

## Original Research Article

# Effect of intrapleural injection of erythromycin on congenital refractory chylothorax in the newborn

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### Abstract

**Purpose:** To investigate the therapeutic effect of intrapleural injection of erythromycin on congenital refractory chylothorax in the newborn, in order to provide a more efficient approach for its treatment.

**Methods:** A retrospective study was conducted with 13 cases of congenital chylothorax in newborns that received conventional treatment and intrapleural injection of erythromycin.

**Results:** A total of 10 out of 13 child patients (76.9 %) received active treatment. Furthermore, the patients who received the intrapleural injection of erythromycin were administered the injection a total of 1 - 3 times ( $1.5 \pm 0.6$ ) on the average with the dose ranging from 80 - 210 mg (mean,  $126.5 \pm 32.7$  mg). Thereafter, they received continuous drainage for 7 - 12 days (mean time, 10.2 d). Drainage volume ranged from 50 - 150ml (mean,  $84.3 \pm 35.2$  mL). Patients that did not receive the erythromycin treatment received continuous drainage for 5 - 13 d (mean, 8.6 day), with the drainage volume ranging from 67 - 132 mL (mean,  $92.3 \pm 25.6$  mL).

**Conclusion:** Therefore, intrapleural injection of erythromycin has a certain therapeutic effect on congenital refractory chylothorax in the newborn.

**Keywords:** Erythromycin intrapleural injection, Congenital refractory chylothorax, Newborn

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## INTRODUCTION

The congenital chylothorax in newborns is mainly due to the rupture of the thoracic duct or the thoracic lymph vessel, which makes the lymph leak into the thoracic cavity; this is the most common reason for pleural effusion in newborns [1]. The incidence of congenital chylothorax is about 0.1 - 0.5 %, and the case fatality rate is as high as 20 - 50 % [2]. There are more males than females that are affected by this disease, and right-sided congenital chylothorax is more prevalent [3]. The occurrence of chylothorax is

congenital, traumatic, tumorous, spontaneous and embolic, etc., and the delay of the disease may lead to severe respiratory, nutritional, and immune dysfunction, which is often the leading cause of death [2].

The principle of treatment includes the chyle drainage, respiratory support, fluid infusion and parenteral nutrition; the total effective rate of treatment is about 80 % [4]. The operative treatment can be considered in cases where there is no improvement in 2 - 4 weeks, but there is a very high death risk [5]. Thus, seeking other

treatments to assist with surgical treatment seems to be particularly important. Studies have argued that [5,6] the intrapleural injection of anhydrous alcohol, erythromycin and growth inhibition have a good application value in decreasing the drainage volume and time and improving the cure rate. Thereby, erythromycin, widely used in the treatment of chylothorax, promotes inflammation on the surface of the pleural serous membrane [7].

Based on the above, this study observed the treatment effects of congenital refractory chylothorax on the newborn with the intrapleural injection of erythromycin at our center in comparison with those without erythromycin.

### Study population

The retrospective summary was conducted with 13 cases of newborns with congenital chylothorax that were diagnosed at our hospital for the first time from January 2013 to January 2016. The diagnosis was based on comprehensive clinical manifestations, chest X-ray, ultrasound and thoracocentesis. The study was approved by the Ethics Committee of the Heji Hospital Affiliated with Changzhi Medical College (approval no. H201505), and conducted according to Declaration of Helsinki [8]. Signed informed consent forms were obtained from all subjects.

### Treatment method

At first, the conventional treatment was applied, which included chest drainage, respiratory support, parenteral nutrition, fluid and protein infusion.  $\alpha$ 10-type color Doppler imager (ALOE, Japan) (the frequency of special convex array probe was 3.5 MHz), including puncture guide frame, 10F one-time pigtail drainage catheter (BONTHE, Taiwan) and 18G puncture needle were used in the guidance of thoracocentesis. The tube was inserted as guided by the ultrasound, and the drainage pack was connected for continuous drainage. Patients with complicated pneumothorax received the closed drainage of the thoracic cavity. The drainage volume and residual liquid volume were evaluated via ultrasonic testing every day, and the degree of pulmonary dilation and the air-liquid level change was observed. This was done in combination with chest radiography. Depending on the reduction in chyme fluid, determine the number of times of use, at intervals 48 h.

