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Research Article

Application of Povidone-Iodine for Treatment of Chylothorax in Children

Kozlov Yuri Andreevich[1-3]*, Kovalkov KA[4], Poloyan SS[5], Baradieva P Zh[1], Zvonkov DA[3], Ochirov Ch B[1], Cheremnov VS[1] and Kapuller VM[6]*

[1]*Regional Children's Teaching Hospital, Irkutsk, Russia*

[2]*Irkutsk State Medical Academy of Postgraduate Education, Irkutsk, Russia*

[3]*Irkutsk State Medical University, Irkutsk, Russia*

[4]*MBHI Children's City Teaching Hospital, Kemerovo, Russia*

[5]*Maternal and Child Health Center, Krasnoyarsk, Russia*

[6]*Assuta University Medical Center, Ben Gurion University, Ashdod, Israel*

***Corresponding Author:** Kozlov Yuri Andreevich, Chief Medical Officer of the Regional State Funded Healthcare Facility, Children's City Teaching Hospital, Irkutsk, Professor of the Department of Pediatric Surgery at the State Budgetary Educational Institution of Higher Professional Education ISMU, Professor of the Department of the State Budgetary Educational Institution of Higher Professional Education Irkutsk State Medical Academy of Postgraduate Education, Russia.

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Abstract

Introduction: The aim of this study is to demonstrate the experience of non-surgical treatment of congenital and acquired chylothorax using povidone-iodine in children.

Research Materials and Methods: The study presents the results of treatment of 10 patients with chylothorax who underwent chemical pleurodesis using the povidone-iodine medication. The study covered a period from 2016 to 2020. The congenital nature of the disease was registered in 2 patients, the acquired nature of the disease was reported with 8 patients. The main surgical indication was the lack of effect on conservative therapy, including feeding cessation and the administration of the octreotide medication. The procedure consisted of intrapleural injection of 4% povidone-iodine solution into the pleural cavity with a calculated dose of 1 ml/kg and exposure dose of the solution for 4 hours.

Results: The interpleural povidone iodine procedure was effective in all patients. Complications of chemical pleurodesis were registered with 2 patients and were associated with pulmonary edema on the injection side. Lymph outflow stopped on the 4th day, at average. One failure due to malformation of the lungs incompatible with life was reported.

Conclusion: Intrapleural administration of povidone-iodine is an effective treatment for chylothorax in children.

Keywords: *Chemical Pleurodesis; Chylothorax; Povidone Iodine*

Introduction

The accumulation of lymphatic fluid in the pleural cavity is most often pathological in nature and is one of the reasons that lead to hydrothorax in young children. Chylothorax is quite rare and occurs from 1: 6000 to 1: 24000 newborn infants [1]. This pathological condi-

tion is often accompanied by early gestational age of the child, low birth weight, fetal edema, and pulmonary hypoplasia [2-5]. The death rate resulting from this disease reaches 60% [6].

Chylothorax can be congenital or acquired, representing one of the intractable therapeutic problems in perinatal medicine [7]. Initial therapy for pleural lymph accumulation involves a modified diet, including medium chain triglycerides, or complete feeding cessation. If complete parenteral nutrition does not lead to disappearance or decrease in the rate of lymph flow, intravenous administration of somatostatin (octreotide) is prescribed [8]. The success of this approach is estimated at about 80% [9]. In the remaining 20% of patients, various treatments are used, such as ligation of the thoracic lymphatic duct, pleuroperitoneal shunting, pleurectomy, and chemical pleurodesis [10,11]. The main effect of chemical pleurodesis is chemical irritation of the pleural sheets that leads to their adhesion, which ultimately contributes to the cessation of lymph flow. The plant extract Viscum album, picibanil (OK-432), bleomycin, and povidone-iodine are used as active substances for this procedure [11-14]. However, there is still no definite answer about this treatment efficacy [15].

Aim of the Study

The aim of this study is to demonstrate the experience of non-surgical treatment of congenital and acquired chylothorax using povidone-iodine in children.

