

Chemical Pleurodesis in Patients with Hepatic Hydrothorax; Management, Morbidity and Mortality

Hepatik Hidrotorakslı Hastalarda Kimyasal Plörodezis; Yaklaşım, Mortalite ve Morbidite

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ABSTRACT

Objective: Chemical pleurodesis is an effective treatment for malignant effusion and pneumothorax. Although this mode of therapy is less widely accepted in the treatment of patients with hepatic hydrothorax, the need for palliative treatment in such patients encouraged us to analyze the outcome of chemical pleurodesis using bovoiodine, vibramycin and talc slurry in the treatment of hepatic hydrothorax.

Material and Method: A prospective study including 23 patients with symptomatic right side hepatic hydrothorax not responding to medical treatment and repeated thoracocentesis was carried out. From March 2007 through March 2008, 19 men and 4 women with a mean age of 54.3 ± 8.1 years (range 42-70 years) underwent medical thosacoscopies to achieve pleurodesis by application of 3 sclerosing agents.

Results: Of the 23 patients pleurodesis was repeated in 20 cases. Three cases were lost during the 3 months follow up period of the study. The procedure was effective in 15 of 20 patients (75%), 7/8 cases treated by bovoiodine (87.5%), 4/6 cases with vibramycin and talc slurry (66.7%) for each. There were 4 recurrences (20%) and a single case of mortality (5%) due to hepatic coma attributable to the course of the disease. We detected minimal morbidity during the follow up period of 3 months.

Conclusion: The procedure appears to be indicated for these fragile patients especially when medical therapy fails. Since efficacy was 75%, chemical pleurodesis deserves to be considered as an alterative therapy in such patients.

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Key words: Hepatic hydrothorax, pleurodesis, chemical sclerosing agents

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ÖZET

Amaç: Kimyasal plörodezis malign effüzyon ve pnömotoraks tedavisinde kullanılan etkin bir yöntemdir. Ancak, hepatic hidrotorakslı hastaların tedavisinde daha az kabul edilmektedir. Buna rağmen, halen hepatic hidrotorakslı hastaların palyasyonunda; bovoiodin, vibramisin ve talk ile yapılan kimyasal plörodezis tedavisinin kullanılması, bizi bu çalışmayı yapmaya yöneltmiştir.

Gereç ve Yöntem: Medikal tedaviye yanıt vermeyen, tekrarlayan plörodezis ihtiyacı olan ve semptomatik hepatic hidrotorakslı 23 olgu, prospektif olarak, çalışmaya dahil edildi. Mart 2007-Mart 2008 tarihleri arasında ortalama yaşı 54.3±8.1 yıl (42-70 arasında) olan, 19'u erkek ve 4'ü kadın hastalara, medikal torakoskopi uygulandı ve 3 sklerozan ajan kullanılarak plörodezis yapıldı.

Bulgular: 23 hastanın 20' sinde plörodezis tekrarlandı. Üç aylık takip süresinde 3 hasta kaybedildi ve morbidite minimal düzeyde kaldı. 20 hastanın 15'inde (%75) uygulanan yöntem etkili oldu. 7/8 (%87.5) olgu bovoiodin, 4/6 olgu vibramisin (%66.7) ve 4/6 olgu talk ile (%66.7) tedavi edildi. Dört (%20) olguda nüks ve sadece 1 (%5) olguda hepatic komaya bağlı ölüm gözlemlendi.

Sonuç: Görüldüğü kadarıyla, kimyasal plörodezis, tedaviye yanıt vermeyen bu özel hasta grubunda uygulanabilir ve etkinliği %75 olduğu için bu hastalarda alternatif tedavi yöntemi olarak tanımlanabilir.

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INTRODUCTION

Hepatic hydrothorax is defined as a pleural effusion usually >500 ml, in patients with cirrhosis without cardiopulmonary disease [1]. A reasonable estimate is that it ranges from 4 to 6%, and even up to 10% with advanced disease [2]. In 85% of cases hepatic hydrothorax

develops on the right side, 13% of cases occurring on the left side and 2% being bilateral. Hepatic hydrothorax may develop even in absence of ascites [3].

The exact mechanism of pleural effusion remains unknown, and a number of different mechanisms have been proposed to explain it [4]. However, several

observations indicate that the most likely cause is passage of a large amount of ascites from the peritoneal to the pleural cavity through diaphragmatic defects [5,6].