The drainage tube was removed when the drainage flow was reduced to about 20 ml/d. The

low-flow oxygen inhalation via a nasal catheter or mask was conducted, and the trachea cannula assisting mechanical ventilation could be performed if necessary. If the chest drainage flow continued to decline, then complete fasting was not needed for the infants but was fed with formula milk containing medium-chain triglyceride. The complete intravenous nutrition was recommended for infants with severe chylothorax. Based on the biochemical index, the albumin was supplied appropriately to maintain a plasma albumin level  $> 30$  g/L.

After the drainage was reduced, a non-fat diet was provided instead. Those patients with no reduction in drainage flow ( $> 10 - 15$  ml/kg/d) and no remission in symptoms or even aggravation were considered to receive the intrapleural injection of erythromycin in time. 30 mg/kg erythromycin was added into the 10ml injection containing 25 % glucose, and then mixed uniformly and injected slowly via the drainage tube. After that, the thoracic cavity was clamped for 12 h. The erythromycin was applied again after 48 h. Pain control was done during the sedation-analgesia agent for preventing the pain manifestations of patients in the injection process.

### Statistical analysis

Comparisons were performed using two-sided Student's *t*-test for continuous variables and chi-square ( $\chi^2$ ) test for categorical variables. Continuous variables were expressed as mean  $\pm$  standard deviation (SD).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Basic clinical characteristics of cases

There were 9 males and 4 females (age range was 1-20d, the median age was 10.5d), including 4 premature infants and 9 full-term infants, 10 cases of spontaneous delivery and 3 cases of cesarean delivery. The birth weight range was 1.8 - 3.3 kg, and  $2.5 \pm 0.8$  kg on average. There were 3 cases of left-sided pleural effusion, 8 cases of right-sided pleural effusion, and 2 cases of bilateral pleural effusion. There were also 2 cases of complicated congenital heart disease, 2 cases of complicated pneumothorax, and 3 cases of complicated pulmonary infection.

### Treatment and outcomes

Patients who did not receive the treatment with erythromycin received continuous drainage ( $n=6$ ). Patients that received the treatment with

erythromycin were administered the injection a total of 1 - 3 times ( $1.5 \pm 0.6$ ) times (based on the decrease of chylous liquid, the number of injection was determined), on average with the injection dose between 80 – 210 mg ( $126.5 \pm 32.7$  mg on average); post-treatment with erythromycin injection, the patients then received continuous drainage ( $n=7$ ). There were 10 cases of active treatment (76.9 %) in total. The other 1 case of respiratory failure, 1 case of severe infection, and 1 case of death.

According to whether treated with erythromycin injected through the chest drainage tube or not, the neonatal patients were divided into the erythromycin group ( $n = 6$ ) and non-erythromycin group ( $n = 7$ ). The data analysis results showed that: There was no statistically significant difference in newborn age and birth weight ( $P > 0.05$ ); compared with the non-erythromycin group, treatment days, and drainage volume in erythromycin group were both statistically significant ( $P < 0.05$ ). The result showed in Table 1.

**Table 1:** Therapeutic effect of erythromycin injection

Group	Erythromycin ( $n=6$ )	Control group ( $n=7$ )	<i>P</i> - value
Newborn age (day)	$10.7 \pm 3.1$	$10.4 \pm 2.8$	0.01
Birth weight (kg)	$2.7 \pm 0.7$	$2.5 \pm 0.9$	0.02
Treatment days	5-13 ( $8.6 \pm 2.3$ )	7-12 ( $10.2 \pm 2.1$ )	0.08
Drainage volume (ml)	67-132 ( $92.3 \pm 25.6$ )	50-150 ( $84.3 \pm 35.2$ )	0.13

## DISCUSSION

The mechanism of action of the treatment of chylothorax with the intrapleural injection of erythromycin is that the saturated lactobionic acid injection of erythromycin is diluted, which shows moderately strong alkalinity. The strong chemical stimulus was used to induce a significant increase of white blood cell count in the serous cavity, thus causing the inflammatory reaction and fibrocyte hyperplasia on the serosal surface. Besides, the intrapleural injection of erythromycin can lead to lung tissue hyperemia, edema, cellulose leakage and other aseptic inflammatory reactions, thus prompting the pleural adhesions in the thoracic duct to break and occlude the pleural cavity, preventing the further leakage of chylous liquid [9].