Materials and Methods

The research article presents the results of treatment of 10 patients with chylothorax who underwent chemical pleurodesis using the povidone-iodine medication. The study covered a period from 2016 to 2020. The congenital nature of the disease was registered in 2 patients, the acquired nature of the disease was reported with 8 patients. Congenital chylothorax was caused by intrauterine asphyxia, an idiopathic accumulation of lymph in the chest. Acquired chylothorax was caused by previous surgeries on thoracic organs, performed in connection with congenital diaphragmatic hernia, esophageal atresia, congenital heart diseases.

The main features that distinguish chylothorax from other types of hydrothorax were a definitive cellular composition, in which lymphocytes accounted for more than 80%, and a triglyceride concentration exceeding 1.24 mmol/l. The primary treatment for chylothorax consisted of placing a drainage tube into the pleural cavity and discontinuing enteral nutrition with a switch to complete parenteral nutrition. If there was no effect of such therapy for 5 days, then intravenous administration of octreotide at a dose of 10 μg/kg/h was prescribed. If octreotide therapy was ineffective for 10 days, that is, lymph flow remained at a level of 10 ml/kg/day or more, then chemical pleurodesis was performed using povidone-iodine.

Chemical pleurodesis technique

A standard 10% povidone-iodine solution (Betadine - manufactured by ZAO Pharmaceutical Plant EGIS) was diluted with saline NaCl until a concentration of 4% was reached. After dilution, the medication was injected into the pleural cavity through a previously installed drainage tube at the rate of 1 ml/kg and remained there for 4 hours. During the exposure period of povidone-iodine, continuous monitoring of gas exchange and hemodynamic parameters was carried out. In the event of the appearance of cardiorespiratory effects, the drainage tube was opened and the medication was removed to the outside. Patients with side effects of povidone-iodine administration underwent measures aimed at restoring impaired functions, involving artificial ventilation of lungs and infusion of cardiotonic medications. In the period after chemical pleurodesis, the daily volume of lymph secreted was recorded. To assess treatment efficacy that was performed, registration of early (side effects, timing of lymph secretion cessation) and long-term (recovery) consequences of treatment was made.

Results

The gender composition of the chylothorax patients included 6 boys and 4 girls and did not show clear sexual dominance. The average age of patients at the time of treatment of chylothorax using chemical pleurodesis was 18,2 days (the range from 10 to 28 days). Average infant weight is 3026,9g (the range from 2164 to 4200g). The duration of prior treatment with complete parenteral nutrition and octreotide averaged 15,1 days (the range from 8 to 24 days). The rate of lymph flow prior to the onset of chemical pleurodesis averaged 127,5 ml (the range from 80 to 300 ml). A single interpleural injection of povidone-iodine was sufficient in 8 patients. Two-fold administration of the medication was required in 2 patients.

Patient	Age (days)	Weight (g)	Reason	Duration of conservative therapy (days)	Maximum lymph volume (ml)	Lymph flow cessation (days)	Complications
1	26	3010	CDH	20	80	4	RDS
2	12	2380	EA	10	125	4	
3	17	4200	Asphyxia	15	120	5	
4	18	2850	CDH	12	300	2	
5	23	2600	CDH	22	180	4	
6	28	2430	EA	24	80	4	
7	10	3740	CDH	8	90	3	Fatal case
8	14	2164	CHD	10	110	6	
9	15	2875	CHD	12	80	2	RDS
10	19	4020	Idiopathic congenital CT	18	110	6	
Averages		3026,9		15,1	127,5	4	

Table 1: *Results of chemical pleurodesis.*

Notes: CT: Chylothorax; CDH: Congenital Diaphragmatic Hernia; EA: Esophageal Atresia; CHD: Congenital Heart Disorder; RDS: Respiratory Distress Syndrome.

Complications of chemical pleurodesis were observed in 2 patients and were associated with pulmonary edema on the injection side, which manifested itself as a clinical picture of total lung atelectasis and respiratory distress syndrome. These patients required artificial lung ventilation, which was carried out for 24 and 48 hours. Lymph outflow stopped on the 4th day, at average (the range from 2 to 6 days).

In the long-term follow-up period (from 1 to 5 years), normal indicators of lung function were observed in 8 patients. Problems associated with pulmonary hypoplasia persisted in 2 patients. One of the patients with congenital diaphragmatic hernia died 10 months after birth of progressive deterioration of gas exchange and pulmonary hemodynamics against the background of pulmonary hypoplasia.

