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# The Management of Neonatal Chylothorax: Experience of a Tertiary Neonatal Referral Center

## Yenidoğanlarda Şilotoraksın Yönetimi: Üçüncü Basamak Tek Merkez Deneyimi

**Yasemin Ezgi Köstekci[1], Elvis Kraja[1], Ergun Ergün[2], Emel Okulu[1], Ufuk Ateş[2], Ömer Erdeve[1], Begüm Atasay[1], Saadet Arsan[1]**

*[1]Ankara University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Ankara, Türkiye*
*[2]Ankara University Faculty of Medicine, Department of Pediatric Surgery, Ankara, Türkiye*

## Abstract

**Objectives:** Chylothorax can be congenital or acquired; however, there are no standardized treatment guidelines in neonates. In this study, we aimed to evaluate the experience of a tertiary neonatal intensive care unit.

**Materials and Methods:** This single center retrospective study included neonates with chylothorax between 2012 and 2020. Demographic and clinical characteristics of patients were evaluated.

**Results:** During the study period, 10 infants were diagnosed with chylothorax. The mean gestational age was 34.2±3.2 weeks, and the mean birth weight was 2,655±685 g. Six (60%) of the cases had congenital chylothorax, and four (40%) had acquired chylothorax. Non-immune hydrops fetalis was identified in four (67%) of the six cases of congenital chylothorax. Intrauterine thoracentesis was performed in three cases. Acquired chylothorax cases (n=4) was occurred postoperatively. All infants were treated with octreotide. One patient underwent thoracic duct ligation. Eight (80%) of the patients were discharged with full recovery, and two (20%) died due to prematurity and heart failure after cardiac surgery. No short-term recurrence was observed in any of the surviving cases.

**Conclusion:** Chylothorax is a rare condition in neonates, and there is limited data about the management. This study will add knowledge of the use of octreotide treatment in neonatal chylothorax cases.

**Keywords:** Chylothorax, congenital chylothorax, octreotide, neonate

## Öz

**Amaç:** Şilotoraks konjenital veya edinilmiş olabilir; ancak yenidoğanlarda standartlaştırılmış tedavi kılavuzları yoktur. Bu çalışmada üçüncü basamak bir yenidoğan yoğun bakım ünitesindeki tedavi deneyimimizi değerlendirmeyi amaçladık.

**Gereç ve Yöntem:** Bu tek merkezli retrospektif çalışmaya 2012-2020 yılları arasında şilotoraks tanısı ile izlenen yenidoğanlar dahil edildi. Hastaların demografik ve klinik özellikleri değerlendirildi.

**Bulgular:** Çalışma döneminde 10 bebeğe şilotoraks tanısı konuldu. Ortalama gebelik yaşı 34,2±3,2 hafta, ortalama doğum ağırlığı 2.655±685 g idi. Olguların 6'sında (%60) şilotoraks konjenital iken, 4'ünde (%40) kazanılmıştı. Altı konjenital şilotoraks olgusunun 4'ünde (%67) immün olmayan hidrops fetalis belirlendi. Üç hastada intrauterin dönemde torasentez öyküsü vardı. Edinsel şilotoraks olguları (n=4) postoperatif dönemde gelişmişti. İzlenen tüm bebeklerin tedavisinde oktreotid kullanıldı. Bir hastaya torasik kanal ligasyonu uygulandı. Hastaların 8'i (%80) şifa ile taburcu edilirken, 2'si (%20) prematüre ve kalp yetmezliği nedeniyle hayatını kaybetti. Yaşayan olguların hiçbirinde kısa süreli nüks görülmedi.

**Sonuç:** Şilotoraks yenidoğanlarda nadir görülen bir hastalıktır ve tedavisine ilişkin çok az veri bulunmaktadır. Bu çalışma neonatal şilotoraks olgularında izlem ve oktreotid tedavisinin kullanımına ilişkin literatüre bilgi sağlayacaktır.