Traditional treatment of hepatic hydrothorax in a patient who fails to respond to aggressive medical management of ascites remains problematic and controversial. Review of literature has revealed that no method is ideal at present [7,8]. This study describes our experience in treating patients with recurrent hepatic hydrothorax by chemical pleurodesis using 3 sclerosing agents as an important palliative option. The effect of pleurodesis will be evaluated with special concern to focus on morbidity and mortality.

MATERIAL and METHOD

A prospective study consists of 23 patients with clinical, laboratory and radiological evidence of liver cirrhosis, portal hypertension, and persistent right side symptomatic hepatic hydrothorax who were admitted to chest and tropical departments, Cairo University Hospital from March 2007 to March 2008. The study was approved by the Human Ethics Committee of Cairo University and all subjects gave a written informed consent before thoracoscopy and chemical pleurodesis. In this study all patients had undergone multiple medical managements in the form of sodium and fluid restriction, together with diuretic therapy and repeated therapeutic thoracentesis (2-5 times), which failed to control moderate to massive transudative pleural effusions. Their serum albumin level was at least 2.7mg/dl and prothrombin concentration PC>55%. Exclusion criteria were evidence of hepatic encephalopathy, massive ascites and recent or past history of haematemesis.

They were 19 men (82.6%) and 4 women (17.4%), their ages ranging from 42 to 70 years (mean, 54.3±8.1 years). All underwent therapeutic thoracoscopy with pleurodesis using bovoiodine in 9 cases, vibramycin (doxycycline) in 7 cases, and talc slurry in 7 cases. During the study period three patients were lost and 20 patients were followed up for 3 months.

Medical thoracoscopy was performed under local anesthesia to all patients. After complete evacuation of the pleural fluid, a chest drain was introduced and followed by pleurodesis. In talc slurry, 2 to 3 grams of

asbestos free talc were suspended in 50ml of saline solution (0.9%), while with vibramycin; instillation of 1 gm vibramycin in 50ml of saline solution and in bovoiodine, 20ml of 10% bovoiodine in 80ml of saline solution were used. An additional 20ml of 1% lidocaine was added to all the sclerosing agents and the drain flushed with 20ml of saline. The drain was then clamped for 4 hours after pleurodesis, and the patient was asked to change position every 15 minutes to allow adequate distribution of the sclerosing agent. Post procedure, medical therapy including albumin, plasma infusion and diuretics was maintained. If one trial of pleurodesis failed, another trial was done after 3-5 days according to the rate of fluid drainage with a maximum of 3 times. Pleurodesis was repeated earlier in patients with a high rate of drainage. Chest tubes were removed when the volume collected remained <100mL in 24 hours. Somtostatin was given to all the patients at a dose of 25-50 µmg / hr, 24 hours before the procedure and continued until the removal of the chest tube.

Serial chest radiographs were performed, 2 hours after pleurodesis, on the second post-procedure day and at subsequent follow up visits every month for 3 months follow ups. The procedure was considered successful if there was absence of pleural fluid on the follow up chest radiographs; any reaccumulation was regarded as a recurrence.

Statistical Analysis

Quantitative data were presented as minimum, maximum, means and standard deviation (SD) values. Student's t-test was used for comparisons between means of two groups. Qualitative data were presented as frequencies and percentages. Chi-square (χ²) test was used for comparisons between different qualitative variables. The significance level was set at P ≤ 0.05. Statistical analysis was performed with SPSS 16.0® (Statistical Package for Scientific Studies) for Windows.

RESULTS

In this study, we used bovoiodine in 9 patients, vibramycin in 7 patients and talc slurry in 7 cases. Using the same agent, a second retrial of pleurodesis was done in 16 cases, while it was repeated 3 times in 4 cases.

Table 1. Frequency, percentages and results of chi-square test for comparison between the three pleurodesis materials

		Povo-iodine		Vibramycin		Talc slurry		P-value
		Frequency	%	Frequency	%	Frequency	%	
Ascitis	No	1	11.1	0	0	0	0	0.771
	Mild	3	33.3	2	28.6	2	28.6	
	Moderate	5	55.6	5	71.4	5	71.4	
Previous thorococentesis	2 times	1	11.1	0	0	0	0	0.343
	3 times	6	66.7	5	71.4	3	42.9	
	4 times	2	22.2	2	28.6	2	28.6	
Number of pleurodesis sessions	5 times	0	0	0	0	2	28.6	0.243
	1 time	1	11.1	1	14.3	1	14.3	
	2 times	8	88.9	5	71.4	3	42.9	
	3 times	0	0	1	14.3	3	42.9	

