Chemical Pleurodesis in the Management of Hepatic Hydrothorax

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Abstract

Background: Chemical pleurodesis is an effective treatment for malignant effusion and pneumothorax. Although this mode of therapy is less widely accepted in treatment of patients with hepatic hydrothorax, the need of palliative treatment in such patients encouraged us to do this work.

Study Objectives: To analyze the outcome of chemical pleurodesis using Iodopovidone, vibramycin and talc slurry in treatment of hepatic hydrothorax.

Patients and Methods: Randomized study on 20 patients with symptomatic right side hepatic hydrothorax not responding to medical treatment and repeated thoracocentesis. All underwent medical thosacoscopies to achieve pleurodesis by application of 3 sclerosing agents.

Results: patients were 16 men and 4 women with a mean age 54.3 ± 8.1 years (range 42-70 years). The procedure was effective in 15 of 20 patients (75%), 7/8 cases treated by Iodopovidone (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 which can be attributed to the course of the disease. We detected minimal morbidity during the follow up period of 3 months.

Conclusion: The procedure appears to be effective in patients with refractory hydrothorax. Chemical pleurodesis deserves to be considered as an alternative therapy in such patients.

Key Words: Hepatic hydrothorax – Pleurodesis – Chemical sclerosing agents.

Introduction

PULMONARY complications of hepatic diseases include; obstructive and restrictive ventilatory defects [1], hepatopulmonary syndrome [2], portopulmonary hypertension [3], interstitial lung disorders [4] and Hepatic hydrothorax which is defined as a pleural effusion (>500 mL) in patients with cirrhosis without coexisting cardiopulmonary diseases [8].

Estimated prevalence of hepatic hydrothorax among cirrhotic patients ranges between 5-10% [6]. Unlike ascites, small volumes (1-2 Liters) of fluid within the pleural space can lead to significant symptoms. The effusions may affect one, commonly the right side, or both pleural spaces [7]. The mechanisms involved in fluid retention in cirrhosis leading to ascites formation involve the combination of portal hypertension and splanchnic arterial vasodilation [8]. The most likely cause of fluid accumulation in pleura is passage of fluid from the peritoneal to the pleural cavity through diaphragmatic defects [9]. Other proposed mechanisms, include azygous vein hypertension, fluid traversing from the abdominal cavity to pleural space across transdiaphragmatic lymphatics, hypoalbuminaemia with decreased colloid osmotic pressure, leakage of the thoracic duct and decreased rate of reabsorption of ascites back into the intravascular compartment [6].

Management of hepatic hydrothorax is difficult. Medical measures includes Sodium restriction with a combination of diuretics (furosemide and spironolactone) increased in stepwise fashion according to response [10,11]. Some studies advocated the use of combination of midodrine and octreotide in the treatment of hepatic hydrothorax [12]. Patients with refractory hydrothorax require more invasive management with options such as repeated thoracentesis, transjugular intrahepatic portosystemic shunt, pleurodesis, and repair of defects in the diaphragm [13]. However, a majority of these patients with hepatic hydrothorax have advanced liver disease and may be potential candidates for orthotopic liver transplantation; the only effective cure to date [7].

Chemical pleurodesis achieving a symphysis between visceral and parietal pleural layers to prevent accumulation of either air or fluid in the
pleural space [14] is an accepted palliative therapy for patients with recurrent, symptomatic malignant pleural effusions. Various chemicals have been used in an attempt to produce pleurodesis. The optimal method for pleurodesis and the optimal agent used remain debatable and is often chosen on the basis of personal experience rather than objective data [15]. Pleurodesis can be performed via either a standard tube thoracostomy [14] or by thoracoscopic pleurodesis [16]. Agents used for chemical pleurodesis include; tetracycline [17], Doxycycline [18], Talc Poudrage or slurry [19], Iodopovidone [20], bleomycin [21], Corynebacterium parvum [22], Quinacrine [23], Fibrin glue [24], Tranexamic acid [25], TGFβ-2 [26], Nitrogen mustard [27], or combined use of various agents [28].