Discussion

Congenital or acquired accumulation of lymph in the chest or chylothorax is an orphan disease that causes respiratory distress due to a lung compression. One of the main ways to drain excess lymph to the outside is to drain the pleural cavity. However, such treatment is very often accompanied by significant losses of fluid, protein, immunoglobulins, lymphocytes, which contributes to the development of generalized infection as a result of weakened immunity and (or) penetration of bacteria into the body at the sites of pleural drainage and central venous catheter [16]. Chylothorax in children, unlike adults, is often the cause of a fatal case. Despite the fact that this disease has been known for a long time, until now there are no universal treatment guidelines necessary to achieve an optimal therapeutic effect.

There are conservative and surgical treatments for chylothorax. Among them, conservative therapy, including the appointment of a diet containing medium-chain triglycerides or nutritional cessation with complete parenteral nutrition administration with the installation of pleural drainage, has received universal approval from the researchers of this problem. The effectiveness of this approach in combination with the administration of somatostatin (octreotide) is about 80% [17]. P. Rimensberger was the first to report the use of somatostatin in a 4-month-old child with chylothorax after cardiac surgery [18]. Further studies confirmed high efficacy of this medication in the treatment of lymph congestion in the chest. Two meta-analyzes of the literature [19,20] have demonstrated success rates of octreotide treatment of 70% and 53%, respectively. The best effect was observed when the medication was prescribed at a concentration of 10 μg/kg/min [21,22]. In addition, somatostatin was used intravenously at a high dose (20 μg/kg/h or even more) without obvious concurrent reactions [23]. However, later reports of collateral damages following the use of this medication, including nausea, bloating, diarrhea or constipation, hyperglycemia, dermahemia, liver dysfunction, necrotizing enterocolitis and transient hypothyroidism, have questioned the safety of such treatment [24,25].

In addition, the fate of the remaining 20% of patients with chylothorax who were not responsive to octreotide treatment is a concern. The main findings that indicate the ineffectiveness of conservative therapy for chylothorax in newborns are the duration of lymph loss and its volume released to the outside through the drainage tube. It remains unclear what value of these parameters is critical? Thus, K. Cleveland admits that the volume of lymph leakage less than 25 ml/kg/day is a criterion for the success of therapy [26]. In the studies of M. Beghetti and V. Büttiker, this parameter is estimated as 10 ml/kg/h [17,27] and F. Scottoni - as 20 ml/kg/h [1]. In this research article, we evaluated the efficacy of octreotide treatment based on the determination of the volume of daily lymph loss, the value of which is less than 10 ml/kg/day.

Various methods are often considered as surgical methods, such as pleuroperitoneal bypass grafting, pleurectomy, surgical pleurodesis, and ligation of the thoracic duct [28,29]. Thoracic lymphatic duct ligation and surgical pleurodesis using pleurectomy are most commonly used as reliable remedies for stopping abnormal flow of lymph from the pleural cavity. However, it has been found that simple ligation of the thoracic lymphatic duct using thoracotomy or thoracoscopy is not always successful, since the anatomy of the lymphatic system can be varied and thus contribute to the occurrence of relapse due to the presence of an extensive network of lymphatic vessels [30,31]. Wide ligation of para-aortic tissue, including thoracoscopy, can increase the efficacy of this surgery up to 90% [32]. Thoracoscopic pleurodesis using pleurectomy was first reported by Le Nuè [7]. Pleuroperitoneal lymph shunting is accompanied by dysfunction of the shunting system and has become a little popular method at the present time [28,29].

Pleurodesis using various chemical substances has been proposed as an alternative to the surgical treatment of chylothorax, especially in young children due to its low aggressiveness. Several medications have been used for this purpose, including povidone-iodine. The use of povidone-iodine was first introduced in 1991 [33] for the treatment of adults with malignant tumors. The mechanism of action of povidone-iodine is associated with the occurrence of aseptic inflammation. This effect was found in an experiment that showed a high content of leukocytes, protein and lactate dehydrogenase in the pleural fluid of rabbits subjected to the introduction of povidone-iodine into the pleural cavity [34]. Iodine in this agent has strong oxidative and cytotoxic properties that induce a powerful inflammatory response in any structure containing fluid [35]. In addition, having a low pH (pH = 2,97), povidone-iodine contributes even more to the development of a local inflammatory reaction [36]. For the first time, this medication was used in adult patients with malignant diseases of pleura and lungs. Scientific research carried out by R. Agarwal demonstrated that treatment efficacy can reach 90% [37].