Table 2. Frequency, percentages and results of chi-square test for comparison between cases with and without recurrence

No. of followed up cases=20		Recurrence		No recurrence		P-value
		Frequency	%	Frequency	%	
Gender	Male	5	100	11	73.3	0.197
	Female	0	0	4	26.7	
Previous thorococentesis	2 times	0	0	1	6.7	0.123
	3 times	4	80	8	53.3	
	4 times	0	0	6	40	
	5 times	1	20	0	0	
Number of pleurodesis sessions	1 time	0	0	2	13.3	0.032*
	2 times	2	40	12	80	
	3 times	3	60	1	6.7	
Complications	Yes	5	100	8	53.3	0.058
	No	0	0	7	46.7	
Severity of pleural effusion	Moderate	0	0	6	40	0.091
	Massive	5	100	9	60	

*: Significant at P ≤ 0.05

Table 3. Collective outcome of the 3 Sclerosing agents in treatment of right side hepatic hydrothorax

Characteristics	Boviodine n=9	Talc n=7	Vibramycin n=7
Success	7	4	4
Lost follow up	1	1	1
Recurrence			
-Encysted effusion	1	-	1
-Minimal Rt.	-	1	1
Side pl. effusion			
Mortality	-	1	-
Surgical emphysema	2	1	1
Left side pl. effusion	-	1	1
Wound infection	2	-	-
Pain	-	1	-
Failure of lung re-expansion	1	-	-
Hepatic precoma	-	-	1
Tense Ascites	1	-	-
Tense Ascites & Hepatic Coma	-	1	-

During the study period, the follow up of 3 cases were lost, one case from the 3 different agents (Table 1).

The outcome of the present work revealed that chemical pleurodesis was effective in the treatment of hepatic hydrothorax in 15/20 patients (75%), there were 7/8 cases (87.5%) treated by bovioidine, 4/6 cases (66.7%) with vibramycin and 4/6 cases (66.7%) with talc slurry. However, a single case treated by talc slurry died of hepatocellular insufficiency (5%) after 14 days following the procedure; this patient failed to respond to 5 sessions of thoracocentesis and also needed pleurodesis to be repeated 3 times due to a high rate of chest tube fluid drainage. In addition, recurrence of pleural effusion occurred in 4 cases (20%); these were 2 cases (50%) with encysted effusion and another 2 cases (50%) with

minimal right side pleural effusion. Cases with recurrence showed statistically significantly higher percentage of 3 sessions of pleurodesis than cases without recurrence (Table 2).

The time needed to remove the chest tube ranged from 4 to 17 days with a mean of 9.8±2.3 days [in bovioidine the range was from 5-9 days with mean of 8.1±2 days, in vibramycin the range was from 6-15 days with mean of 9.4±4.3 days and in talc slurry the range was from 4-17 days with mean of 10.3±3.6 days]. Post-procedure hospital stay ranged from 5 to 18 days.

Post procedure results showed that 7 out of the 22 cases reported absence of any complications and were not associated with recurrence of hepatic hydrothorax. The remaining cases (15 patients) showed early and mostly minimal and limited morbidity. There were 4/22 patients (18.2%) suffering from surgical emphysema, 2 cases (9.1%) with minimal left side pleural effusion which disappeared spontaneously after few days, 2 cases (9.1%) with superficial wound infection, one case (4.5%) with mild thoracic pain, another single case (4.5%) who complained of failure of the lung to expand immediately after the procedure and was treated by negative suction with complete lung expansion and a single case (4.5%) developed prehepatic coma 4 days after the procedure, was cured by medical therapy and had no recurrence of hepatic hydrothorax.

However, during the follow up period, 2 out of 19 patients (10.5%) developed late, more serious complications. A case treated with bovioidine suffered from tense ascites 2 months after the procedure, (3 liters were tapped) but with no associated recurrence of hepatic hydrothorax. The second case treated with talc slurry developed tense ascites and hepatic coma at the end of the follow up period (3 months), recovered with medical therapy and was associated with recurrence of encysted right side pleural effusion. There were no reported episodes of respiratory distress syndrome, pneumonitis or empyema in our cases. Significantly higher

Table 4. Frequency, percentages and results of chi-square test for comparison between cases with and without complications

