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Propranolol As a Treatment Option for Chylous Effusions and Chylous Ascites in Fetuses and Neonates: A Systematic Review

Brianna Courteau, PA-S; Gabriella Zarlenga, PA-S; Sandy P. Narciso-Owen, MS, MSPAS, PA-C; Eric C. Nemec II, PharmD, MEHP; and Suzanne J. Rose, MS, PhD

OBJECTIVE Chylous effusion and chylous ascites are rare but serious conditions that affect both fetuses and neonates. Previous studies have documented chylous effusions or chylous ascites treatment with medications as an adjunct to respiratory support and dietary modifications, but no formal recommendations have been made. New literature suggests propranolol as an effective and safe treatment option, though no randomized clinical studies have been published to date. This review aims to assess the efficacy and safety of propranolol in the treatment of chylous effusion and chylous ascites in fetuses and newborns from case reports.

METHODS A comprehensive search of 10 databases and grey literature was completed. The inclusion criteria for articles were age at diagnosis less than 40 days old and case report/series. Articles were excluded if they were animal studies or not published in English.

RESULTS Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 4 articles were ultimately included in the study for a total of 10 reported cases. Propranolol administered to mother and neonates was effective in 100% of cases. The most common oral dose for mothers was 20 mg, 4 times daily, titrated to 40 mg, 4 times daily. The maximum dosage varied for administration orally to neonates, with the median being 3 mg/kg/day. Side effects, including bradycardia and transient hypoglycemia, were seen in 20% of the cases and resolved with dose adjustment.

CONCLUSION Propranolol is a relatively effective and safe treatment option for chylous effusion and chylous ascites that can be administered prenatally or to neonates.

ABBREVIATIONS CINAHL, Cumulated Index to Nursing and Allied Health Literature; DOL, day of life; EBSCO, Elton B. Stephens Company Information Services; GA, gestational age; JBI, Joanna Briggs Institute; MEDLINE, Medical Literature Analysis and Retrieval System Online; MCT, medium-chain triglyceride enriched diet; NICU, neonatal intensive care unit; NIH, National Institutes of Health; OK-432, picibanil; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Q6h, every 6 hours; Q8h, every 8 hours; TPN, total parenteral nutrition; TRIP, Turning Research Into Practice; VEGF, vascular endothelial growth factor

KEYWORDS chylous ascites; chylous effusion; infant; newborn; propranolol

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Introduction

Chylous effusion and chylous ascites are rare but serious conditions that affect both fetuses and neonates. Chylous effusion, also known as chylothorax, is a rare cause of pleural effusion due to the extravasation of chyle from the thoracic duct or its tributaries.[1] Mortality rates of chylous effusions range from 15% to 57%.[2] There are several types of chylous effusions, including congenital, traumatic, and idiopathic.[3] In pediatric patients, one of the leading causes of chylous effusion is congenital, which can occur antenatal or postnatal. Congenital chylous effusion can be caused by myotubular myopathy, carotid arteriovenous malformation, pulmonary lymphangiectasia, pulmonary hypoplasia, malformations of the lymphatic system,[3,4] or chromosomal abnormalities such as Trisomy 21, Noonan, and Turner syndromes.[3] Traumatic chylous effusions can be iatrogenic from cardiothoracic surgery or from penetrating or blunt chest trauma.[4] If an exact cause cannot be identified after appropriate diagnostic procedures, chylous effusion is considered to be idiopathic.[5]

Chylous ascites, or chyloperitoneum, has a similar pathophysiology as chylous effusion, except in chylous ascites, the thoracic or intestinal lymph fluid accumulates in the peritoneal cavity. Loss of this fluid into the third space can result in dehydration, malnutrition, electrolyte imbalance, and immunosuppression. Blockage, exudation, or trauma to lymph vessels can lead to excess lymph fluid buildup in the peritoneal space. In pediatric patients, the majority of cases of chylous ascites are due to congenital lymph malformations or trauma. The same congenital lymph malformations that cause chylous effusions can also result in chylous ascites, and though rare, both may clinically present together.[6]

Clinical presentation of patients with chylous effusion typically includes dyspnea, hypoxia, and a large pleural effusion seen on chest radiographs. Patients with chylous ascites typically present with painless abdominal distention, dyspnea, enlarged lymph nodes, early satiety, fevers, and night sweats. On physical examination, the patient may have cachexia, temporal wasting, evidence of pleural effusions or chylous ascites, abdominal masses and hernias, and lower extremity edema.[6] The current standard of care for both chylous effusions and chylous ascites includes respiratory support, drainage of fluid, medium-chain triglyceride enriched (MCT) diet, and/or total parenteral nutrition (TPN).[3]

