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# Pleurodesis with povidone–iodine for refractory chylothorax in newborns: Personal experience and literature review

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ABSTRACT

*Introduction:* Refractory chylothorax is a severe clinical issue, particularly in neonates. Conventional primary approach is based on diet with medium-chain fatty acids and/or total parenteral nutrition. In nonresponders, proposed second line treatments include chemical or surgical pleurodesis, thoracic duct ligation, pleuroperitoneal shunting and pleurectomy but none of these have been shown to be superior to other in terms of resolution rate and safety. Our aim is to report our experience on povidone–iodine use for chemical pleurodesis in newborn infants with chylothorax unresponsive to conservative treatment.

Our aim is to report our experience on povidone–iodine use for chemical pleurodesis in newborn infants with chylothorax unresponsive to conservative treatment.

*Methods:* Since 2013, povidone–iodine pleurodesis was attempted in all patients with persistent chylothorax who failed conservative treatment (no response to at least 10 days of total parenteral nutrition and maximum dosage of intravenous octreotide). Pleurodesis consisted in the injection of 2 ml/kg of a 4% povidone–iodine solution inside the pleural space, leaving the pleural tube clamped for the subsequent 4 hours.

*Results:* Five patients were treated with chemical pleurodesis of persistent chylothorax. Four of 5 patients had their pleural effusion treated by one single povidone–iodine infusion. Median time for resolution was 4 days. A patient with massive superior vena cava thrombosis did not benefit from pleurodesis. None of the patients experienced long term side effects of the treatment.

*Conclusion:* Our data suggest that povidone–iodine pleurodesis may be considered a safe and effective option to treat refractory chylothorax in newborns.



Refractory chylothorax either congenital or iatrogenic is a severe clinical issue difficult to solve, particularly in neonates [1]. Conventional primary approach is based on diet with medium-chain fatty acids and/or total parenteral nutrition. Treatment with intravenous administration of somatostatin or octreotide, serial thoracentesis or continuous chest drainage is frequently needed [1,2]. This conservative approach is widely applied as first line treatment, because of a reported success rate reaching 80% [3]. In nonresponders, proposed second line treatments include chemical or surgical pleurodesis, thoracic duct ligation, pleuroperitoneal shunting and pleurectomy [1,3–6]. In particular, pharmacologic or chemical pleurodesis has been suggested also in pediatric patients as a possible alternative step before surgery, with instillation of various agents (povidone–iodine, OK-432, bleomycin, tetracycline) in the pleural space [5,7–9]. Despite the attractiveness of these nonsurgical second line approaches, their indications and timing are still debated and their results ill-defined [1,5,7–11]. Our aim is to present our experience on chemical pleurodesis with povidone–iodine for persistent chylothorax in five consecutive newborn babies to add knowledge to this controversial issue.

## 1. Materials and methods

Records of 5 consecutive newborns treated by povidone–iodine pleurodesis for congenital (1 patient) and acquired (4 patients) chylothorax, have been retrospectively reviewed. The diagnosis of chylothorax was based on the presence of lymphocytes' rate >80% and triglycerides level >110 mg/dl in the pleural fluid. Vena cava thrombosis was actively investigated in all patients. First line therapeutic approach was conservative with total parenteral nutrition and pleural drainage in all patients. Intravenous octreotide therapy was started within 2 to 10 days in case of nonresponse to TPN, and progressively increased, reaching the dose of 7 mcg/kg/h. Chemical pleurodesis was considered in case of failure of conservative treatment, defined as persistence of chylous leak higher than 20 ml/kg/day after 10 days of maximum dosing of intravenous octreotide, or daily drainage volume higher than 50 ml/kg/day while on intravenous octreotide. Informed consent was obtained in all cases. The procedures were performed under general anesthesia. A saline solution diluted 4% povidone–iodine was injected into the pleural space at the dose of 2 ml/kg, and the chest tube clamped for 4 hours. During their hospital stay, the patients underwent continuous monitoring of cardiorespiratory parameters. After the procedure, FLACC (Face, Legs, Activity, Cry, Consolability) pain score scale for children [12] was recorded every four hours for the first three days and

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every six hours thereafter. Additional recordings were performed as needed. Daily chyle output (ml/kg/day) and drainage duration (days) were recorded. Complete blood cells count and differential were performed every 48 hours during the first week and at least once a week thereafter. Thyroid function was evaluated after two weeks from the procedure and at least at one month of follow-up. Adverse drug effects were recorded for two weeks after procedure and at follow-up clinic.

## 2. Results

Patient characteristics are reported in Table 1. US color Doppler screening showed a massive superior vena cava thrombosis in one patient who required heparin treatment. Duration of conservative treatment before pleurodesis and maximal daily chest tube output ranged from 10 to 27 days and 90 to 180 ml/kg/day, respectively. The mean daily chyle output just before pleurodesis was 42 ml/kg/day. In one patient (patient no. 3), octreotide was immediately stopped because of severe hypotension related to drug infusion.

Four patients had their pleural effusion treated by one single povidone–iodine infusion. Median time for resolution was 4 days (range 2–8). In one patient with bilateral chylothorax, a single povidone–iodine infusion in the right emithorax was effective to treat both sides. The patient with massive superior vena cava thrombosis did not benefit from pleurodesis. He was an extremely low birth weight infant who died because of progressive multiple organ failure.