**Anahtar Kelimeler:** Şilotoraks, konjenital şilotoraks, oktreotid, yenidoğan

**Address for Correspondence/Yazışma Adresi:** Yasemin Ezgi Köstekci
Ankara University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Ankara, Türkiye
**Phone:** +90 541 325 18 61 **E-mail:** ezgikostekci@gmail.com **ORCID ID:** orcid.org/0000-0002-4580-3128
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## Introduction

The accumulation of lymphatic fluid in the pleural space is known as chylothorax. It is caused by obstruction or leakage of the thoracic duct and its branches. Neonatal chylothorax is a rare condition with an incidence of 1 in 5,775 to 24,000 and a high mortality rate (1,2). Congenital chylothorax is caused by disorders of the lymphatic system, while thoracic surgeries that result in thoracic duct injury, such as congenital diaphragmatic hernia repair, cardiac anomalies, or esophageal atresia repair, are the most common causes of acquired chylothorax (3,4). Pleural fluid drainage, respiratory and hemodynamic support, and total parenteral nutrition followed by feeding with enriched medium-chain triglyceride (MCT) formulas are common treatment options (5). Although there was no strong evidence, octreotide has been used in the treatment of neonatal chylothorax (6). In limited cases of massive chylothorax, surgery has provided therapeutic benefit (7). Medical and conservative management, as well as the best timing and type of surgical intervention, vary among neonatal intensive care units (NICUs) (1,2,7-10). There are currently no published prospective approaches to neonatal chylothorax. As a result, there are no standardized treatment guidelines.

In this study, we reviewed our experience with neonates with chylothorax and compared it with other studies in the field to determine optimal management.

## Materials and Methods

This single-center, retrospective study included all neonates diagnosed with chylothorax between January 2012 and December 2020. The Ankara University Faculty of Medicine Human Research Ethics Committee approved the study (approval no: İ02-98-23). Patient characteristics, management, and outcomes were reviewed from the hospital's electronic database. Imaging tests such as X-ray, chest ultrasound, and/or chest computed tomography were used to diagnose chylothorax. The diagnosis of chylothorax was confirmed if the pleural fluid sample had a cell count of >1,000/mL (with a predominance of lymphocytes) and a triglyceride level of more than 1.1 mmol/L in a neonate who had been enterally fed (6,11). Patient management included respiratory support, replacement of pleural fluid loss, nutritional support with enriched MCT formulas, and initiation of octreotide infusion. In the absence of international or national guidelines or unit protocols, the initiation time, dose, and maximum infusion rate of octreotide treatment, as well as the response to treatment were at the discretion of the attending neonatologist. Based on the volume of chylous fluid, the octreotide dose was increased or decreased. Surgery was performed in neonates with persistent pleural effusion despite treatment.

Demographic findings, prenatal, perinatal, and postnatal characteristics, associated anomalies, duration of pleural effusion, medical or surgical treatment, duration of neonatal hospitalization, and survival were recorded.

### Statistical Analysis

Descriptive statistics were performed on demographic findings and clinical outcomes. Data were presented as numbers and percentages and as mean ± standard deviation (SD).

## Results

During the study period, 10 infants (five males, five females) were diagnosed with chylothorax. Table 1 summarizes the characteristics of the patients. Eight of the infants (80%) were born prematurely. The mean gestational age of the neonates was 34.2±3.2 weeks, and the mean birth weight was 2,655±685 g. Nine infants (90%) were delivered by cesarean section. Six (60%) had congenital chylothorax and four (40%) had acquired chylothorax.

Non-immune hydrops fetalis was found in four (67%) of the six cases of congenital chylothorax. Intrauterine pleural fluid drainage by thoracentesis was performed in three of these cases. Acquired chylothorax (n=4) occurred postoperatively in three patients (esophageal atresia repair, total anomalous pulmonary venous return surgery, and bronchogenic cyst excision). One of the acquired chylothoraces was a complication of chest tube insertion.

Five infants had bilateral effusions. Chest tube drainage was performed in all patients. All patients required invasive respiratory support with a mean duration of mechanical ventilation of 16.8±14.3 days. At some point during hospitalization, all infants were fed a MCT-enriched formula. Albumin replacement was performed in 6 patients (60%). Patients required transfusions of erythrocytes (60%; n=6), platelets (20%; n=2), and fresh frozen plasma (10%; n=1) due to additional problems.

One patient with a poor response to treatment required lymphoscintigraphy (patient #3) and no congenital anomaly of the lymphatic system was found.