If supportive care modalities fail, somatostatin or synthetic octreotide has been used as adjunctive therapy off-label for chylous effusions and chylous ascites with evidence of clinical benefit. Somatostatin inhibits splanchnic vasodilation through the inhibition of glucagon and intestinal peptides, which reduces portal pressure, fats in the gut, fats absorption, and triglyceride and lymph flow in major vessels, notably the thoracic duct.[2,7,8] A 2018 systematic review of octreotide for chylous effusions in neonates found that octreotide administration for a mean duration of 22 days (range, 3–151 days) cleared chylous effusions in 47% of the cases. There was no optimal dosing strategy, efficacy, or safety of octreotide that could be determined from the study.[2] Reported adverse effects of octreotide included hyperglycemia, mildly distended abdomen, transient mild cholestasis, transient hypothyroidism, bloody stools, pulmonary hypertension, necrotizing enterocolitis, severe hypotension, and elevated liver enzymes.[2,7]

Surgical interventions such as thoracic duct ligation, pleuroperitoneal shunts, and pleurodesis can treat chylous effusions when conservative treatments fail but have been shown to extend hospital stay and increase morbidity including pneumonia, colitis, bleeding and peritonitis.[9] Prenatal interventions might improve survival in fetal chylous effusion as fetal drainages and subsequent pleurodesis with OK-432 (picibanil, a sclerosant and immunostimulant) seemed promising with a 67% survival rate. These results from a recent systematic review of published cases of congenital chylous effusion from 1990–2018 found that treatment modalities have not drastically changed and pharmacologic options have not been well studied.[3]

Recently, multiple case reports[10–13] have suggested using propranolol as adjunctive therapy for treating both chylous effusions and chylous ascites. Propranolol is a non-selective beta-adrenergic receptor antagonist that reduces portal blood pressure by producing splanchnic vasoconstriction, leading to a possible subsequent decrease of lymph production at the level of the liver.[14] It also acts on the fibrosarcoma mitogen-activated protein kinase signaling pathway, causing reduced expression of vascular endothelial growth factor (VEGF) levels and direct induction of apoptosis in capillary endothelial cells of lymphatic vessel malformations. As it has already been studied in treating infantile hemangiomas, propranolol shows potential for treating chylous effusions and chylous ascites.[15] This systematic review aims to update the literature for adjunctive options for chylous effusion and chylous ascites treatment by assessing the efficacy and safety of propranolol in the prenatal and neonatal populations.

Materials and Methods

A systematic search of articles was performed between February 1, 2023, and February 16, 2023. Through the Elton B. Stephens Company Information Services (EBSCO) host platform, the following 7 databases were searched beginning from their inception date: Cumulated Index to Nursing and Allied Health Literature (CINAHL) Ultimate, Academic Search Premier, CINAHL with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Medical Literature Analysis and Retrieval System Online (MEDLINE) with Full Text, and Child Development & Adolescent Studies. Simultaneously, PubMed, Nursing and Allied Health Premium, and Turning Research Into Practice (TRIP) databases were searched. The following Boolean/Phrase was used to search all databases: (chylous effusion OR pleural effusion OR chylous pleural effusion OR chylous ascites OR chylothorax OR chyloperitoneum) AND ((propranolol OR Hemangeol (propranolol hydrochloride, Parsippany, New Jersey) OR Inderal (propranolol hydrochloride, Baudette, Minnesota) OR InnoPran (propranolol hydrocholoride, Baudette, Minnesota)). Grey literature was searched using the same search terms on medRxiv.org, bioRxiv.org, clinicaltrials.gov, National Institute of Health (NIH) Clinical Center Trials, and European Union clinical trials register.

Articles found using the search strategy above were exported to Covidence.org to allow evidence synthesis amongst multiple collaborators. Two reviewers (BC and GZ) independently screened the abstracts of the articles for eligibility based on predetermined inclusion and exclusion criteria. Articles were included

if the age of patients at the time of diagnosis were prenatal or before 40 days of life and if the articles were case reports or case series and excluded if they were animal studies, not published in English. Chylous effusion is most frequently diagnosed in the neonatal population, as such, this population was the focus of our work. Before finalizing our systematic search strategy, we reviewed the literature and identified at least 1 relevant case study that included patients in the first 40 days of life; thus, we employed it as our cut-off to retain as many relevant examples as possible. After reviewing abstracts and titles, those articles that met the criteria underwent full-text review by 2 independent reviewers. The study selection process is delineated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram guidelines in the Supplemental Figure.[16] Four articles were critically appraised for risk of bias before inclusion in the review.