Reports of the use of povidone-iodine for the treatment of chylothorax include several small series of patients [1,6,7,11,15,38-40]. In these studies, the concentration of the povidone-iodine solution varied significantly, ranging from 2 to 10%. We used a solution with a concentration of 4%, which was injected into the pleural cavity, based on the calculation of 1 ml/kg. The lack of consensus on the protocol for such a procedure has led to great variability in treatment outcomes. The results of studies available to date demonstrate the effec-

tiveness of pleurodesis using povidone-iodine, ranging from 100 to 64% [1,7,11,15,38]. In our study, we received a 100% effect, but in 2 patients it was achieved by two-fold injection of the medication into the pleural cavity.

The currently known contraindications for the use of chemical pleurodesis with the use of povidone-iodine are diseases associated with thrombosis of the superior vena cava [1], as well as lung abnormalities, accompanied by lymphangiectasia [39,40]. Thereby, computed tomography of lungs is recommended for the detection of lymphangiectasia in idiopathic chylothorax [40].

Collateral damages may be associated with povidone-iodine therapy. The most dangerous complications include respiratory distress syndrome, acute and chronic renal failure, hemodynamic collapse, and respiratory distress syndrome [39]. Other collateral damages are associated with the presence of iodine in the medication and include hyperthyroidism, hypothyroidism, allergic reactions, and pain [11,37]. It was found that the risk of toxic effects of the medication and subsequent renal failure is highest in patients with pulmonary lymphangiectasis [15]. B. Resch reports 2 cases of failures after the use of povidone-iodine in newborns with congenital chylothorax caused by pulmonary lymphangiectasia. It is assumed that this anomaly contributes to an increase in the absorption of povidone-iodine, which leads to severe intoxication.

The most serious complication of chemical pleurodesis with the use of povidone-iodine is associated with the development of respiratory distress syndrome caused by pulmonary edema in response to the introduction of a chemical agent [11]. We inform of 2 patients with pulmonary edema.

Several studies have reported the occurrence of acute renal failure after introduction of povidone-iodine into the pleural cavity, which is apparently associated with the absorption of the medication and its general toxic effect on the body [11,15]. It is obvious that a decrease in the toxic effect of povidone-iodine can be ensured by a decrease in the concentration of the injected solution from 4% to 2%, which was reported in one of the experimental studies carried out on rabbits [34].

Despite these warnings, the effect of chemical pleurodesis remains quite high and approaches 100%. A similar success rate for treatment of chylothorax in newborns was confirmed in our study.

Thus, pleurodesis using povidone-iodine is a simple and highly effective treatment option for chylothorax in newborns. Prevention of adverse reactions is critical to the successful use of chemical pleurodesis in infants.

Evaluation

The lack of effective treatments for chylothorax prompted the authors of this study to seek new treatments. We have defined that intrapleural administration of povidone-iodine is an effective treatment for chylothorax in children. Despite the fact that this treatment may be accompanied by complications in the form of pulmonary edema in 20% of cases, due to the reversibility of these negative effects, the use of chemical pleurodesis can be recommended as a second line of treatment for pathological lymph accumulation in the pleural cavity. The only limitation of this research article is a small sample of patients, amounting to 10 patients. Therefore, multicenter studies are needed to finally determine the place of chemical pleurodesis in the treatment of chylothorax in children.

Conclusion

Intrapleural administration of povidone-iodine is an effective treatment for chylothorax in children.

Conflict of Interest

The authors declare no conflict of interest.

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Participating Authors

Research concept and design - Kozlov Yu.A.

Collection and processing of material - Poloyan S.S., Baradieva P.Zh., Zvonkov D.A.

Statistical processing - Kovalkov K.A.

Writing - Kozlov Yu.A.

Illustrations - Ochirov Ch.B., Cheremnov V.S.

Editing - Kapuller V.M.

All authors - approval of the final version of the article, responsibility for the integrity of all parts of the article.

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