All infants with chylothorax were treated with octreotide at some point. Octreotide infusion was started on average 1.5±1.3 days after the appearance of the chylous effusion. Treatment was initiated on the same day as effusion in four (40%) patients, two days later in three (30%) patients, and three days later in three (30%) patients. The initial dose of octreotide infusion was 1-4 µg/kg/h and was increased to a maximum of 5-12 µg/kg/h (mean 6.1±3.9 µg/kg/h). The duration of octreotide treatment ranged from 2 to 59 days with a mean of 26.7±21.1 days. In all patients, pleural effusion eventually resolved between 1 and 25 days (mean 11.8±7.4 days). During treatment, the mean volume of chylous effusion was 74.5±44 mL/kg/d. Details of effusion,

**Table 1: Characteristics of patients**

| No. | Gender | Gestation age (w) | Birth weight (g) | Mode of delivery | Antenatal diagnosis | Type | Main diagnosis | Intrauterine management | Apgar (1/5 min.) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Male | 34.4 | 2570 | C/S | Pleural effusion | Congenital | Congenital chylothorax | Yes[a] | 4/7 | Alive |
| **2** | Male | 34 | 2745 | C/S | Pleural effusion | Congenital | Pulmonary sequestration | Yes[b] | 6/7 | Alive |
| **3** | Female | 33 | 2700 | C/S | NIHF | Congenital | Congenital chylothorax | No | 2/4 | Alive |
| **4** | Male | 32.5 | 2230 | C/S | NIHF | Congenital | Congenital chylothorax | No | 5/6 | Alive |
| **5** | Female | 38 | 3020 | C/S | Bronchogenic cyst | Acquired | Postoperative (cyst excision) | No | 7/8 | Alive |
| **6** | Female | 26.5 | 1080 | C/S | Prematurity | Acquired | Traumatic chest tube insertion (pneumothorax) | No | 5/7 | Died |
| **7** | Male | 38 | 3295 | VD | TAPVR | Acquired | Postoperative (TAPVC) | No | 7/8 | Died |
| **8** | Female | 36 | 2300 | C/S | No (polyhydramnios) | Acquired | Postoperative (esophageal atresia) | No | 7/8 | Alive |
| **9** | Female | 36 | 3170 | C/S | NIHF | Congenital | Mediastinal teratoma | No | 3/6 | Alive |
| **10** | Male | 35.1 | 3440 | C/S | NIHF | Congenital | Congenital chylothorax | Yes[c] | 8/8 | Alive |

[a]: Pleural drainage on week of 33 and 34, [b]: Pleural drainage on week of 32, [c]: Pleural drainage on week of 32 and 35
CS: Cesarean section, NIHF: Non-immune hydrops fetalis, TAPVC: Total anomalous pulmonary venous connection, VD: Vaginal delivery

ventilation, and octreotide treatment in the study population are summarized in Table 2.

One patient underwent thoracic duct ligation due to lack of improvement with MCT formula and octreotide therapy (patient #6).

Of the six cases treated solely with octreotide, one infant with acquired chylothorax was discharged in stable condition and two infants died; while one infant with congenital chylothorax was discharged in stable condition and two infants died. The average time from the beginning of octreotide treatment until the chylous fluid resolved was 12.83 SD 9.19 days in congenital chylothorax and 10 SD 1 day in acquired chylothorax ($p>0.05$).

Two patients experienced adverse events thought to be caused by octreotide. At a dose of 10 µg/kg/h of octreotide, one patient developed hemodynamically insignificant ventricular extra beats (patient #5). Reducing the dose to 8 µg/kg/h improved the extra beats. In one patient with acquired chylothorax, hypertension was observed at the 8 µg/kg/h dose and blood pressure was normalized by reducing the drug dose to 5 µg/kg/h (patient #7).

Eight patients (80%) were discharged with full recovery and two (20%) died due to prematurity and heart failure after cardiac surgery. Two patients were discharged with additional treatments (patient #1: subcutaneous octreotide treatment; patient #4: supplemental oxygen). No short-term recurrence was observed in any of the surviving cases.

