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Somatostatin analog (octreotide) and sirolimus immunosuppressive therapy in the treatment of chyloperitoneum and chylothorax in newborns and infants

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KEYWORDS

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ABSTRACT

Background: Chyloperitoneum (CP) and chylothorax (CT) are rare conditions that have a high mortality rate and unclear treatment options. Their incidence in neonates ranges from 1 in 20000 to 1 in 187000 live births. This study aims to evaluate the effectiveness of synthetic somatostatin analog (octreotide) and sirolimus therapy in treating chylous pleural and peritoneal collections in newborns and infants.

Methods: We conducted a retrospective analysis of 10 children with either chylothorax or chyloperitoneum, treated in our department between 2018 and 2023. The study was approved by the Local Independent Ethics Committee of The National Medical Research Center of Children's Health, under Protocol №7, dated 11 May 2023. The parents voluntarily signed an informed consent form for the off-label use of the drug. We reviewed the medical records for demographic information, clinical presentation, management, and outcome.

Results: Our study looked at patients aged between 0 and 5.5 months, with seven cases of chyloperitoneum and three cases of chylothorax. We initially used octreotide, which was then switched to sirolimus if there was no improvement. Octreotide was effective in five children after 10-18 days of treatment, while the effect of sirolimus was observed 8-14 days after starting treatment. One patient, who had a history of a giant omphalocele with primary closure, experienced complications after 8 weeks of sirolimus therapy, including bilateral knee arthritis, leukopenia, and lymphopenia. Fortunately, there were no fatal outcomes.

Conclusion: Sirolimus therapy is effective in treating newborns with chylothorax or chyloperitoneum, with a low risk of complications even in those cases not responding to octreotide therapy. It is recommended that octreotide therapy should not exceed 10 days, after which sirolimus can be prescribed.

INTRODUCTION

Chyloperitoneum (CP) and chylothorax (CT) are pathological conditions where lymphatic fluid exudes into the abdominal and thoracic cavities. Their incidence in small infants varies from 1 in 20000 to 1 in 187000 live births. [1] Primary lymphatic malformations, also known as congenital lymphatic system malformations, result from persistent dilation or constriction of lymphatic vessels, commonly referred to as lymphangiomas. These anomalies contribute to lymphatic stasis and subsequent lymphorrhea. Lymphatic malformations may be linked to genetic disorders, including Shershevsky-Turner, Down, Klippel-Trenaunay-Weber, Gorham, and Noonan syndromes. [2,3].

Chyloperitoneum (CP) and chylothorax (CT) can cause several health issues such as hypoalbuminemia, anemia, lymphopenia, and coagulation disorders. These disorders can be fatal in about 30-50% of cases. To diagnose CP/CT, ultrasound or computed tomography and biochemical tests of drainage aspirate are performed. Chylous exudate contains a high concentration of triglycerides, and cell counts more than 0.001×109 /l with lymphocytes up to 80-90%. Their management is very tricky and ranges from simple drainage to drug therapy or even surgical interventions. [4-10]

Our study aims to share our experience of treating CP/CT in newborns using octreotide and sirolimus.

METHODS

We conducted a retrospective analysis of 10 children with chylothorax or chyloperitoneum, treated in our department between 2018 and 2023. We obtained informed consent from all parents or legal guardians of the patients who were included in the study. The study was approved by the Local Independent Ethics Committee of The National Medical Research Center of Children's Health, under Protocol №7, dated 11 May 2023. The parents provided informed voluntary consent for the off-label use of the drug.

