CASE REPORT

Intrapleural injection of OK-432 as the primary in-utero treatment for fetal chylothorax

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Chylothorax is a rare congenital condition associated with significant perinatal mortality and morbidity. Previous treatments with repeated thoracocentesis or thoracoamniotic shunting were technically demanding, and associated with significant procedure-related complications and neonatal complications. Here we report the first successful case in Hong Kong treated by a simple and effective intervention, namely pleurodesis with OK-432, in a fetus presenting at 20 weeks of gestation with bilateral pleural effusion.

Introduction

Congenital chylothorax is a rare condition which occurs in 1 per 10 000 to 15 000 pregnancies. The natural history of this disease is variable. The condition may resolve spontaneously, remain static, or cause significant pressure effects on the developing fetal heart and lung. It is a serious condition with an overall mortality up to 53%.[1] The major cause of death is pulmonary hypoplasia especially if the condition occurs before 24 weeks, during which the lung development is most sensitive to external compression. Accordingly, the presence of fetal hydrops, bilateral pleural effusion, and preterm delivery are associated with poor perinatal outcome.

Although spontaneous resolution of this condition occurs in about 22% of cases,[2] fetal intervention is warranted in those cases with severe pleural effusion causing mediastinal shift, hydrops, rapid accumulation of effusion and polyhydramnios. Thoracocentesis is usually not helpful as the fluid often re-accumulates soon and repeated attempts are unavoidable. Thoracoamniotic shunting is the mainstay of treatment but is a highly demanding technique with high rate of complications, which include procedure failure, shunt blockage, shunt dislodgement,[3] and recurrent pleural effusions. Despite treatment, most newborns still require neonatal interventions such as chest drainage, mechanical ventilation, and prolonged hospitalisation, until pleural fluid production stops either spontaneously or following neonatal pleurodesis. In-utero pleurodesis may have an advantage in that it is technically simpler and requires no further neonatal intervention. We report our recent experience of in-utero pleurodesis, using OK-432 as the primary treatment modality in a case of hydrops fetalis due to chylothorax at 22 weeks.

Case report

A 35-year-old nulliparous woman was referred to our fetal medicine unit for fetal hydrothorax and ascites at 20 weeks in December 2010. She enjoyed good past health and had no history of any infection or febrile illness during pregnancy. First-trimester combined screening revealed low risk for chromosomal abnormality. A routine morphology scan at 20 weeks and 6 days revealed a hydropic fetus with bilateral pleural effusions, more severe on the right side with mediastinal shift to the left. There was also mild ascites but no other features of hydrops. The fetal anatomy, growth parameters, liquor volume, and umbilical artery Doppler findings were otherwise normal. Right thoracocentesis was performed for complete aspiration of pleural fluid, analysis of which confirmed the presence of lymphocytes (chyle) that was negative for cytomegalovirus (CMV). Amniocentesis was performed which showed a normal karyotype, and was negative for CMV. In addition, maternal blood was negative for toxoplasmosis and parvovirus antibody; maternal urine culture for CMV was also negative. One week later (22 weeks and 1 day), the right pleural effusion recurred causing significant mediastinal shift as before. There was also persistent mild left pleural effusion and ascites, for which intervention was considered necessary. However, in this case there was increased risk from thoracoamniotic shunting because the placenta covered nearly the whole anterior uterine wall. Thus, pleurodesis with OK-432 was discussed and the patient accepted this procedure. During the first attempt, 12 mL of pleural fluid from right pleural cavity was aspirated with a 20 G needle under continuous

Key words
Chylothorax; Picibanil; Pleural effusion

Hong Kong Med J 2012;18:156-9

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ultrasound guidance. To avoid vascular damage by the needle, the aspiration was incomplete so that the pleural cavity could be visualised. Then, 10 mL of OK-432 was injected into the pleural cavity (0.1 mg in 20 mL normal saline).

Ultrasound scan 1 week later at 23 weeks and 1 day revealed complete resolution of left pleural effusion and ascites, but a moderate right pleural effusion remained. Therefore, a second pleurodesis using OK-432 was performed. This time we used a higher concentration of OK-432 in the pleural cavity by aspirating as much pleural fluid as possible (around 20 mL), and by injecting a more concentrated solution of OK-432 (0.1 mg in 10 mL normal saline).

Ultrasound scan 1 week later revealed only minimal residual right pleural effusion with some internal echos inside, which represented the formation of adhesion in the pleural cavity. There was no accumulation of fluid in other parts of the body. Serial follow-up scans revealed complete resolution of chylothorax without recurrence.