## Discussion

Chylothorax is a rare condition in newborns. It causes severe morbidity regardless of etiology. There is insufficient evidence to guide medical and surgical approaches. In this study, we attempted to evaluate neonatal chylothorax cases from a tertiary NICU in terms of clinical presentation and management strategies. Ten neonatal chylothorax cases with various etiologies were presented in this cohort. The infants were treated with generally accepted conventional therapies such as pleural fluid drainage, respiratory support and MCT enriched formula. Octreotide infusion was also initiated in all neonates. Previous studies of octreotide treatment for neonatal chylothorax have shown conflicting results with variable success rates (2,7-10). In the present study, 8 out of 10 patients had successful remission of chylous effusion after initiation of octreotide therapy.

The exact mechanism of action of octreotide is unclear. It may act on somatostatin receptors in the splanchnic circulation, reducing lymphatic fluid production by decreasing gastric, intestinal, and pancreatic secretions, as well as hepatic venous

**Table 2: Details of pleural effusion, ventilation, and octreotide treatment in the study population**

| No. | Chest tube drainage duration (days) | Non-per oral | Initial octreotide dose (µg/kg/h) | Max. octreotide dose (µg/kg/h) | Chylous effusion (mL/kg/day, max.) | Octreotide initiation day after chylous effusion was appeared | Octreotide duration (days) | Day of response to treatment | Side effect of octreotide | Invasive ventilation duration (days) | Duration of hospitalization |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 37 | No | 1 | 7 | 50 | 0 | 59 | 12 | - | 10 | 62 |
| **2** | 16 | No | 1 | 1 | 47 | 2 | 6 | 6 | - | 5 | 24 |
| **3** | 40 | Yes | 2 | 12 | 140 | 0 | 51 | 25 | - | 45 | 59 |
| **4** | 11 | No | 1 | 1 | 10 | 2 | 2 | 1 | - | 3 | 36 |
| **5** | 30 | Yes | 1 | 10 | 95 | 3 | - | 11 | Ventricular extra beats | 7 | 37 |
| **6** | 5 | No | 1 | 1 | 66 | 2 | - | - | - | 12 | 13 |
| **7** | 26 | Yes | 1 | 8 | 60 | 3 | 18 | 10 | Hypertension | 33 | 38 |
| **8** | 23 | Yes | 4 | 7 | 130 | 3 | 20 | 9 | - | 18 | 36 |
| **9** | 28 | Yes | 3 | 5 | 30 | 0 | 16 | 11 | - | 22 | 34 |
| **10** | 28 | Yes | 3 | 9 | 117 | 0 | 42 | 22 | - | 8 | 46 |

pressure and splanchnic blood flow (12). Although octreotide is the most commonly used drug for chylothorax, there are insufficient data on dose, duration, and efficacy.

In a meta-analysis of 19 cases of congenital chylothorax treated with octreotide, it was reported that the chylothorax regressed in 14 cases, four cases did not benefit from treatment, and the outcome of one case was uncertain (6). White et al. (9) reported on six neonates with chylothorax, three of whom were treated with octreotide and showed no significant effect on pleural output. A cohort study showed that patients with surgically induced chylothorax did not benefit from octreotide treatment (8). In a retrospective analysis of 11 neonates with congenital chylothorax, while somatostatin was required in only one case, while the chylous effusion was resolved with only conservative management in the other patients (13). Downie et al. (2) reported on ten infants with chylothorax, three of whom were treated with octreotide, two of whom showed a significant clinical response and one of whom showed no significant improvement. In an another report, there was no clear and consistent effect of octreotide therapy in seven neonates with congenital chylothorax (10). In the present study, all neonates were treated with octreotide and in eight of them the chylous effusion resolved successfully. In one case, the chylous effusion did not resolve despite octreotide infusion, and a thoracic duct repair was performed. Another case could not be evaluated as a therapeutic response because the effusion resolved one day after the start of the octreotide infusion.

The recommended dose of octreotide is variable. In a systematic review by Bellini et al. (14), octreotide was used at doses ranging from 1 µg/kg/h to 10 µg/kg/h and was reported to be effective in 47% of patients. In an another case series of seven neonatal chylothorax patients, octreotide was initiated at a dose of 212 µg/kg/h, and none of them required surgery (10). In the present study, the initial dose of octreotide infusion was 1-4 µg/kg/h and was increased to a maximum of 5-12 µg/kg/h. In seven patients who were successfully treated, the maximum octreotide infusion rates were all ≥5 µg/kg/h, while only one patient received a dose of 1 µg/kg/h. Based on the cases in this study, it may be thought that doses of ≥5 µg/kg/h are more effective in treating chylothorax, but it could not be concluded as a result of this study.