Table 1: Summary of study patients

Patient no.	Diagnosis	Surgical treatment before the manifestation	Age of surgery (day of life)	Type	Day of CP/CT development, drainage placement (postoperative day)
1	Congenital chyloperitoneum	No surgery		CP	From birth (abdominal drainage was placed at the 122 day of life)
2	VATER syndrome (Anorectal malformation; distal TEF, EA; atresia of duodenum; left kidney anomaly)	Thoracoscopic ligation of TEF; duodenal atresia repair (Kimura diamond duodenoduodenostomy), colostomy, gastrostomy, esophagostomy	1	CP	22
3	Intestinal atresia, type I	1) Resection of intestinal membrane*	1		
		2) Primary intestine repair (anastomosis)	18	CP	22
4	Giant omphalocele (size of the defect 7x8 cm)	Primary closure of omphalocele	3	CP	7
5	Distal TEF, EA; dextrocardia; craniosynostosis	Thoracoscopic ligation of TEF, primary EA repair	3	CT	4
6	Meconium ileus	1) Ileostomy*	14		
		2) Re-ileostomy*	25		
		3) Ileostomy closure (anastomosis)	122	CT	3
7	Proximal and distal TEF, EA; Meckel's diverticulum	1) Thoracotomy, ligation of distal TEF, primary EA repair*	0		
		2) Laparotomy, resection of Meckel's diverticulum, fundoplication, gastrostomy*	20	CP	15
		3) Ligation of proximal TEF, re- fundoplication, re-gastrostomy	47		
8	Cystic lymphatic malformation of the mesentery of the ileum	Laparotomy, partial intestinal resection, intestinal anastomosis	156	CP	6 (abdominal drainage was placed during the initial operation)
9	Additional vena cava superior draining into the coronary sinus; open arterial duct. Duodenal web, intestinal malrotation	1) Pulmonary artery banding, ligation of the open arterial duct*	81		
		2) Duodenal atresia repair (Kimura diamond duodenoduodenostomy); operation for intestinal malrotation	122	CP	12
10	Congenital chylothorax, unilateral pneumothorax	No surgery		CT	From birth (chest drainage was placed on the 2nd day of life)

*Operations were performed in other regional hospitals of Russia; TEF – tracheoesophageal fistula; EA – esophageal atresia. CT: chylothorax, CP: chyloperitoneum.

The age of the patients at the time of presentation ranged from 4 to 162 days, with a median of 42 days. Two patients were presented during the neonatal age. Our series consisted of 5 boys and 5 girls. All patients underwent ultrasound examinations, as well as drainage of the fluid, and blood biochemical tests. In our series, 7 patients were diagnosed with CP, while 3 patients were diagnosed with CT. Two patients had no previous surgery, so they were considered to have congenital (primary) CP/CT. The other patients were operated on due to various congenital malformations, with further manifestation of secondary CP/CT (Table

1). All children received parenteral nutrition, and octreotide was started at a dose of 5-10 mcg/kg/hour (24-hour infusion through a separate peripheral venous access). If there was no decrease in drainage fluid after 10-14 days of octreotide therapy, we started immunosuppressive therapy with sirolimus. The decision was made by a multidisciplinary team in line with the International Society for the Study of Vascular Anomalies (ISSVA) guidelines.

To prevent infections (specifically pneumocystis infection), children were given co-trimoxazole at a dosage of 36 mg/kg/24h, divided into two doses, three times a week throughout their immunosuppressive therapy. The initial dose of sirolimus was 0.05 mg (suspension 1 mg/ml) every 12 hours, regardless of the child's body weight or gestation. The dosage was adjusted based on sirolimus concentration blood tests, with a therapeutic concentration range of 8-14 ng/ml. Sirolimus concentration blood tests were conducted on the 10-14th day of treatment, and then every two weeks while in the hospital and once a month during outpatient care. All patients diagnosed with CP/CT received abdominal or chest drain placement.

RESULTS

Most patients were preterm newborns (n=6) with body weights ranging from 800 g to 2900 g. Seven patients were diagnosed with Chyloperitoneum, while three patients had Chylothorax. There were five boys and five girls in our study. Eight patients had undergone surgery due to various congenital malformations before the development of chylous collection, and two children had chylous collections since birth (Table 1). One patient had cystic lymphatic malformation of the mesentery of the ileum (patient no. 8).

Table 2 describes study variables. Regarding drainage, the amount of drain varied from 30 to 600 ml per 24 hours. Specifically, 4 patients had a drainage volume of 30-100 ml/24h, 2 patients had a volume of 100-300 ml/24h, and 3 patients had a volume of 300-600 ml/24h (Table 3). Out of the 7 patients who had a drainage volume of 100-600 ml/24h, octreotide therapy was ineffective for 5 children. Patients 1 and 4 had the highest protein losses, and during therapy, they required multiple albumin infusions (9 for patient #1 and 8 for patient #4) and immunoglobulin infusions (5 for each child) (Table 4).

