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Congenital Chylothorax Treated with Oral Sildenafil—Case Report from Nigeria and Review of Literature

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Abstract

Congenital chylothorax, a condition in which chyle accumulates in the pleural cavity, is extremely rare. The reported incidence is 1 in 24,000 births. Medical treatment using octreotide as well as chemical and surgical pleurodesis has been reported, but also few reports on the successful use of Sildenafil exists. We herein report a case of congenital chylothorax referred to our Hospital at 7 days-old. Sildenafil was introduced on day 6 post intubation. Before the introduction of sildenafil, the peak total daily drainage was 106 ml/kg/day (340 mls/day), and after sildenafil was introduced, the total daily drainage dropped progressively to 10 ml/kg/day by day 11 post intubation. This case report highlights the successful use of oral Sildenafil for treatment of congenital chylothorax and also peculiarities of management related to a resource-constrained developing country setting in Africa.

Keywords

Chylothorax, Congenital, Sildenafil, Children

1. Introduction

Congenital chylothorax, a condition in which chyle accumulates in the pleural cavity, is extremely rare. The reported incidence is 1 in 24,000 births [1] and the cause of primary congenital chylothorax is mostly unknown. The mortality can be as high as 64% [1]. Medical treatment using octreotide as well as chemical and surgical pleurodesis has been reported [2] [3], but also few reports on the successful use of Sildenafil exists [4]. Apart from case reports and case series,

there are yet no trials into treatment of chylothorax. To the best knowledge of the author informed by careful literature search, this is the first case of congenital chylothorax being reported in Nigeria. This case report highlights the successful use of oral Sildenafil for treatment of congenital chylothorax and also peculiarities related to a resource-constrained developing country setting in Africa.

2. Case Report

Baby O, 7 days old was referred to our neonatal intensive care on account of persistent dyspnea from birth. No associated fever, cough or perinatal risk factors for sepsis. The baby is a product of emergency caesarean section due to post datism at 41 weeks + 2 days. Apgar scores were 8 at one minute and 10 at five minutes and birth weight was 3200 g. Pleural effusion was observed in the prenatal abdominal scan at 36 weeks gestational age but prior scans were reportedly normal. Prior to referral, the baby was on respiratory support with supplemental oxygen only. She was transferred severely dyspnoeic with saturation of 90% - 94% on oxygen at 5 L/min and 71% on room air. The respiratory rate at the time we received the baby was 82 cpm. Breath sounds were remarkably reduced on the right lungs. The baby was in congestive cardiac failure with heart rate of 170 bpm and tender hepatomegaly. No syndromic facie was present. Chest radiograph showed homogenous opacity in the right hemi thorax with blunting of the right costophrenic angle and mediastinal shift to the left (Figure 1). Needle thoracentesis yielded a milk-coloured free flowing fluid. Under local anaesthesia, pleural catheter was inserted into the right chest using Seldinger technique. A total of 185 mls of milk-coloured fluid was drained in 3 hours. Subsequently, the

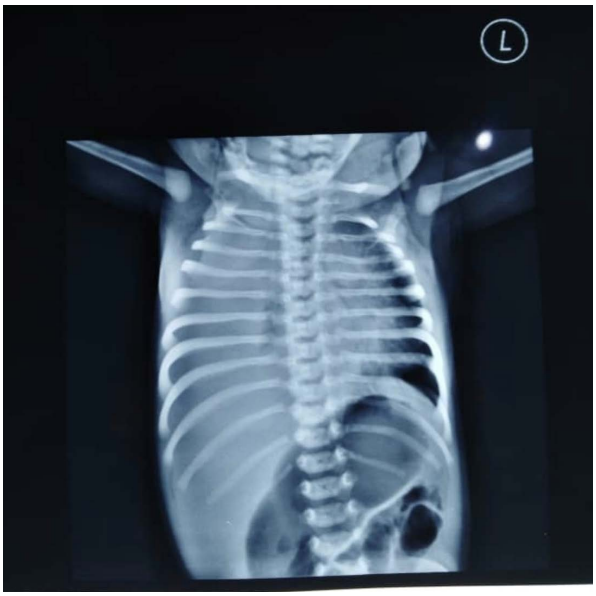

Figure 1. Chest radiograph showed homogenous opacity in the right hemi thorax with blunting of the right costophrenic angle and mediastinal shift to the left.