Following pleurodesis, three patients experienced a massive, but transient, homolateral lung atelectasis (Fig. 1) and acute respiratory distress, requiring intubation and mechanical ventilation for 36, 72 and 140 hours respectively. Chest x-rays abnormality resolved spontaneously in all patients. No modifications of FLACC pain score were observed and no additional analgesic drug was required. In all patients in whom the procedure was effective lymphocyte count returned within normal limits after an average of 13 days (range 9–22).

At follow-up, ranging between 24 and 27 months, all survivors had normal thyroid function. Respiratory function was normal in 3 of them. The fourth had high risk CDH with severe pulmonary hypoplasia, causing abnormal pulmonary function.

## 3. Discussion

Persistent chylothorax is associated with high morbidity rate because of either lymphatic leak (leading to protein, immunoglobulin and lymphocytes loss, infections and/or sepsis, thrombosis) or side-effects of therapy itself (parenteral nutrition, mechanical ventilation, chest tube drainage, central venous catheters) [13]. The ideal approach for neonatal chylothorax should allow a success rate close to 100%, being as less invasive as possible. Conservative management, such as nutritional modifications (medium chain triglyceride diet or total parenteral nutrition) and chest drainage, has gained general consensus as first step treatment, because of their success rate ranging between 75% and 80% [14]. Conversely, the optimal management of patients unresponsive to conservative treatment raises concerns, in particular regarding two aspects: the timing when conservative management should be considered failed and the best second-line treatment.

Classically, two parameters are used to define the failure of conservative treatment: volume and duration of persistent lymphatic leak. Cleveland et al. [15] divided their patients in three different categories depending on the volume of daily drainage: more than 50 mL/kg/day; 25–49 mL/kg/day; and 5–24 mL/kg/day. The treatment was defined effective when the drainage went below the lower limit for the departing category. Surgery was then indicated only when the effective reduction was not obtained after 3, 6 and 12 days in the first, second and third categories, respectively. In two previous series, of 51 patients each, failure of conservative treatment was defined in case of lymphatic output >10 ml/kg/day after four weeks of therapy [6,14]. In our experience, we consider conservative treatment ineffective in case of persistence of chylous leak higher than 20 ml/kg/day after 10 days of maximum dosing of intravenous octreotide, or daily drainage volume higher than 50 ml/kg/day while on intravenous octreotide. Our criteria are more cautious than other previously reported to avoid general failure in these fragile patients with high chyle daily output.

Regarding the best second-line treatment, different surgical approaches (pleuroperitoneal shunting, pleurectomy, surgical pleurodesis, thoracic duct ligation) have been proposed, with no definitive success [16–20]. Surgical duct ligation and video-assisted surgical pleurodesis/pleurectomy are the most commonly used surgical procedures after õfailure of conservative treatment [16]. The surgical duct ligation by right thoracotomy or thoracoscopy is not always successful, since variable ductal anatomy may facilitate lymphatic leak recurrence [21]. Identification of leaking sites on the side of effusion and ligation of all tributaries together with the main duct is reported to increase the success rate up to 90% [13,21,22]. Thoracoscopic pleurodesis/pleurectomy was performed, by Le Nué et al. [1], in 5 patients with complete resolution in 4; one patient died because of severe acute respiratory distress syndrome. Pleuroperitoneal shunting is less performed today in newborn babies because of severe complications such as shunt occlusion reported in 30% to 50% of cases [17–20].

In order to limit aggressive procedures in young, fragile, infants, chemical pleurodesis has been proposed as an alternative to surgery, with increasing attention during the last years. Several agents have been used in newborn babies [1,5–10] including povidone–iodine. The use of povidone–iodine was first reported in 1991 [23] for the treatment of adults with malignant pleural effusions. The precise mode of action of povidone–iodine is not clear. Inflammation is certainly part of the process, as suggested by experimental studies [24] that showed high protein and LDH levels and total WCC in the pleural fluid of rabbits that underwent intrapleural povidone–iodine infusion. Corticosteroids administration was associated with significant reduction of local inflammatory response and povidone–iodine efficacy. Iodine has strong oxidative and cytotoxic properties, which induce a potent inflammatory response in the wall of any fluid containing structure, possibly also through antiexudative properties related to the chelation of proteins [25]. In addition, the low pH of povidone–iodine (2.97) may contribute to the local inflammatory response [26]. In adults, its use has

**Table 1**
Patients characteristics.

| Pt | BW (g) | GA (weeks) | Diagnosis | Type | Side | Age at procedure (days) | Conservative treatment (days) | Mean Leak (ml/kg/day) | Lowest WBC count (blood; n × $10^3$ μL) | Lowest lymph. count (blood; ×$10^3$ μL) | Lymph. rate (blood) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2650 | 40 | Perinatal asphyxia | Congenital | Bilateral | 67 | 27 | 15 | 6.1 | 0.66 | 6% |
| 2 | 2830 | 35 | Type C EA | Acquired | Right | 34 | 23 | 20 | 2.74 | 1.36 | 33% |
| 3 | 3670 | 41 | CDH | Acquired | Left | 34 | 14 | 72 | 8.84 | 0.96 | 11% |
| 4 | 672 | 28 | SVC thrombosis prematurity | Acquired | Bilateral | Right 36 Left 42 | 10 | 65 | 3.87 | 0.26 | 2.5% |
| 5 | 2970 | 39 | CDH | Acquired | Left | 27 | 15 | 37 | 7.42 | 0.97 | 8.5% |

Abbreviations: BW: birth weigh; CDH: congenital diaphragmatic hernia; EA: esophageal atresia; Lymph: lymphocytes; Pt: patient; SVC: superior vena cava; WBC: white blood cells.