Table 2: Octreotide and sirolimus therapy parameters

Patients **Parameter**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Gestation (weeks)	34	33	35	37	36	28	38	39	37	40
Body weight at birth (g)	2050	1982	2900	2490	2430	800	2970	3190	2600	3700
Body weight at admission (g)	5400	2470	3500	2870	2340	2280	3870	6415	3730	3715
Diagnosis	CP	CP	CP	CP	CT	CT	CP	CP	CP	CT
Drainage discharge maximum (ml/24h)	600	150	260	600	40	30	100	50	350	100
Age of octreotide therapy start (days)	122	35	42	10	4	127	35	162	134	117
Dose of octreotide (mcg/kg/h)	10	10	10	10	5	10	10	10	10	10
Octreotide therapy (days)	18	10	10	14	10	10	12	14	10	18
Octreotide therapy effect	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No
Age of sirolimus therapy start (days)	140			24			47		144	135
Dose of sirolimus (mg/m^2/24h)	0.9			0.9			0.7		0.7	0.7
Sirolimus therapy effect: no discharge, drainage was removed (day)	12			13			14		8	8
Total course of sirolimus therapy (weeks)	18			10*			10		9	12

*Treatment was stopped due to complications; patients receiving sirolimus therapy are marked by gray color.

Most of the patients (8/10) developed chylous collections after previous surgery. Of these patients (n=8), in half of the patients (n=4) chylous collections were observed after 3-22 days of the surgery.

We administered octreotide therapy for 10-18 days. Out of the 10 patients, 5 showed good response without any adverse events or complications. The remaining 5 patients were switched to sirolimus/rapamycin therapy, which proved to be effective for all of them. The optimal dose for octreotide was found to be 5-10 mcg/kg/hour, while for sirolimus, the effective dose was 0.7-0.9 mg/m2/24h with a target concentration of 8-14 ng/ml.

The study observed that the resolution of chylous collection due to sirolimus therapy occurred within 8-14 days (average 12 days) from the start of treatment.

Patients were discharged from the hospital and continued to receive sirolimus for a total course of therapy that varied from 9 to 18 weeks. However, one child with giant omphalocele (patient 4) experienced complications after 8 weeks of sirolimus therapy, including bilateral knee arthritis, leukopenia, and lymphopenia. At that time, the concentration of sirolimus was 8ng/ml, and the treatment was stopped. After complete recovery, the child did not experience a recurrence of CP. There were no fatal outcomes, and the long-term follow-up ranged from 7 months to 4 years.

Table 3: Biochemical tests of drainage discharge at admission

Patients	Cell counts ($\times 10^9$/l)	Lympho-cytes (%)	Total protein (g/l)	Triglycerides (mg/dl)
1	8,4	96	10,6	4.5
2	11,7	95	33,9	682.5
3	6,9	83	24,4	3.4
4	4,9	89	29,8	11.3
5	0,6	87	26,7	1.8
6	0,1	78	4,1	34.9
7	19,8	88	31,2	163.9
8	1,1	65	31,7	107.6
9	13,1	65	27,0	316.2
10	1,3	75	24,3	46.3

Patients who received sirolimus therapy, are marked by gray color.

To summarize, patients who did not respond to octreotide therapy (duration of therapy 12-18 days), followed by sirolimus for 8-12 days, resulted in positive outcomes such as no chyle production and removal of drainage tubes. Subsequently, all patients underwent prolonged sirolimus therapy for a total duration of 9-18 weeks.

DISCUSSION

Most of our patients with CP/CT had a history of surgical operations. However, some authors have suggested that all symptoms occurring within the first three months of life should be considered congenital. [1,5]

The surgical treatment of CP/CT in children is rare. In adults, lymphography is employed to verify the source of lymphorrhea, but it is not universally applicable. In infants and small children, lymphography is not feasible due to technical challenges and potential serious side effects. [4]

Lymphatic vessels identified intraoperatively can be successfully sutured, yielding positive outcomes in 85% of cases. However, when the source of lymphorrhea is unclear or multiple defects are present, fibrin glue may be used, although it carries the risk of causing severe adhesive processes or inadvertently entering the bloodstream. [11] Various sclerosants, including calibrated talc, tetracycline, and betadine, are also employed. In complex cases, peritoneo-venous shunts have been utilized. [1]

Surgical treatment in newborns and infants is generally ineffective due to anatomical features; the thoracic duct cistern and abdominal lymphatic vessels are poorly differentiated. Notably, in our study, surgical intervention for CP/CT was not performed.