This study shows that the intrapleural injection of erythromycin for patients with inadequate response to conventional conservative treatment

could significantly reduce the drainage flow, and the effective treatment rate was 76.9 % (10/13). Some studies also suggest [10] that the intrapleural injection of erythromycin in the early stage can significantly shorten the drainage time, reduce the drainage flow, improve the cure rate and reduce the severe complications and mortality. The primary adverse reaction of erythromycin is acute chest pain, with an incidence of about 30 - 65 % [11]. Erythromycin is also used in renal cyst sclerotherapy [12]. In addition, there are also many pleural fixatives, such as talcum powder and hypertonic glucose. Talcum powder can increase the risk of pulmonary mesenchymoma [13], while hypertonic glucose can increase the difficulty of pleural effusion extraction [14]. Studies have also found that anhydrous alcohol injection can cause cell dehydration and solidification and cystic wall adhesion [15]. Also, the treatment dose for chylothorax is less than that of erythromycin, which has definite treatment effects and fewer complications. Anhydrous alcohol is widely used in the treatment of cysts and liver cancer [16] but is rarely used in the treatment of chylothorax [17]. Somatostatin is a small-molecule peptide hormone, and the long-acting preparation of octreotide in terms of the molecular structure and biological function, as the somatostatin analog, can be applied via intravenous injection, subcutaneous injection and intramuscular injection. Studies have suggested that the treatment of chylothorax in the newborn may significantly reduce arteriovenous blood perfusion, inhibit the stomach, intestine, and pancreas from secreting proteins and bile and reduce the intestinal absorption and lymphatic formation through strengthening visceral vasoconstriction, eventually healing the thoracic duct break [18]. Somatostatin achieves this definite treatment effect with good tolerance, and therefore, it should be chosen as soon as possible after conservative treatment failure, which has an essential value in shortening the treatment time and reducing the complications [19].

The study used the ultrasonic guidance for thoracocentesis and catheter drainage, and therefore, it has accurate positioning, a high success rate of puncture, the reduced failure rate of blind puncture, and the operation could be repeated, which is especially suitable for patients with encapsulated pleural effusion, the necessity of repeated thoracic cavity positioning and complicated pneumothorax [20]. Ultrasound can also assist in the qualitative diagnosis of chylothorax, including the viscosity, whether it is separated or wrapped, effusion form, pleural thickness, drainage risk and benefit, chest fluid-

covered mass [21]. Moreover, ultrasound can visually and clearly display the anatomical relationship between effusion and surrounding tissues, thereby accurately keeping off the great vessels, nerves, and lung tissue. It can also repeatedly check and reflect whether the effusion compresses the peripheral viscera, affects the lung volume, and mediastinal displacement in a non-invasive, continuous, and dynamic way. According to the effusion amount, the drainage flow can be determined every day, and the outcome of the disease can be evaluated in order to guide the next treatment, etc. [22]. Reasonable release amount of chyle: If the chyle amount is increased rapidly after the thoracocentesis drainage, the negative-pressure suction continuous chest drainage should be considered in order to reduce the interruption and repetition of thoracocentesis, increase the occurrence risk of pneumothorax, hemothorax or wrapped chylothorax [23]. Continuous chest drainage can promote the two layers of pleura in viscera and wall to get close to each other tightly, which effectively prevents lymphatic leakage, reduces the capacity of chylothorax, and shortens the treatment time.

### Limitations of the study

The number of clinical samples used in this study was small, thus limiting the application of the findings. Furthermore, the study did not involve the determination of inflammatory serological indicators; also, the method used for the evaluation of erythromycin effect was relatively simple.

### CONCLUSION

During the treatment of congenital refractory chylothorax in the newborn, intrapleural injection of erythromycin has a specific effect on congenital refractory chylothorax: Early intrapleural injection of erythromycin reduces drainage time and drainage flow, but improves cure rate, and mitigates severe complications and mortality.

### DECLARATIONS

#### Conflict of interest

No conflict of interest is associated with this work.

#### Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. Yun Shi conceived the idea, analyzed the data drafted and revised the manuscript while Ying Zhang collected data, arranged the image, monitored data collection for the whole process and revised the paper. Yun Shi and Ying Zhang designed the study, drafted and revised the paper; he is responsible for the integrity of this study.

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