The fluid is characteristically cloudy or milky but may present without the milky appearance, especially if the patient is not receiving enteral nutrition. Chyle fistulas can be confirmed with laboratory studies of triglyceride concentration and presence of chylomicrons in the fluid. In a review of patients with chylothorax, the mean triglyceride level was 728 mg/dL, but there is wide variability.
Triglyceride concentration of greater than 110 mg/dL is supportive of a diagnosis of chyle fistula, but 14% of patients may not meet this threshold,17,12,13 in which case chylomicrons are diagnostic.

Reports of failure rates of nonsurgical management are sparse, but several studies demonstrate the high failure rate (18%-33%) of MCT diet, TPN, and use of pressure dressings alone. In a study of 4 patients with neck chylous fistula treated with aspiration, compression dressing, and TPN, 1 patient’s leak failed to resolve after 30 days and required surgical reexploration, and a second patient died as a result of deterioration of health and hypercalcemia; the mean length of hospital stay was 33.5 days. In another analysis, 11 patients with a chylous fistula were treated with suction drains and MCT diet followed by TPN. Five patients’ leaks resolved with MCT diet, and 4 patients’ leaks resolved with TPN. Two patients (18%) with high-output leaks (>4000 mL) required surgical reexploration with pectoralis major muscle transfer and fibrin sealant due to hypoalbuminemia 28 and 36 days postoperatively despite a trial of both MCT diet and TPN.4 In another review of 3 patients with postoperative neck chylous fistula, 2 fistulas resolved with TPN after 10 and 21 days, with 1 patient requiring pectoralis major myocutaneous flap with fibrin sealant after failure of TPN and skin flap necrosis.5 The reported literature rates contrast with the 100% chyle fistula resolution (0 of 12 patients requiring revision surgery) and mean hospital length of stay of 8.7 days in the present study using octreotide.

Treatment with somatostatin, or its synthetic analogue octreotide, is a potential alternative to surgical management of chyle leaks. These drugs have many inhibitory functions on hormones, but their proposed effects on closing chyle leaks derive from their abilities to decrease absorption of triglycerides and inhibit splanchnic circulation and gastrointestinal motility, all factors that affect lymph flow. Intravenous administration of somatostatin has been shown to reduce chyle flow by 91% in the thoracic duct in dogs.16 Octreotide’s advantage over somatostatin is that it does not require concurrent intravenous infusion, but rather, use of subcutaneous injection can sustain long-lasting effects. At a mean wholesale cost of $9.48 for a 100-mcg dose, the daily cost per patient is $28.44 on the basis of the most common dosing of 100 mcg subcutaneously every 8 hours. Given that octreotide therapy can reduce hospital length of stay, it appears to be cost-effective.

More recently, other methods have also been proposed for management of chyle leaks. Negative-pressure wound therapy, which involves covering and sealing the wound with a drape and applying subatmospheric pressure to the wound to remove fluids from the site, has been shown to lead to wound shrinkage and resolution in preliminary reports.17 Orlistat, a pancreatic lipase inhibitor proposed by Bellaso et al,18 interferes with the breakdown of lipid at the duodenum and consequently prevents the micelle formation necessary for lipid absorption at the intestinal level. Thorascopic ligation has also been suggested for high-output leaks prior to a return to the operating room.19 Sclerotherapy has also been reported to be an effective method to manage leaks, but not without risks. As a result of the adverse effects documented, it has been suggested that it be used only with extreme caution in cases of chyle leak until further investigation is done to explore the risk involving use in this area.20 Others have suggested the use of fibrin adhesive sets.24 Our suggested treatment algorithm consists of subcutaneous octreotide therapy along with MCT oral diet and monitoring of drain output for resolution. The single patient who was given octreotide prophylactically after identification of an intraoperative thoracic duct injury did not go on to develop a postoperative chyle fistula; however, given the small sample size, definitive conclusions and recommendations cannot be made to endorse the use of octreotide in this manner.

Octreotide is used for a variety of indications with a low incidence of serious adverse events. The most common associated adverse effects are nausea, abdominal pain, and diarrhea, but it has also been associated with cholelithiasis, hypothyroidism, hyperglycemia, musculoskeletal pain, bradycardia, and chest pain. In less than 1% of patients, it has been associated with anaphylactic shock, biliary obstruction, stroke, gastrointestinal bleeding, and pulmonary embolus. This medication should be used with caution in patients with pre-existing heart disease, conduction abnormalities, and liver disease. Many adverse effects are dose and duration dependent, with a higher risk in patients with acromegaly. Octreotide therapy has been tolerated by patients and used safely in adults and children in safety studies for a variety of indications.22-29 In addition, no serious adverse events were reported in this study of 12 patients treated with subcutaneous octreotide. The metabolic risks of prolonged chyle leak and the morbidity of other treatment options support the short-term use of octreotide in patients with postoperative chyle fistulas.

Conclusions

Octreotide therapy is safe and effective in resolving neck chylous fistulas. In this study, all patients had resolution of their chyle fistula with conservative measures with octreotide therapy, with no patients requiring revision surgery. Use of octreotide seems to be superior to traditional conservative measures of diet restriction and pressure dressings in light of literature rates of fistula closure and length of hospital stay with these methods. A prospective study is needed to confirm results, but octreotide therapy should be considered as first-line conservative management for neck chyle fistulas that occur after neck surgery.
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ORIGINAL INVESTIGATION


REFERENCES