The aim of this study is to assess the safety and efficacy of chemical pleurodesis as a palliative option for management of recurrent hepatic hydrothorax and to compare the efficacy of three sclerosing agents used for pleurodesis.

Patients and Methods

This study was carried out on 20 patients with clinical, laboratory and radiological evidence of liver cirrhosis, portal hypertension and persistent right sided symptomatic hepatic hydrothoraces who were admitted to Tropical Medicine and Chest departments, Cairo University Hospital over 18 month period starting from March 2006. After giving informed consent all patients were initially subjected to full history and physical examination, full labs including liver function tests, coagulation profile, chest x-ray postero-anterior and lateral views, Abdominal U/S, and diagnostic thoracocentesis with physical, chemical, cytological and bacteriological analysis of pleural fluid.

Inclusion criteria were liver cirrhosis, transudative effusion, serum albumin of at least 2.7 mg/dl, history of repeated aspiration of pleural effusion at least 3 times in spite of the maximal tolerated conservative management (with salt restriction, diuretics, albumin infusion, and vit K supplements when needed), moderate to massive pleural effusion, Prothrombin concentration more than 60%.

Exclusion criteria included hepatic encephalopathy, massive ascites, history of recent haematemesis, or evidence of infection or malignancy in pleural fluid, hepatocellular carcinoma.

Octreotide was given to all the patients in a dose of 25-50µg/hour. 24 hours before the procedure and continued till removal of the intercostal tube.

Fiber optic thoracoscopy was performed in the Chest department, Cairo University under conscious sedation using the OLYMPUS LTF type V3 thoracoscope with a video camera. Thoracoscope was introduced and all residual pleural fluid was aspirated and the entire pleural surface was inspected. At the end of thoracoscopy, chest tube was inserted at the point of entry and the first session of pleurodesis was done immediately according to previously validated technique [29]. Pleurodesis was repeated after 3-5 days according to rate of tube drainage. And a third session of pleurodesis may be needed after extra 3-5 days if tube drainage is more than 100 mL/day. Patients were randomly assigned to one of the three sclerosant groups using blocked randomization:

1- Pleurodesis with Iodopovidone using 10ml of 10% Iodopovidone added to 40ml of 0.9% saline solution and 20ml of 1% lidocaine.

2- Pleurodesis with doxycycline using 1 gram of doxycycline dissolved in 50 ml of 0.9% saline solution with 20ml of 1% lidocaine.

3- Pleurodesis with asbestos free talc slurry using 2 to 3 grams of asbestos free talc were suspended in 50ml of saline solution (0.9%) with 20ml of 1% lidocaine.

Patients were closely monitored till discharge one day after removal of chest tube. The patients were followed up for next the 3 months clinically and radiologically. The procedure was considered successful if there was absence of pleural fluid on the follow-up chest radiographs; any re-accumulation was regarded as 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.

One way ANOVA (Analysis of Variance) was used to compare between means of more than two groups. Duncan’s test for pair-wise comparisons was used to determine significant differences between means when ANOVA test is significant.

Qualitative data were presented as frequencies and percentages. Chi-square (x²) test was used for comparisons between different qualitative variables.

Spearman’s correlation coefficient was used to determine significant correlations between number of sessions, duration of intercostal tube, recurrence and complications.
The significance level was set at $p \leq 0.05$. Statistical analysis was performed with SPSS 16.0 (Statistical Package for Scientific Studies) for Windows.

**Results**

The study included 20 patients, 16 (80%) were males and 4 (20%) females. The mean age was 54.3±8.1 years. Subjects were selected according to the above mentioned inclusion/exclusion criteria and then randomized to one of the three sclerosants used. The majority of patients 19/20 had ascites which was mild in 6/20 patients and moderate in 13/20 patients with one patient having no ascites. The amount of pleural effusion was moderate in 6/20 and massive in 14/20 patients. The number of previous thoracocentesis ranged from 3 to 5 times with an average of 3.5 times. Table (1) shows there was no significant difference in the patient's baseline characteristics between the three treatment groups.