The patient had spontaneous onset of labour at 40 weeks and 5 days and delivered a 2965 g baby vaginally. The baby was born in good condition with Apgar scores of 9 at first minute and 10 at the fifth minute. Interventions such as mechanical ventilation or chest drainage were not required. The neonatal chest X-rays on days 1 and 3 of life were normal and the baby was discharged on day 6 of life having achieved complete delivery of a healthy neonate at term and an uneventful postnatal course.

Discussion

Despite the natural prenatal history of congenital chylothorax being variable, most fetuses who can survive the neonatal period usually do well without residual morbidity. High mortality and morbidity were due to lack of effective fetal therapy and poor perinatal outcome was usually related to the development of fetal hydrops and pulmonary hypoplasia.

Thoracocentesis was first proposed as a treatment of primary fetal hydrothorax by Petres et al in 1982.[4] Although the procedure is relatively simple, the pleural fluid very often re-accumulates within 24 to 48 hours, thus repeated tapping is required and the risk of miscarriage, or preterm labour escalated with increasing numbers of repeated procedures. The cumulative risk of these probably outweighed that of a single thoracoamniotic shunt. In our case, the initial thoracocentesis was only performed for diagnostic purposes.

Thoracoamniotic shunt for treatment of primary fetal hydrothorax was first proposed by Seeds and Bowes in 1986.[5] It allows continuous drainage of pleural fluid into the amniotic cavity. The perinatal survival rate was significantly higher among those treated with shunting than thoracocentesis, irrespective of whether the fetus was hydropic (67 vs 10%) or non-hydropic (100 vs 60%).[2] However, the shunting procedure is technically highly demanding and requires high levels of co-ordination between operators. It is a complicated procedure, which entails placement of a large cannula well into the fetal pleural cavity, and the placement of a double pigtail catheter, half into the pleural cavity and half to be left in the amniotic cavity. The access for this procedure is highly influenced by fetal and placental position, which are very difficult to control by the operator. Intra-operative complications are common, including failure of shunt placement, damage to the intrathoracic vessels or organs, and misplacement of the shunt into the fetal thoracic cavity, or partly outside the uterine wall. Even after successful shunt placement, shunt blockage, kinking, migration or displacement into the pleural or the amniotic cavity may ensue, and recurrence of pleural effusions is common. In addition, due to the invasive nature of the procedure, it could give rise to preterm premature rupture of membranes, chorioamnionitis, provoked preterm labour, placental abruption or fetal loss. Even though fetuses survive through the antenatal period, most of them still need intensive neonatal care and intervention including mechanical ventilation or chest drainage because of continuous pleural fluid production.

OK-432 (picibanil) is an inactivated preparation of *Streptococcus pyogenes* of human origin, which is thought to cause pleurodesis by inducing a strong cellular and cytokine-mediated inflammatory response. It is shown to be non-teratogenic, nor is it a fetal toxin in animals. It had been used in the treatment of lymphangioma in paediatric and adult patients.[6,7] The latter reports show that children who had undergone this non-invasive treatment had fewer complications, no recurrences and good cosmetic outcomes compared to open head and neck surgical intervention. Watari et al[8] first reported the successful use of OK-432 in the in-utero treatment

胸腔內注射OK-432作原發性宮內治療乳糜胸胎兒

乳糜胸是一種罕見先天性病症，患有此症的胎兒一般都有嚴重的圍產兒死亡率和發病率。過往的處理方法有重覆進行胸腔穿刺術或胸膜腔羊膜腔分流治療，可惜這些技術難度很高，且往往會引發與手術相關的併發症及新生兒併發症。本文報告一名妊娠20周患有雙側胸腔積液的胎兒，使用OK-432進行肋膜黏連術成功治療的病例。這亦是香港首宗成功用簡單有效的方法治療此症的病例。

TABLE 1. Summary of reported cases of intrapleural injection of OK-432[9-15]