Articles were evaluated for risk of bias and study inclusion using the Joanna Briggs Institute (JBI) Checklist for Case Reports.[17] Independently, data from the eligible articles were extracted by the 2 reviewers and included age of diagnosis, other interventions, propranolol dose and route, birth information, days to chylous effusion or chylous ascites resolution, treatment duration, side effects, and etiology.

Results

Study Population. Following evaluation for risk of bias,[17] Borcyk et al,[10] Handal-Orefice et al,[11] and Liviskie et al,[12] were deemed high-quality case studies answering yes to all 8 domains (Figure). Mitchell et al[13] had 2 questions for which the answer was determined to be "unclear." Ultimately, it was decided to include the article due to multiple quality case studies within the series. Therefore, 4 articles were chosen for analysis of the efficacy and safety of propranolol. Two articles were case reports,[10,12] and the other 2 were case series,[11,13] for a total of 10 patient cases. Of the 10 case reports, 7 (70%) were congenital chylous effusion or chylous effusion/ascites[10–13] cases while 3 (30%) were post-operative chylous ascites or chylous effusion/ascites cases.[13] The post-operative chylous ascites or chylous effusion/ascites cases occurred after the following surgeries: patent ductus arteriosus ligation in 2 patients and patent ductus arteriosus stent placement for Tetralogy of Fallot in 1 patient. The following disease states caused the 7 congenital chylous effusion cases: hydrops fetalis (7 patients) and Trisomy 21 (1 patient with both hydrops fetalis and Trisomy 21). Of the 7 congenital cases, 2 of them reported administration of propranolol to the mother, while the other 5 reported oral administration to the neonate after birth (Table).[10–13]

The majority of patients included in this systematic review are female neonates, at a total ratio of 7:3 female to male.[10–13] However, the commonly reported incidence of congenital chylous effusion is 2:1, males to females.[18] This discrepancy could be due to the small sample size of this systematic review and novel approach of treatment with propranolol (Table).

Propranolol Administration. Propranolol was administered orally to the neonates in 8 out of 10 total cases, between 1 to 4 times a day.[10–13] The initial dose of propranolol ranged from 0.3 to 1 mg/kg daily with a maximum titrated dose between 0.5 to 6 mg/kg/daily. The differences in dosing strategies for post-operative and congenital etiologies are shown in the Table.[10–13]

The median duration of propranolol treatment in the post-operative group was 26 days compared with 608 days in the congenital group (Table).

Direct administration of propranolol to the neonate was efficacious, supported by radiologic imaging showing decreased chylous drainage.[10–13] Of the 3 post-operative cases, the longest duration of propranolol administration was 38 days, with an average duration of 22 days.[13] In congenital chylous effusion cases that reported resolution or clinical improvement, the average length of days to improvement and/or resolution was 418 days.[10–13]

Propranolol was administered orally to the mother in the remaining 2 cases for an average of 124 days with initial dose 20 mg, 4 times a day, titrated to maximum dose 40 mg, 4 times a day (Table).[11]

Propranolol Efficacy. Efficacy was defined as the resolution or clinical improvement of chylous effusion or chylous ascites, evidenced by radiologic imaging

Figure. Joanna Briggs Institute critical appraisal of case reports.

