

# Five Cases of Congenital Chylothorax Treated by Intrapleural Minocycline

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## Abstract

### Keywords

- ▶ neonate
- ▶ chylothorax
- ▶ pleural effusion
- ▶ minocycline
- ▶ pleurodesis

Minocycline pleurodesis was performed on five infants with congenital chylothorax in our institutions. They could not achieve sufficient efficacy though they had received other conservative therapies. Four of the five cases obtained reduction of pleural effusion using the minocycline pleurodesis. We concluded that minocycline pleurodesis is a safe and an effective technique for congenital chylothorax.

Congenital chylothorax is characterized by abnormal accumulation of chyle within the pleural cavity. Although chylothorax is a rare cause of respiratory distress in newborns and a potentially life-threatening condition, it is sufficiently treatable.<sup>1</sup>

Conventional treatment includes a brief period of fasting or a diet of medium chain triglyceride (MCT) formula<sup>2</sup>; however, some cases are refractory to these treatment strategies.

Minocycline has been used as a chemical pleurodesis agent for treating adult pleural effusion, and its efficacy has been described<sup>3</sup>; however, few studies have reported the use of minocycline as a treatment for congenital chylothorax.

We report the cases of five patients with congenital chylothorax treated with minocycline as a chemical pleurodesis agent.

## Patients and Methods

We investigated the cases of five patients with congenital chylothorax who had been treated with intrapleural administration of minocycline in our institution from April 2003 to December 2010. Chylothorax was diagnosed according to the specific diagnostic features: presence of milky fluid in the pleural space and pleural fluid containing either >110 mg/dL

triglycerides or a predominance of mononuclear cells in the fluid.<sup>4</sup> We followed the following procedure for treating pleural adhesion with minocycline: 100 mg minocycline (Minomycin<sup>®</sup>, Pfizer Japan Co. Ltd, Tokyo, Japan) was dissolved in 10 mL normal saline and injected into the pleural cavity via a chest tube at 0.4 to 0.8 mL/kg body weight (4 to 8 mg/kg body weight) several times every 12 to 72 hours. The effect of this treatment was evaluated by ultrasound examination or radiographic findings, and the maximum volume of chyle drainage was recorded every 24 hours and related to body weight. The medical records for each case were examined for background, symptoms of pleural effusion, usage and duration of minocycline, other treatments, and outcomes.

## Results

The clinical features of the subjects are summarized in ▶**Table 1**. The subjects consisted of four males and one female, ranging from 31 to 39 weeks gestational age (median, 34.6 weeks), and from 1368 to 3328 g in birth weight (median, 2072 g). Antenatal diagnosis was established by ultrasound examination in all infants (pleural effusion, three; fetal hydrops, two), but intrauterine therapy was not administered to any of the subjects. Two infants exhibited the trisomy 21 chromosomal abnormality.

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**Table 1** Summary of Five Cases Treated by Intrapleural Minocycline in Our Institution

1A						
Case No	Gender	Gestational Age (wks)	Birth Weight (g)	Abnormality	Antenatal Diagnosis	Max Volume of Pleural Effusion (mL/kg/day)
1	M	39	3328	None	Pleural effusion	78.7
2	M	34	2072	Trisomy 21	Pleural effusion	29.6
3	M	37	2898	Trisomy 21	Pleural effusion	62.1
4	F	31	1368	None	Hydrops	43.9
5	M	34	2620	None	Hydrops	22.9
1B						
Case No.	Other Postnatal Treatment	Max Dosage and Period of Octreotide	Max Dosage and Times of Minocycline	Chest Tube Removal	Outcome	
1	MCT feeding	Not used	8mg/kg × 8 every 24 h	At 40 days	Discharged in survive	
2	MCT feeding	Not used	8 mg/kg × 3 every 12 h	At 3 days	Discharged in survive	
3	MCT feeding SS <sup>a</sup> + HDC	30µg/kg/day	8 mg/kg × 12 every 24 h	Not able	Died on 34 days	
4	MCT feeding SS <sup>a</sup> + PDN	8µg/kg/day	4 mg/kg × 8 every 24 h	At 24 days	Discharged in survive	
5	MCT feeding HDC	Not used	4 mg/kg × 7 every 72 h	At 25 days	Discharged in survive	

HDC, hydrocortisone; MCT, medium-chain triglycerides; PDN, prednisone; SS, somatostatin.