No. of cases =22		Complications		No complications		P-value
		Frequency	%	Frequency	%	
Gender	Male	15	100	3	42.9	0.001*
	Female	0	0	4	57.1	
Previous thorococentesis	2 times	0	0	1	14.3	0.047*
	3 times	12	80	2	28.6	
	4 times	2	13.3	4	57.1	
	5 times	1	6.7	0	0	
Number of pleurodesis sessions	1 time	1	6.7	1	14.3	0.822
	2 times	11	73.3	5	71.4	
	3 times	3	20	1	14.3	
Severity of pleural effusion	Moderate	4	26.7	2	28.6	0.926
	Massive	11	73.3	5	71.4	

*: Significant at P ≤ 0.05

Table 5. Frequency, percentages and results of chi-square test for comparison between recurrence and complications of the three pleurodesis materials

No. of cases =20		Povo-iodine		Vibramycin		Talc slurry		P-value
		Frequency	%	Frequency	%	Frequency	%	
Recurrence	Yes	1	12.5	2	33.3	2	33.3	0.574
	No	7	87.5	4	66.7	4	66.7	
Complications	Yes	6	66.7	5	71.4	4	66.7	0.975
	No	3	33.3	2	28.6	2	33.3	
Severity of pleural effusion	Moderate	2	22.2	1	14.3	3	42.9	0.450
	Massive	7	77.8	6	85.7	4	57.1	

complications were reported in males and in cases of three sessions of thoracocentesis (Table 3 and 4).

The comparison between the 3 sclerosing agents showed there was no statistical significant difference concerning recurrence and complications (Table 5).

DISCUSSION

Despite numerous reports describing the clinical features, pathogenesis and treatment of hepatic hydrothorax, the optimal or standard therapy has not been established [8]. The term refractory hepatic hydrothorax is used when medical treatment with salt restriction and diuretics are ineffective, as prolonged diuretic treatment may result in depletion of the intravascular volume and impaired renal function. Medical therapy has proved to be effective in approximately one third of the reported patients, but the effect has been chiefly temporary. Many authors also consider that clinical management of hepatic hydrothorax is usually difficult and ineffective and can result in deterioration of the clinical status [2,5,8].

There have been a variety of mechanisms to explain the shift of ascitic fluid into the pleural space, including hypoalbuminemia, azygos vein hypertension, leakage from the thoracic duct, transdiaphragmatic lymphatic migration and most important, the pressure - gradient - directed flow through diaphragmatic defects [8].

In contrast to ascites which becomes massive (<10L) to mild symptoms in most patients, relatively small volumes of

fluid (< 1L) within the chest cavity cause significant symptoms and occasionally need urgent rapid removal [9]. Although, thoracocentesis is the most effective method for rapid relief of dyspnea secondary to massive pleural effusion associated with hepatic hydrothorax, it carries the risk of substantial protein depletion without preventing fluid reaccumulation, especially if repeated thoracocentesis is required [7].

Pleural drainage by chest tube thoracostomy can be very dangerous in patients with massive ascites and pleural effusion. Runyon et al., [10] reported two deaths resulting from associated massive protein and electrolyte depletion. Also, prolonged drainage through the chest tube may cause renal failure, impaired immunological functions and iatrogenic infection as common sequelae [11].

Pleural drainage by chest tube thoracostomy and chemical pleurodesis was attempted in 1977 by Falchuk et al., [12] using tetracycline. Tetracycline has been successfully employed in chemical pleurodesis for many years. Subsequently it was shown that doxycycline and minocycline were comparable in efficacy to tetracycline [13,14].

Of the 20 cases that have been followed up during this work, we used vibramycin in 6 cases, with a success rate of 66.7%. Our results are comparable to the success rate in the literature (67%) with tetracycline and (72%) with doxycycline. They reported adverse effects of pain in 14% and fever in 10% with tetracycline and pain in 40% with doxycycline [15]. In our work the patient number was small; pain and fever were not reported with the use of vibramycin. However, recurrence occurred

in 2 patients, one suffered from encysted effusion and the other from minimal right side pleural effusion. Also, surgical emphysema, left side pleural effusion and hepatic precoma was found in a single case.

When tetracycline became unavailable, talc was the choice of many physicians because it is an inexpensive, widely available and effective agent with reported success rate of 90% [15]. Talc can be administered either as an aerosol (insufflation) or a suspension (slurry). In animal studies, there appears to be no difference between slurry and poudrage talc pleurodesis in malignant effusion [16]. Data in human studies are inconclusive [17].

In our study we selected asbestos free talc slurry for use in 6 patients to avoid the claims associated with the hazards of asbestos. We reported success in 4 patients (66.7%). Recurrence occurred in a single case and complications in the form of chest pain, surgical emphysema, left mild pleural effusion, tense ascites and hepatic coma were noticed in one patient. Also, the only case of mortality in our work was treated by talc slurry and occurred 14 days after the procedure due to rapid increase of bilirubin and creatinine, followed by hepatic coma and death. This can be attributable to the course of the disease since the patient medical status necessitated thoracentesis 5 times before our procedure.