The study outcome is shown in Table (2). Chemical pleurodesis was effective in treatment of hepatic hydrothorax in 15/20 patients (75%), they were 7/8 cases (87.5%) treated by Iodopovidone, 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 times thoracocentesis and also needed pleurodesis to be repeated 3 times due to high rate of chest tube fluid drainage. Recurrence of pleural effusion occurred in 4 additional cases (20%); they were 2 cases (50%) with encysted effusion and another 2 cases (50%) with minimal right side pleural effusion.

Complications reported during the study included hepatic encephalopathy in two cases (responded to medical treatment), two cases of tense ascites (managed by diuretics, albumin and therapeutic abdominal paracentesis), failure of lung re-expansion in one patient (resolved by negative suction), pleural thickening in one patient (asymptomatic with good lung expansion), self limiting surgical emphysema in 3 patients, wound infection in two patients (local antiseptics and systemic antibiotics), mild pleuritic pain in one patient (analgesics), transient left sided pleural effusion in one patient and fluid leakage around the tube in one patient.

There was no significant difference between the three sclerosant groups as regards the total number of complications or the nature of complication in each group as shown in Table (2).

The volume of pleural fluid drained by thoracocopy was comparable in the three sclerosant groups. The time needed to remove the chest tube ranged from 4 to 17 days with a mean of 9.8 ± 2.3 days. There was also no significant difference in the time needed till removal of the intercostal tube in the three groups (Table 3).

The outcome of the pleurodesis showed no significant correlation with the gender, age, amount of ascitic fluid, amount of pleural fluid, number of previous thoracocentesis sessions, type of sclerosing agent used or the occurrence of complications.

### Table (1): Baseline characteristics of patients in the three groups (n=20).

<table>
<thead>
<tr>
<th></th>
<th>Iodopovidone (n=8)</th>
<th>Doxycycline (n=6)</th>
<th>Talc slurry (n=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (87.5%)</td>
<td>4 (66.7%)</td>
<td>5 (83.3%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>1 (12.5%)</td>
<td>2 (33.3%)</td>
<td>1 (16.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td>53.9±5.6</td>
<td>57.4±11.5</td>
<td>51.6±7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Ascites:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mild</td>
<td>3 (37.5%)</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (50%)</td>
<td>4 (66.7%)</td>
<td>4 (66.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Amount of pleural fluid:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (25%)</td>
<td>1 (16.7%)</td>
<td>3 (50%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Massive</td>
<td>6 (75%)</td>
<td>5 (83.3%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous thoracocentesis:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 times</td>
<td>5 (62.5%)</td>
<td>4 (66.7%)</td>
<td>3 (50%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>4 times</td>
<td>2 (25%)</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>5 times</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>1 (16.7%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table (2): Success, recurrence and complications of pleurodesis in the three sclerosant groups.

<table>
<thead>
<tr>
<th></th>
<th>Iodopovidone (n=8)</th>
<th>Doxycycline (n=6)</th>
<th>Talc slurry (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success:</strong></td>
<td>7 (87.5%)</td>
<td>4 (66.7%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td><strong>Recurrence:</strong></td>
<td>1 (12.5%)</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td><strong>Complications:</strong></td>
<td>6 (75%)</td>
<td>4 (66.7%)</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td><strong>Death:</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tense ascites</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pleural thickening</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Failure of re-expansion</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgical emphysema</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Leak around tube</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Transient L-pleural effusion</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$p > 0.05$ (Non significant)
Table (3): Volume of pleural fluid drained by thoracoscopy and time till removal of intercostal tube in the three sclerosant groups.