<sup>a</sup>Discontinued somatostatin because of abdominal distension due to side effect.

All survival cases were discharged, and there is no serious complication at present.

All subjects required mechanical ventilation and chest drainage from the day of birth, and they were all fed MCT formula for postnatal treatment. Somatostatin was administered to two patients, but they did not show signs of improvement; for one patient, somatostatin had to be discontinued because of abdominal distension, likely due to drug side effects. Because pleural effusion did not decline with these treatments, we achieved pleurodesis by administering minocycline. Four of the five patients demonstrated successful and prompt clearance of pleural effusion by minocycline; they were therefore discharged and experienced no recurrence. One patient (case 3) died from pulmonary hypertension, and although complete improvement was not achieved, he did exhibit a temporary reduction in effusion.

## Discussion

Congenital chylothorax often causes serious complications such as respiratory distress, electrolyte and fluid imbalance,<sup>1</sup> malnutrition,<sup>5</sup> or persistent immunodeficiency.<sup>6</sup> Thus, it is critical to decrease pleural effusion promptly. Fasting, total parenteral nutrition, and MCT formula are conventional treatments for chylothorax. However, a percentage of cases do not respond to conventional therapies. Furthermore,

prolonged fasting is not desirable for early neonates, particularly premature infants because malnutrition affects future growth and development. Octreotide (a somatostatin analogue) has been used to manage patients with refractory chylothorax who do not respond to conservative management. However, several patients have experienced serious side effects from octreotide such as transient hypothyroidism,<sup>7</sup> hypoglycemia, or necrotizing enterocolitis<sup>8</sup> (which has been reported in one patient). Moreover, consensus regarding dosage, efficacy, and safety has not been determined yet.<sup>9,10</sup>

Despite using the MCT formula treatment for all of our patients, we obtained insufficient efficacy. Two patients were administered octreotide, but their condition did not improve, and one of these two patients was admitted for abdominal distension believed to be due to the drug side effects. Other three cases have not admitted octreotide because of its side effects, so we used minocycline as first step in treatment.

Intrapleural administration of minocycline has been used for pleural effusion in adults, and its effectiveness has been well described.<sup>3</sup> However, few neonates have been treated with this therapy. Out of our five patients, four showed improvement without fasting; therefore, we concluded that this therapy might also be useful for neonates.

The exact mechanism underlying the action of minocycline in the pleural space is unknown. However, animal experiments have shown that minocycline induces a dose-dependent neutrophil influx and increases the number of pleural macrophages and lymphocytes. Furthermore, animal studies suggest that the inflammatory reaction induces pleural fibrosis and adhesion.<sup>11</sup>

We treated five patients with intrapleural instillation of minocycline through a chest tube, and obtained sufficient response in four of five patients without recurrence.

In our cases, the side effects of minocycline such as liver or renal dysfunction, skin rash, and, pigmentation were not appeared, however, it is necessary to follow-up in their growth process about the teeth discoloration which is another side effect of minocycline for children.

Although one patient (case 3) showed temporary reduction in effusion, complete improvement of pleural effusion could not be achieved. Trisomy 21 increases the incidence of lymph vessel anomaly, which may have been a contributing factor in the development of chylothorax in this patient<sup>12</sup>; therefore, some different treatment might be necessary for a case of trisomy 21.

We conclude that pleural adhesion therapy with minocycline may be useful for treating neonatal chylothorax if conservative therapies are not effective. However, further studies on a larger patient population are necessary to determine the method, usage, and period of administration of minocycline, as well as its safety.

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