drainage was 91 ml/kg/day (283 mls/day) in the subsequent 24 hrs post chest intubation. The pleural drainage peaked at 106 ml/kg/day (340 mls/day) on day 2 post intubation. The diagnosis of chylous effusion was made by pleural fluid triglyceride level of 11.24 mmol/l (diagnostic range is >1.2 mmol/l) [5] and cholesterol of 1.35 mmol/l (>1.2 mmol/l is diagnostic) [5]. We provided respiratory support using supplemental oxygen until day 19 of life. Oral sildenafil was introduced on day 13 of life (day 6 of admission). Before the introduction of sildenafil, the peak total daily drainage was 106 ml/kg/day, after sildenafil was introduced, the total daily drainage dropped progressively to 10 ml/kg/day on day 18 of life (day 11 of admission). There was no drainage on day 19 of life and therefore chest tube was discontinued. The dose of sildenafil used was 0.25 mg/kg/dose 8 hourly. Due to unavailability of commercially prepared medium chain triglyceride formula in Nigeria, we used preterm milk preparation (Pre-Nan) which is rich in medium chain triglyceride and discontinued breast milk. Some of the challenges encountered were tube blockage on day 6 of intubation, dislodgment on day 7 and these were resolved by adjusting and re-passing the tube respectively. Fluid and electrolytes were strictly monitored. Daily fluid losses via the tube drainage was replaced by adding additional volume of normal saline to daily fluid requirement. The baby developed hyponatraemia (119 meq/L), metabolic acidosis (HCO_3 = 17 meq/l) on day 13 of life and these were corrected by reconstituting the intravenous fluid regimen. On 13th day of life, we observed severe hypoproteinaemia with total protein of 1.64 g/dl (normal range = 6.0 - 8.0 g/dl) and hypoalbuminaemia (Serum albumin = 0.89 g/dl, normal range = 3.4 - 5.4 g/dl). Parenteral albumin was given and these values increased to 5.4 g/dl and 3 g/dl by day of life 22.

The baby developed sepsis on day 23 of life with fever, chest crepitations and radiological evidence of bronchopneumonia. Blood culture yielded growth of coagulase negative staphylococcus. She was treated with intravenous antibiotics.

Baby was discharged on 29 day of life. She has not had any re-accumulation of pleural fluid and is now two years old at the time of this report and doing well.

3. Discussion

This is the first reported case of which we are aware, of congenital chylothorax in a Nigerian Hospital. It is one of the few reported uses of oral sildenafil in the management of congenital chylothorax. Mallesk and Yoder [4] first reported in 2015, the successful use of oral sildenafil for treatment of congenital chylothorax. While their patient had bilateral chylothorax, our patient had right sided unilateral chylothorax. Both patients resolved on medical treatment with oral sildenafil, theirs within 15 days and our patient within 7 days.

Congenital chylothorax is a very rare condition but the commonest cause of pleural effusion in the perinatal period [2]. The reported prevalence is 1 in 24,000 live births [1]. The mortality rate is high, reaching 64% [1]. Bilateral congenital chylothorax is more common than unilateral presentation [2] [6]. Due to

the rarity of the condition, there is yet no randomized clinical trial on treatment modalities but rather case reports, case series and systematic reviews.

The goals of treatment in congenital chylothorax are firstly, to drain the accumulated pleural fluid, secondly to prevent further re-accumulation, thirdly to treat complications and finally supportive care (nutrition, fluid and electrolyte balance, respiratory support). Drainage of accumulated pleural fluid is achieved by thoracentesis. Carefully controlled drainage is advised to prevent untoward hemodynamic instability due to rapid drainage. One way to achieve this is to clamp the chest tube and allow drainage of controlled quantity of fluid intermittently. In our patient, we allowed not more than 20 - 30 mls drainage hourly in the initial period. It is important to note that pleural fluid re-accumulation is usually the case in congenital chylothorax and this causes prolonged chest tube drainage. The duration of chest tube drainage can be quite long, in those that respond to medical treatment, about 2 - 4 weeks [2] [4] [6] while in one patient, chest tube duration was as long as 81 days [2] despite chemical pleurodesis on day 65. With prolonged chest intubation and drainage, blockage of tube could occur as was the case in our patient on day 6 of drainage. Mallesk and Yoder [4] also reported multiple chest tube obstruction in their patient. However, a careful re-adjustment of the tube is usually sufficient to re-establish flow. Care must be taken to avoid dislodgement as this could occur with crying babies.