A systematic analysis of neonatal chylothorax has recently been reported (15). This report included only cases of congenital chylothorax. Octreotide treatment data were documented in 138 cases with a mean duration of 22 days (range 3-151 days). Treatment with octreotide was started between day 2 and day 109, and the initial intravenous dose varied between 3 and 4 µg/kg/h, and the maximum dose varied between 6 and 12 µg/kg/h. Octreotide therapy failed in 30 cases, leading to subsequent

surgery. The success rate was consistent with our results, but our sample included both congenital and acquired chylothorax.

Yin et al. (16) reported that octreotide is effective in high volume pleural drainage (>20 mL/kg/g). In the study by White et al. (9), the median maximum pleural output was 218 mL/kg/d (range: 86-310 mL/kg/d), the patients who were treated with octreotide did not benefit significantly from the therapy. Cleveland et al. (7) reported that out of 23 cases of neonatal chylothorax, six required surgery due to massive chylothorax (>50 mL/kg/d). They recommended early surgery in patients with massive pleural effusion to avoid complications of prolonged medical therapy. In the present report, the mean maximum pleural fluid output was 74.5±44 mL/kg/day, and the pleural fluid volume was >50 mL/kg/d in six of eight infants successfully treated with octreotide. In one infant with a pleural fluid volume of 66 mL/kg/d, octreotide failed to reduce the effusion and surgery was ultimately performed (patient #6). In the present study, octreotide was reported to be beneficial even in infants with massive chylothorax.

Although octreotide has been reported to be safe and effective in the treatment of chylothorax in newborns, adverse effects such as necrotizing enterocolitis, hypothyroidism, cholelithiasis, retinal problems, pulmonary hypertension, hyperglycemia, and hematochezia have been reported in case series (1,10). Systemic hypertension and cardiac arrhythmias were observed in two cases in the current study and improved with dose reduction and are therefore considered adverse reactions of octreotide. These two conditions may not be considered direct pharmacologic side effects, and there are insufficient data to conclude that octreotide is safe in neonates.

### Study Limitations

The retrospective nature and the inclusion of patients from a single center are major limitations of the study. Our data cannot provide an estimate of the time of initiation, as all patients received octreotide within the first three days. Due to the lack of guidelines or national protocols for octreotide treatment of chylothorax, there is variation in dose regimens, initiation time, and duration, and there is also no exact definition of treatment response. Under these circumstances, statistical analysis could not be performed. Because virtually all available data from tertiary NICUs are case reports or small case series of neonatal chylothorax, comparison with other research was also limited. In contrast to some previous studies, this study shows that octreotide can be effective even in cases of massive neonatal chylothorax. Although there is a lack of data to conclude that the use of octreotide in neonatal chylothorax is safe, none of the patients in this study experienced significant adverse effects. In our opinion, octreotide could be a beneficial treatment option in cases of neonatal chylothorax, but the development of evidence-based guidelines would be critical.

## Conclusion

Randomized controlled trials are essential for the development of evidence-based interventions. However, conducting such trials, especially in multicenter studies, appears to be infeasible. Currently, treatment options are mostly based on clinical experience and expert opinion. To obtain additional data, national and worldwide multicenter databases should be established.

### Ethics

**Ethics Committee Approval:** The Ankara University Faculty of Medicine Human Research Ethics Committee approved the study (approval no: İ02-98-23).

**Informed Consent:** The ethics committee is not required to obtain informed consent due to the retrospective design of the study.

### Authorship Contributions

Surgical and Medical Practices: E.T., S.S., Concept: Z.B., Design: M.E., S.S., Data Collection and/or Processing: B.G.D., Analysis and/or Interpretation: E.T., M.E., Literature Search: B.G.D., Writing: B.G.D.

**Conflict of Interest:** According to the authors, there are no conflicts of interest related to this study.

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