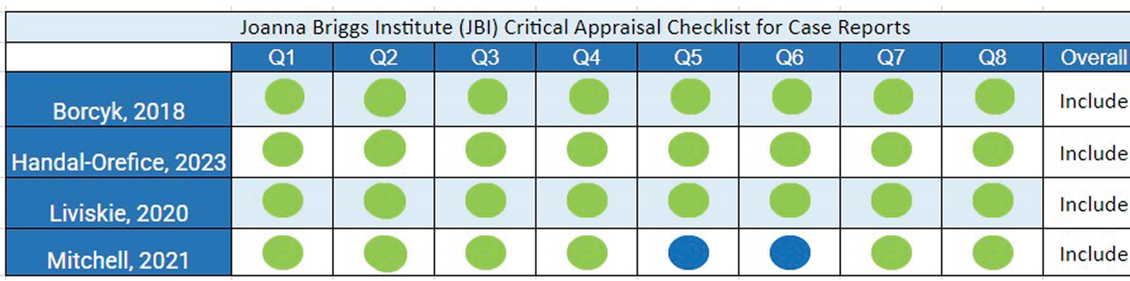

Table. Safety and Efficacy of Propranolol Treatment

Author	Diagnoses	Age at Diagnosis	Age at Propranolol Initiation	Propranolol Dose Range	Propranolol Administration (route, to whom)	Propranolol Duration	Efficacy	Side Effects
Borcyk[10]	Chylous effusion	31w0d GA	DOL 40	0.5 mg/kg/dose Q8H increased to 2 mg/kg/dose Q8H over 9 days	Oral, Neonate	365 days	No recurrence of effusion	None reported
Handal-Orefice[11]								
Case 1	Unilateral chylous effusion	18w4d GA	18w4d	20 mg/dose QID increased to 40 mg/dose QID over 4 days	Oral, Mother	129 days	Resolution at 24w3d, no effusion on chest radiograph at birth	Hypoglycemia in neonate*
Case 2	Unilateral chylous effusion	21w5d GA	22w3d	20 mg/dose QID increased to 40 mg/dose QID over 25 days	Oral, Mother	119 days	USG demonstrated resolution at 30w4d	None reported
Case 3	Bilateral chylous effusion	29w6d GA	DOL 108†	0.3 mg/kg/dose QD increased to 2 mg/kg/dose QD over 22 days	Oral, Neonate	1095 days	Significant radiologic improvement at 29 days after propranolol initiation	None reported
Case 4	Bilateral chylous effusion	27w1d GA	DOL 22	0.3 mg/kg/dose QD increased to 0.7 mg/kg/dose QD over 3 days	Oral, Neonate	840 days	Resolution at 8 months on chest radiograph	None reported
Liviskie[12]	Bilateral chylous effusion	DOL 4‡	DOL 16	0.3 mg/kg/dose Q8H increased to 0.5 mg/kg/dose Q8H	Oral, Neonate	20 days	Significant radiologic reduction by day 4, complete resolution by day 10	None reported
Mitchell[13]								
Case 1	Unilateral chylous effusion	33w6d GA	DOL 4	0.25 mg/kg/dose Q6H. increased to 0.75 mg/kg/dose Q6H. increased to 1.5 mg/kg/dose Q6H D/C at 1 mg/kg/dose Q6H	Oral, Neonate	Unspecified in the Case Study	Chest radiograph revealed improvement of after 24 hr	None

(*Continued*)

Table. Safety and Efficacy of Propranolol Treatment (*Cont.*)

Author	Diagnoses	Age at Diagnosis	Age at Propranolol Initiation	Propranolol Dose Range	Propranolol Administration (route, to whom)	Propranolol Duration	Efficacy	Side Effects
Case 2	Bilateral chylous effusion and abdominal chylous ascites	DOL 3§	DOL 31	0.25 mg/kg/dose Q6H increased to 1 mg/kg/dose Q6H over 8 days	Oral, Neonate	Weaned off after 2 wk	Peritoneal drainage cessation after 2 days, resolution over 2 wk	None
Case 3	Chylous ascites	DOL 7¶	DOL 7	0.5 mg/kg/dose Q6H increased up to 1 mg/kg/dose Q6H	Oral, Neonate	2 wk	No worsening of chylous ascites with breast milk feeds	None
Case 4	Chylous ascites	DOL 38#	DOL 38	0.25 mg/kg/dose Q6H and increased to 0.5 mg/kg/dose Q6H; increased to 1 mg/kg/dose Q6H and decreased to 0.75 mg/kg/dose Q6H	Oral, Neonate	38 days	Worsened d/t sepsis then cleared after 1 wk as evidenced by abdominal radiograph	Bradycardia

d, day; DOL, day of life; GA, gestational age; QD, daily; USG, ultrasound sonography test; W, week

*Hypoglycemia was thought to be due to low birth weight of neonate and not propranolol administration to mother.
†Patient was treated with propranolol on second hospital admission on DOL 108.
‡Gestational age at birth: 34w4d.
§Gestational age at birth: 22w4d.
¶Gestational age at birth: 23w3d.
#Gestational age at birth: 37w5d.

or no worsening of lymph accumulation with enteral breast milk feeds.[2] The length of time of propranolol administration was not considered when looking at efficacy. In most cases, improvement and/or resolution occurred within 24 hours to 8 months. Overall, propranolol was effective in treating chylous effusion and chylous ascites in all 10 case reports.[10–13]