<table>
<thead>
<tr>
<th></th>
<th>Iodopovidone (n=8)</th>
<th>Doxycycline (n=6)</th>
<th>Talc slurry (n=6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of pleural fluid drained. ML (mean±SD)</td>
<td>2955.6±591.8</td>
<td>2914.3±555.1</td>
<td>2428.6±573.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time till removal of intercostal tube. Days (mean ±SD)</td>
<td>8.1±2</td>
<td>9.4±4.3</td>
<td>10.3±3.6</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

**Discussion**

Management of hepatic hydrothorax is difficult. Therapy rests primarily on conservative measures such as sodium restriction and diuretic therapy. Thoracocentesis, helps ameliorate dyspnea, but pleural effusion tend to recur. Chest tube placement is generally not recommended, since the associated protein and fluid loss carries a high morbidity and mortality risk [30]. More invasive treatment regimens, including surgical shunts as well as repair of diaphragmatic defects, have been tried with variable success. Liver transplantation remains the most definitive therapy in these refractory cases. Transjugular intrahepatic porto-systemic shunt, or pleurodesis are effective strategies in those who are not transplant candidates or those awaiting organ availability [6,31].

The major indication of pleurodesis is diffuse pleural malignancy, however, there are few benign conditions where pleurodesis may be indicated [14]. The inclusion/exclusion criteria of the current study were selected in accordance with the criteria stipulated by Sudduth and Sahn for pleurodesis in non-malignant pleural effusion, namely: 1) the effusion must be symptomatic; 2) the presence of a trapped lung should be excluded; and 3) pleurodesis should be reserved for those cases where there is no other therapeutic alternative, or when this has already failed [32]. For the sake of patient safety, we adopted stringent criteria regarding coagulopathy and serum albumin. During analysis all the recruited patients were found to be Child grade B, hence the effect of the severity of underlying liver disease on the outcome of the procedure can be excluded.

We identified (up to the time of preparation of this manuscript) 39 published Midline studies of pleurodesis in hepatic hydrothorax, most of them were case reports or case series with only few prospective studies including mostly fewer than 25 patients with mixed results.

In the present study pleurodesis was performed using medical thoracoscopy as it allows the rapid removal of fluid from the pleural space by suction and also the proper inspection of the pleural surface [33].

The overall success of chemical pleurodesis via thoracoscope in patients with hepatic hydrothorax resistant to medical treatment was 75% (15/20).

Success was achieved in 87% in the Iodopovidone group (7/8), 66.7% in the Doxycycline group (4/6) and 66.7% in the talc slurry group (4/6). Previous studies showed variable response rate of 46% [34], 73% [38], and 80% [36]. Success of Talc pleurodesis in hepatic hydrothorax was reported to be 86% in patients without ascites and only 40% in ascitic patients [37]. In the current study there was only one patient without ascites, so we cannot address the impact of presence of ascites on response to pleurodesis. However, the amount of ascitic fluid showed no correlation with response. The reported complications in the current study were mostly minor and easily controllable with medical treatment. Major complications included hepatic encephalopathy in two patients and tense ascites in two other patients which responded well to medical treatment. There was however one mortality (5%) from liver cell failure with progressive rise of bilirubin and creatinine followed by hepatic coma which may be related to the progression of his liver disease. Our results were similar to those reported by Cerfolio and coworkers with only one mortality in their retrospective analysis of 41 patients [36] but was much better than the 39% mortality reported by Milanez de Campos and coworkers [34] this may be attributable to the stringent inclusion/exclusion criteria adopted as that study had many Child grade C patients.

Infusions of Octreotide were reported to reduce the output from chest tube in patients with hepatic hydrothorax in a dose dependant manner [38]. Accordingly, in the current study, octreotide was given to all the patients in a dose of 25-50 microgram/hour, 24 hours before the procedure and continued till removal of the intercostal tube this was in an attempt to improve the outcome of the procedure and speedup the removal of chest tube. The major limitation is that Octreotide is expensive.
In conclusion, pleurodesis was successful for control of hepatic hydrothorax in three forth of patients combined with standard medical treatment and Octreotide infusion with mostly controllable complications. The decision to use it to treat hepatic hydrothorax must be weighed against the threat of possible deterioration of hepatic function and ascites.

References