The second goal of treatment is to prevent further re-accumulation of pleural fluid. Dietary modifications beginning with total parenteral nutrition and subsequently low-fat, medium chain triglyceride diet eliminate the need for enteral digestion of fats, thereby leading to reduced production of chyle while maintaining essential nutrient requirements. Medium chain triglycerides get directly absorbed into the portal system, thereby bypassing the lymphatic drainage. These formulae are available in commercial preparations but not widely available across all countries. Some people have achieved similar goal of MCT-based formulae by improvising available products. In our patient, we used Nestle Pre-Nan which is a preterm formula that is also rich in MCT and is widely available in Nigeria.

Medical treatment with drugs, chemical and surgical pleurodesis is other interventions that have been employed in order to prevent reaccummulation of chyle [2] [3] [4]. Sildenafil is established for use in management of pulmonary hypertension, but its possible use for treatment of lymphatic malformations had been suggested [7] [8]. Mallesk and Yoder [4] were the first to report its successful use specifically for congenital chylothorax in 2015. In their case report, oral sildenafil proved to be successful where octreotide had failed. Their patient was placed on octreotide on day 9 but the baby continued to reaccumulate chyle by day 22. Subsequently, the infant was started on Oral Sildenafil on day 23. The chylous fluid reaccumulation in their patient was successfully halted by 15 days of the use of oral sildenafil. Their report however did not mention the dose of oral Sildenafil used. In our patient, the chylous fluid reaccumulation stopped by 7 days of introducing oral Sildenafil. We did not try octreotide in our patient

due to its numerous side effects and the convenience of an orally administered drug as an alternative was a strong attraction that informed our choice of Sildenafil over Octreotide. We used Sildenafil dosage of 0.25 mg/kg/dose Q8hrs, similar to the dosing for pulmonary artery hypertension. Although, we were prepared to increase the dose, this was not necessary because of the satisfactory response. It has been thought that sildenafil stimulates the development of new lymphatic vessels, a process called lymphangiogenesis [9] [10]. This physiologic lymphangiogenesis is achieved by selective inhibition of phosphodiesterase-5 [11]. The latter causes degradation of cyclic guanosine monophosphate which in turn mediates lymphatic endothelial cells proliferation, migration and tube formation, hence promotes lymphatic cell growth [12]. Octreotide, on the other hand, is a somatotropin analogue. The side effects of Octreotide must be monitored and this includes arrhythmia, hyperglycaemia, transient impairment of liver function, transient hypothyroidism, nectrotizing enterocolitis, hypoxaemia, and pulmonary hypertension of the newborn. On the contrary, sildenafil has no such myriad of side effects.

The third goal of treatment is management of complications. Some of the complications of congenital chylothorax include hydrops fetalis, sepsis and heart failure [13]. Others are malnutrition, hypoproteinaemia, hypoalbuminaemia and dyselectrolytaemia [13]. Our patient had Sepsis due to coagulase-negative staphylococcus by day 20, but responded well to antibiotic treatment. Sepsis in congenital chylothorax is probably due to secondary immunodeficiency due to loss of lymphocytes and gamma globulins in chylous fluid. Wasmuth-Pietzuch *et al.* [14] reported nosocomial infection in four out of seven (57%) infants with congenital chylothorax. Kovacikova *et al.* [15] reported decreases in absolute numbers of B lymphocytes, T lymphocytes, helper T cells and suppressor T cells in patients with congenital chylothorax. Another complication that our patient manifested was severe hypoproteinaemia, this was managed by administering parenteral albumin infusion.

Supportive treatment is an important component of care. This includes respiratory support, attention to fluid and electrolyte balance and nutrition. While optimal caloric, protein and fat intake is needed for growth, there are certain adjustments that become necessary in management of congenital chylothorax. Eliminating the need for intestinal digestion of fats and protein while still maintaining the supply of these vital nutrients is the ultimate goal.

Chemical pleurodesis using povidone Iodine has also been used where other modalities failed [2]. Surgical intervention may be required. It is suggested that surgery should be considered after 4 - 6 weeks of unsuccessful medical management. The surgical modalities are thoracic duct ligation/embolization and pleuroperitoneal shunt.

Some important perspectives from this developing country setting are worthy of mention. The most pertinent is the issue of late referral. Since the prenatal scan at 36 weeks gestation had suggested "pleural effusion", it is expected that

the mother would have been referred prenatally to a center that has requisite capacity to fully evaluate the baby from birth and institute required care but this was not done. Even after birth, the baby was referred at 7 days old in critical condition. This issue of poor referral system reflects peculiar limitations of under-developed health systems. The intervention of governmental and non-governmental organizations in improving healthcare access through affordable social health insurance scheme will go a long way.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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