Adverse Effects. Propranolol was overall well tolerated, and adverse effects were rarely described.[10–13] Out of the 10 cases included in our review, only 2 reported side effects.[11,13] In the case report of Handal-Orefice et al[11] where the mother was administered the propranolol, the neonate was transferred to the neonatal intensive care unit (NICU) on day of life (DOL) 2 for hypoglycemia. However, it was suspected after evaluation that the hypoglycemia was due to low birth weight rather than a side effect of propranolol. The neonate left the NICU on DOL 3 and was discharged on DOL 4 with no long-term sequelae.[11] In case report 4 of Mitchell et al,[13] bradycardia was the only reported side effect. The lowest heart rate recorded was 70 beats per minute following an increase in dosage from 0.5 mg/kg per dose to 1 mg/kg per dose every 6 hours on DOL 69. The dose was lowered to 0.75 mg/kg per dose, and resolution of bradycardia was achieved.[13]

Discussion

Chylous effusion and chylous ascites are life-threatening conditions that lack clear consensus for treatment protocol. There are limited available adjunctive pharmacologic treatment options for chylous effusion and chylous ascites without established optimal initial dosing, time of initiation, and duration.[2,3,7] Propranolol has recently emerged as a potential treatment option for the prenatal and neonatal populations, as evidenced by the 10 case studies included in our review.[10–13] It is noted that our results are limited by the small number of cases and variability in the patient's clinical condition and age (in utero vs postpartum). In most cases, the underlying etiology of chylous effusion and chylous ascites involved

multiple diagnoses and comorbidities that could affect the outcome of the treatment course. However, due to improvement in condition in cases presented here, it does not appear to be a significant confounder.[10–13]

Treating chylous effusion and chylous ascites in utero with propranolol was effective in both cases, and propranolol administration was continued throughout the remainder of the pregnancy. Although 1 of the cases had a side effect of hypoglycemia in the neonate, who was not directly treated, this may be due to the fast titration of treatment of the mother, over 4 days to maximum dosage, compared with 25 days in the other case, which reported no adverse effects. Therefore, slow titration to the maximum dose of propranolol is potentially the best treatment plan.[11]

Compared with octreotide, propranolol can be given during pregnancy, making propranolol a better candidate for congenital chylous effusion treatment. Octreotide is a somatostatin analog, a potent suppressor of growth and growth hormone-releasing hormone[19] and not generally recommended in pregnancy due to the risk of adverse effects in the fetus, such as intrauterine growth restriction and necrotizing enterocolitis in the newborn.[20] Therefore, the risks would likely outweigh the benefits of treating congenital chylous effusion and chylous ascites. Beta-blockers, such as propranolol, are well-studied in pregnancy for the treatment of maternal hypertension and have a well-documented side effect profile of bradycardia, hypoglycemia, hypotension, and respiratory depression in the neonate. Monitoring the neonate for 48 hours after delivery is recommended to assess for and quickly identify adverse events.[14] OK-432 (picibanil, a sclerosant and immunostimulant) has also been utilized with a survival rate of 67% of 87 cases,[3] indicating propranolol may be a safer and more efficacious alternative.

It was noted that the resolution of chylous effusion or chylous ascites was reached more quickly in cases of post-operative etiology compared with congenital etiologies.[10–13] The reason for the shorter duration of treatment in postoperative cases is unclear in the literature. It could be attributed to a combination of natural lymphatic vessel epithelial regeneration following traumatic injury, as lymphatic leakage is usually a self-limiting complication, which may heal within 2 to 3 weeks without intervention.[21] More research needs to be done to determine if chylous disorders of traumatic etiologies are more responsive to propranolol or if they have a quicker spontaneous resolution; this trend could suggest etiology is a determining factor for dosing strategy and duration of therapy.

There are some limitations among the articles used in the systematic review and within the review itself. The case reports do not all report efficacy and duration of administration in the same manner, making it difficult to determine the exact end point of the chylous effusion or chylous ascites. This systematic review has a few limitations, as well. Ten case reports were analyzed, but there is a need for a multicenter retrospective or prospective cohort study looking at specific endpoints to assess the efficacy of propranolol in the treatment of chylous effusions and chylous ascites for formal recommendations on its use to be made.

Conclusion

The use of propranolol to treat chylous effusions and chylous ascites appears safe and effective in the prenatal and neonatal periods based on the review and analysis of 10 reported cases. Propranolol is, therefore, likely to be a safer drug, easier to dose and titrate, associated with lower morbidity, and safer and more useful in pregnancy, proving superior to octreotide and other previously studied treatment modalities.