Guidelines for conservative treatment of CP/CT remain contentious. Typically, conservative therapy, combined with abdominal or chest drainage, is recommended. Nutritional strategies often involve the use of a medium-chain triglyceride feeding formula. [12] However, the most effective approach to reducing lymph production is total parenteral nutrition. [2,4,5] Some authors propose a duration of parenteral nutrition for 3-4 weeks. [13,14] Yet, it is crucial to consider the associated elevated risks of liver disorders, intestinal atrophy, and infections stemming from the use of a central venous catheter or drainage tube. [4,13,14] Neonates who were not fed from birth may exhibit a negligible increase in triglycerides in drainage discharge. [2]

In current literature, the administration of somatostatin (octreotide) is described as the most common conservative treatment. Although exact guidelines are not standardized, the treatment period is individualized for each patient and can range from 1 to 8 weeks. [4,6,9,15,16] This approach is generally not associated with severe complications, except for rare cases of necrotizing enterocolitis resulting from ischemic disorders of the intestine. [17] However, further research on safety is warranted. The outcomes of octreotide treatment are somewhat controversial, but it is currently the most used and considered safe. [4,16]

Given this, we initiated octreotide therapy in all cases, and children with no observed effect underwent sirolimus therapy. Some authors have proposed that if drainage of chyle exceeds 20 ml/kg on the 10th day of octreotide therapy, further administration of the drug may be ineffective. [18] In our experience, we found that no decrease in lymphatic discharge by the 5th or 6th day of octreotide therapy indicated a lack of effectiveness. Contrary to many studies suggesting weeks of octreotide therapy, we employed it for 10-18 days and advocate for reducing this period to 7-10 days. If there is no reduction in chylous fluid production, the treatment approach should be reconsidered. Prolonged waiting for an effect in small children may lead to protein losses, severe dehydration, coagulation issues, and immune system disorders, even in cases with minimal chylous discharge. In our group, the duration of effective octreotide therapy aligned with literature data and ranged from 10 to 14 days (with an average of 11 days). [4,16]

We based our treatment on the successful experience of sirolimus/rapamycin therapy of vascular malfor-

mations (including lymphangiomas). Sirolimus/rapamycin, originally employed as an antibacterial drug, acts as both an immunosuppressive and antitumor agent. It functions by inhibiting the mammalian target of rapamycin kinase (mTOR kinase), a pivotal enzyme in cell cycle regulation. In the absence of mTOR kinase activity, the cell cycle is arrested during the DNA replication phase. This interruption causes endothelial cells to cease responding to pro-angiogenic factors, leading to a deceleration of angiogenesis. Additionally, sirolimus/rapamycin inhibits microvascular leakage induced by vascular endothelial growth factor (VEGF). [19]

Table 4: Protein loss and replacement therapy (blood tests)

Patient no.	Total protein minimum (normal range 51-73 g/l)	Total albumin minimum (normal range 26-43 g/l)	Immunoglobulin G minimum (normal range 2.32-14.11 g/l)	Infusion of albumin (5 ml/kg)	Infusion of immunoglobulin (0.4 g/kg)
1	28	16	0.82	9	5
2	34	25	1.82	-	-
3	32	22	2.27	2	-
4	20	11	0.92	8	5
5	37	24	4.02	3	-
6	38	23	0.53	2	-
7	46	27	2.65	-	-
8	32	24	2.54	-	-
9	43	26	1.21	1	3
10	44	21	2.75	1	1

Patients who received sirolimus therapy are marked with gray color.

Our experience with sirolimus revealed that the average duration of treatment until the observed effect (absence of lymphorrhea) was 12 days, nearly equivalent to the duration seen with octreotide. It is noteworthy that our patients received sirolimus following octreotide, and this sequencing may potentially influence the outcomes, necessitating additional research. The total duration of sirolimus intake in our cases ranged from 9 to 18 weeks, while some authors reported periods ranging from 2 to 22 weeks. [12] In the recent literature, we did not find specific guidelines regarding the duration of immunosuppressive therapy or criteria for determining when to discontinue it. Nonetheless, Mizuno et al. conducted research on the pharmacokinetics of sirolimus and proposed dosing regimens for neonates and infants. [20] In our series, we achieved the same target concentration with lower doses.

Few authors have demonstrated effectiveness with both higher and subtherapeutic concentrations. [12] Currently, concentrations are empirically extrapolated from dosing regimens designed for the treatment of cystic lymphatic malformations. However, there is a possibility that lower concentrations could also be effective. Consequently, further research is required to elucidate the precise correlations among age, body weight, target sirolimus blood concentrations, and dosing regimens.

It is important to note that our study has limitations owing to the rarity of this pathology, and our experience is based on a small series of patients. Therefore, further multicenter research is essential to broaden our understanding of this condition.

CONCLUSION

Our research demonstrated the effectiveness of sirolimus therapy in cases of CP and CT in neonates and infants, with a low incidence of complications. We propose that octreotide therapy, when used before sirolimus, should be limited to 7-10 days. If no effect is observed during this period, patients should be transitioned to sirolimus intake. Prolonged waiting for an effect in newborns can result in severe protein losses and worsen their condition.

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