Case	Authors	Gestational age at onset	Side of effusion	Prior treatment	OK-432 dosage (mg)	No. of attempts (at weeks)	Outcome*
1	Okawa et al[9] (2001)	25 years	Unilateral	Thoracocentesis x 2	0.01	1 (27)	Delivered at term and survived
2	Tanemura et al[12] (2001)	19 years	Bilateral	Thoracocentesis x 2	0.007	3 (23-25)	Delivered at 37 weeks and survived
3	Jorgensen et al[13] (2003)	25 years	Bilateral	Nil	0.28 (R) / 0.28 (L) 0.28 (R) / 0.28 (L) 0.8	3 (25-28)	Delivered at 38 weeks and survived
4	Tsukihara et al[14] (2004)	21 years	Unilateral	Thoracocentesis x 2	0.1 0.2	2 (24 and 25)	Delivered at 33 weeks and survived
5	Chen et al[15] (2005)	29 years	Bilateral	Thoracocentesis x 3	0.1	2 (33 and 34)	Immediate NND at 34 weeks
6	Chen et al[10] (2005)	23 years	Bilateral	Not available	0.1	1	IUD at 29 weeks
7	Chen et al[10] (2005)	12 years	Bilateral	Not available	0.1	1	IUD at 24 weeks
8	Chen et al[10] (2005)	31 years	Bilateral	Not available	0.1	1	Delivered at 32 weeks
9	Chen et al[10] (2005)	21 years	Bilateral	Not available	0.1	1	Delivered at 38 weeks and survived
10	Nygaard et al[11] (2007)	18 years	Bilateral	Nil	0.2 (R) / 0.2 (L)	1 (18+2)	Delivered at 35 weeks and survived
11	Nygaard et al[11] (2007)	15 years	Unilateral	Nil	0.2	1 (15+4)	Delivered at 39 weeks and survived
12	Nygaard et al[11] (2007)	19 years	Unilateral	Nil	0.3	1 (19+3)	Delivered at 38 weeks and survived
13	Nygaard et al[11] (2007)	18 years	Unilateral	Nil	0.3 0.6	2 (17+6 and 20+3)	Delivered at 32 weeks and survived
14	Nygaard et al[11] (2007)	20 years	Bilateral	Nil	0.4 (R) / 0.4 (L) 0.5 (R) / 0.3 (L)	2 (20+4 and 23+2)	Delivered at 40 weeks and survived
15	Nygaard et al[11] (2007)	19 years	Bilateral	Nil	0.9 1.0	2 (19+1 and 19+5)	Delivered at 40 weeks and survived
16	Nygaard et al[11] (2007)	19 years	Unilateral	Nil	0.9	1 (19+2)	Delivered at 41 weeks and survived

* IUD denotes intra-uterine death, and NND neonatal death

TABLE 2. Comparison between thoracoamniotic shunting and pleurodesis

Factor	Thoracoamniotic shunting	Pleurodesis
Effect of fetal movement during procedure	More	Less
Limitation by placenta position	Yes	No
Co-ordination between specialists required	High	Less
Fetal distance from uterine wall required	More	Less
Needle size	Larger	Smaller
Entry to chest	Relatively difficult	Easier
Other problems	Shunt problem May need repeated procedure	May need repeated procedure

of cystic hygroma in 1996. In 2001, Okawa et al[9] first reported its successful use to treat fetal chylothorax.

Till now, there were 16 reported cases of its use for the treatment of fetal chylothorax worldwide (Table 1[9-15]), of which 13 were successful. In four cases, OK-432 was used as second-line treatment after either failed thoracocentesis or thoracoamniotic shunting.[9,12,14,15] While as in our case, in eight it was first-line therapy and resulted in good outcomes.[11,13] For the remaining cases, it was not clear whether it was used as a primary or secondary treatment.[10]

Compared to shunting, pleurodesis is less technically demanding and requires less operator co-ordination. It can be easily performed even when the fetal or placental position is unfavourable, or when there is oligohydramnios. Since the size of the needle

for fluid aspiration and injection of OK-432 is smaller (20 G, ie diameter of 1.1 mm) compared to instruments for shunting (6-9 F, ie diameter of 2-3 mm), insertion into the chest wall is easier and less traumatic to the fetus. It avoids potential shunt problems and has fewer failures due to technical problem. Although it may require repeated pleurodesis, the success rate was high, based on the previous case reports. In most cases, success was achieved after one or two attempts and only one entailed three attempts (Table 2). Our case illustrates that OK-432 is an effective primary treatment for fetal chylothorax. Because it is simple and safe compared to shunting, it should be considered even when shunting is technically feasible.

The optimal dosage of OK-432, however, is not yet well known. Depending on the regimen, doses ranging from 0.007 to 1 mg have been used. We believe a high local concentration of OK-432 is the main contributor to success, which depends on the concentration of the drug to be injected, the gestational age of the fetus, and the residual volume of pleural fluid at the time of injection. These factors may explain why our first attempt had not resulted in complete resolution.

We report the first successful case in Hong Kong treated by pleurodesis with OK-432 in a fetus with bilateral pleural effusion. Pleurodesis with OK-432 is a technically simple procedure, for which there are many theoretical and technical advantages over alternative treatment modalities. It can be considered as a primary treatment for congenital chylothorax deemed to require intervention.

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