Article Information

Affiliations. Masters of Science in Physician Assistant Studies (BC, GZ, SPNO, ECN, SJR), Sacred Heart University, Fairfield, CT; Department of Research and Discovery (SJR), Stamford Health, Stamford, CT.

Correspondence. Suzanne J. Rose, MS, PhD; srose@stamhealth.org

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References

1. Senarathne UD, Rodrigo R, Dayanath BKTP. Milky pleural effusion in a neonate and approach to investigating chylothorax. *BMJ Case Rep*. 2021;14(9):e245576.
2. Bellini C, Cabano R, De Angelis LC, et al. Octreotide for congenital and acquired chylothorax in newborns: a systematic review. *J Paediatr Child Health*. 2018;54(8):840–847.
3. Resch B, Sever Yildiz G, Reiterer F. Congenital chylothorax of the newborn: a systematic analysis of published cases between 1990 and 2018. *Respiration*. 2022;101(1):84–96.
4. Shih YT, Su PH, Chen JY, et al. Common etiologies of neonatal pleural effusion. *Pediatr Neonatol*. 2011;52(5):251–255.

5. McGrath EE, Blades Z, Anderson PB. Chylothorax: aetiology, diagnosis and therapeutic options. *Respir Med*. 2010;104(1):1–8.
6. Lizaola B, Bonder A, Trivedi HD, et al. Review article: the diagnostic approach and current management of chylous ascites. *Aliment Pharmacol Ther*. 2017;46(9):816–824.
7. Zaki SA, Krishnamurthy MB, Malhotra A. Octreotide use in neonates: a case series. *Drugs RD*. 2018;18(3):191–198.
8. Sooklin L, Anand AJ, Rajadurai VS, Chandran S. Management of large congenital chylous ascites in a preterm infant: fetal and neonatal interventions. *BMJ Case Rep.* 2020;13(9):e235849.
9. Pieper CC, Geiger S, Kupczyk P, et al. Post-interventional infectious complications in percutaneous transabdominal lymphatic interventions: an observational study. *Sci Rep*. 2023;13(1):17643.
10. Borcyk K, Kamil A, Hagerty K, et al. Successful management of extremely high-output refractory congenital chylothorax with chemical pleurodesis using 4% povidone-iodine and propranolol: a case report. *Clin Case Rep*. 2018;6(4):702–708.
11. Handal-Orefice R, Midura D, Wu JK, et al. Propranolol therapy for congenital chylothorax. *Pediatrics*. 2023;151(2):1.
12. Liviskie CJ, Brennan CC, McPherson CC, Vesoulis ZA. Propranolol for the treatment of lymphatic malformations in a neonate – a case report and review of literature. *J Pediatr Pharmacol Ther.* 2020;25(2):155–162.
13. Mitchell K, Weiner A, Ramsay P, Sahni M. Use of propranolol in the treatment of chylous effusions in infants. *Pediatrics*. 2021;148(1):e2020049699.
14. Propranolol: drug information. In: Post T, ed. *UpToDate*. Waltham, MA: UpToDate. Accessed February 17, 2023. https://www-uptodate-com.sacredheart.idm.oclc.org/contents/propranolol-drug-information?source=auto_suggest&selectedTitle=1~2--1~2--propran&search=propranolol#F214865
15. Ozeki M, Fukao T, Kondo N. Propranolol for intractable diffuse lymphangiomatosis. *N Engl J Med*. 2011;364(14):1380–1382.
16. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst Rev*. 2022;18(2):e1230.
17. JBI Manual for Evidence Synthesis - JBI Global Wiki. Accessed February 17, 2023. https://jbi-global-wiki.refined.site/space/MANUAL
18. Attar MA, Donn SM. Congenital chylothorax. *Semin Fetal Neonatal Med*. 2017;22(4):234–239.
19. Octreotide: drug information. In: Post T, ed. *UpToDate*. Waltham, MA: UpToDate. Accessed March 7, 2023. https://www-uptodate-com.sacredheart.idm.oclc.org/contents/octreotide-drug-information?search=octreotide&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F202918
20. Geilswijk M, Andersen LL, Frost M, et al. Octreotide therapy and restricted fetal growth: pregnancy in familial hyperinsulinemic hypoglycemia. *Endocrinol Diabetes Metab Case Rep.* 2017;2017:16-0126.
21. Shao P, Meng X, Li J, et al. Laparoscopic extended pelvic lymph node dissection during radical cystectomy: technique and clinical outcomes. *BJU Int*. 2011;108(1):124–128.