Vargas et al., used talc pleurodesis in 6 patients. In five patients treatment was completely successful and one patient needed to repeat pleurodesis 4 months later [18]. Also, Glazer et al., used talc in four patients, pleurodesis was successful in all patients (3 complete and one partial) [19]. Milanez de Campos et al., performed talc poudrage in 18 patients with persistent hepatic hydrothorax with a 3 month follow up period. In 10 patients (47%) the aerosolized talc was effective in preventing the recurrence of effusion, while recurrence occurred in 43% of their cases. They reported several complications including, fever, chest pain, empyema, incomplete expansion of the lung, pneumonia and wound infection. Their patients had a high morbidity (57.1%) and mortality (38.9%) [7]. Also, there are at least 32 cases in the literature of ARDS occurring after the administration of intrapleural talc and in 8 instances the patients died [20]. It seems that an important factor in the development of ARDS associated with talc pleurodesis is the size of talc powder. Also another risk is the development of mesothelioma from talc pleurodesis which is very small, but the possibility still exists [20].

In our study, we used bovoiodine in 8 cases with complete control of the effusion in 7 cases (87.5%). Recurrence in the form of encysted pleural effusion was noted in one patient (12.5%). Complications in the form of surgical emphysema in 2 patients (25%), wound infection in 2 patients (25%), failure of lung to expand which was treated by negative suction with complete expansion of the lung in one case (12.5%) and tense ascites in another single case (12.5%) but there was no pleuritic pain or hypotension seen in any of our patients treated with bovoiodine.

Lodopovidone has been extensively used in Mexico for almost 10 years without any serious side effects [21]. Olivares-Torres et al., administered iodopovidone either through a chest tube or at the time of thoracotomy in 52 patients. Complete control of the effusion was seen in 50 patients (96%). Three patients experienced intense pleuritic pain and systemic hypertension after installation of the sclerosing agent, but they recovered without incident [22]. The argument about the use of iodopovidone because of these 2 complications can be explained by the fact that the use of any effective pleural irritant, including talc [23] can and will produce intense pleuritic pain and a vasovagal reaction if analgesia and anesthesia are inadequate and the control of pain should be individualized.

We used somatostatin in all of our patients to reduce drainage volume and shorten the duration of chest tube removal. Somatostatin and its analogues act via somatostatin receptor subtypes 2 and 5 to reduce splanchnic and hepatic blood flow as well as portosystemic pressure gradient. Therefore, these are now widely used in the treatment of acute oesophageal varices [24]. TIPS (Trans jugular intrahepatic portosplenic shunt,) which was originally used to treat incurable variceal bleeding and mainly acts through reduction of portosystemic pressure gradient is used as an alternative treatment. However, it has some important side effects as it aggravates hepatic encephalopathy and the possibility of shunt occlusion [25]. In contrast to TIPS, somatostatin and its analogues have few, mostly minor side effects. The only drawback is that it is expensive.

Our data revealed that using 3 sclerosing agent gave a total success rate of 75%, bovoiodine 87.5%, vibramycin and talc slurry 66.7% for each, which is comparable to the analysis of the results of patients subjected to pleurodesis with talc, tetracycline derivatives or bleomycin, with the conclusion that all agents were approximately 80% effective [26].

In the present work, the comparison of the rate of recurrence and complications of the 3 sclerosing agents used were comparable. There were 2 cases complicated with tense ascites after the procedure. There is an opinion about the need for these cases to have chest tube thoracotomy and pleurodesis as it may block the passage of fluid through the diaphragmatic defects to the pleural cavity accompanied by deterioration of the hepatic condition. However, the fact that the volume of fluid (<1L) capable of causing symptoms in the pleural cavity is much less than that in the peritoneal cavity (<10L) [9] necessitating the medical decision in such patients to be individualized and a balance between treating hepatic hydrothorax and the deterioration of the hepatic condition and ascites should be weighed.

In conclusion, refractory or recurrent hepatic hydrothorax can be successfully treated by pleurodesis. In our series, we used 3 sclerosing agents with a successful outcome and minimal complications. Although aggressive treatment of hepatic hydrothorax and ascites can lead to hepatic encephalopathy, as with every technique, success depends on the operator and in selected patients, this procedure can be performed safely.

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