A case series: Egyptian experience in using chemical pleurodesis as an alternative management in refractory hepatic hydrothorax

Nariman Helmy1, Yosri Akl1, Safy Kaddah1, Hamed Abd El Hafiz1, Hisham El Makhzangy1

Abstract

Introduction: 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 for palliative treatment in such patients encouraged us to do this work. The aim of study was analysing the outcome of chemical pleurodesis using bovoiodine, Vibramycin and talc slurry in treatment of hepatic hydrothorax.

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

Results: Out of the 23 patients pleurodesis was repeated in 20 cases. Three cases did not attend their follow-up so their responses to pleurodesis are not known. The follow-up period of the study was 3 months. The procedure was effective in 15 of 20 patients (75%): 7/8 cases treated with bovoiodine (87.5%), and 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.

Conclusions: The procedure appears to be indicated for these fragile patients especially when medical therapy fails. Chemical pleurodesis deserves to be considered as an alternative therapy in such patients.

Key words: hepatic hydrothorax, pleurodesis, chemical sclerosing agents.

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 most cases (85%) 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 the 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. A review of the literature has revealed that no method is ideal yet [7, 8]. This study describes our experience in treating patients with refractory hepatic hydrothorax by chemical pleurodesis as an important palliative option using 3 sclerosing agents. The effect of pleurodesis will be evaluated with special focus on morbidity and mortality.

**Material and methods**

**Study population**

This case series randomized study consisted of 23 patients with clinical, laboratory and radiological evidence of liver cirrhosis, portal hypertension, and refractory right side symptomatic hepatic hydrothorax who were admitted to the chest and tropical departments of 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 written informed consent before thoracoscopy and chemical pleurodesis. In this study all the 23 patients had refractory hepatic hydrothorax, i.e. multiple medical managements in the form of sodium and fluid restriction together with diuretic therapy and repeated therapeutic thoracocentesis (2-5 times) failed to control moderate to massive transudative pleural effusions. Exclusion criteria were evidence of hepatic encephalopathy, massive ascites and recent or history of haematemesis.

**Chemical pleurodesis**

Medical thoracoscopy was performed under local anaesthesia on the 23 patients included in the study. After complete evacuation of the pleural fluid, a chest drain was introduced, followed by pleurodesis. In talc slurry, 2 to 3 g of asbestos-free talc were suspended in 50 ml of saline solution (0.9%), while with Vibramycin instillation of 1 g vibramycin in 50 ml of saline solution and in boviodine 20 ml of 10% boviodine in 80 ml of saline solution were used. An additional 20 ml of 1% lidocaine was added to all the sclerosing agents and the drain was flushed with 20 ml of saline. The drain was then clamped for 4 h after pleurodesis, and the patient was asked to change position every 15 min to allow adequate distribution of the sclerosing agent. Post procedure, medical therapy including albumin, plasma infusion and diuretics was maintained. If the trial of pleurodesis failed another trial was done after 3-5 days according to the rate of fluid drainage, to 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 < 100 ml in 24 h. Somatostatin was given to all the patients in a dose of 25-50 µg/h, 24 h before the procedure and continued until removal of the chest tube.

**Follow-up**

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

**Statistical analysis**

Quantitative data were presented as minimum, maximum, means and standard deviation (SD) values. Qualitative data were presented as frequencies and percentages. Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) version 13 for Microsoft Windows.

**Results**

**Characteristics of subjects**

The 23 patients were 19 men (82.6%) and 4 women (17.4%). Their age ranged from 42 to 70 years (mean 54.3 ±8.1 years). They all had clinical, laboratory and radiological evidence of liver cirrhosis, portal hypertension, and refractory right side symptomatic hepatic hydrothorax, i.e. they had undergone multiple medical managements that failed to control moderate to massive pleural effusions. All had Child Pugh B score and the chemical analysis of their pleural effusion showed evidence of transudative effusion. All underwent therapeutic thoracoscopy with pleurodesis using boviodine in 9 cases, Vibramycin (doxycycline) in 7 cases, and talc slurry in 7 cases. The selection of the sclerosing agent to be used was randomized. During the study period, 3 patients did not attend their follow-up visits so their response to chemical pleurodesis is not known. These 3 cases were 1 case from each of the 3 sclerosing agents used. The rest of the 20 patients were followed up for 3 months. Using the same agent, a second retrial of pleurodesis was done in 16 cases, while it was repeated 3 times in 4 cases (Table I).

**Outcome of chemical pleurodesis**

The outcome of the present work revealed that chemical pleurodesis was effective in treatment of
hepatic hydrothorax in 15/20 patients (75%); they were 7/8 cases (87.5%) treated with bovoiodine, 4/6 cases (66.7%) with Vibramycin and 4/6 cases (66.7%) with talc slurry. However, a single case treated with talc slurry died of hepatocellular insufficiency (5%) after 14 days following the procedure; this patient failed to respond to thoracocentesis repeated 5 times 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%); they were 2 cases (50%) with encysted effusion and another 2 cases (50%) with minimal right side pleural effusion. Cases with pleurodesis repeated 3 times showed more possibility of recurrence and complications (Table II).

### Table I. Frequency, percentages and results of the 3 pleurodesis materials

| No. of followed up cases = 20 | Povo-iodine | Vibramycin | Talc slurry |
|------------------------------|-------------|-------------|-------------|
|                              | Frequency   | %           | Frequency   | %           | Frequency   | %           |
| Ascites                      |             |             |             |             |             |             |
| No                           | 1           | 12.5        | 0           | 0           | 0           | 0           |
| Mild                         | 3           | 37.5        | 2           | 33.3        | 2           | 33.3        |
| Moderate                     | 4           | 50          | 4           | 66.7        | 4           | 66.7        |
| Previous thoracocentesis     |             |             |             |             |             |             |
| 2 times                      | 1           | 12.5        | 0           | 0           | 0           | 0           |
| 3 times                      | 5           | 62.5        | 4           | 66.7        | 3           | 50          |
| 4 times                      | 2           | 25          | 2           | 33.3        | 2           | 33.3        |
| 5 times                      | 0           | 0           | 0           | 0           | 1           | 16.7        |
| Number of pleurodesis sessions |             |             |             |             |             |             |
| 1 time                       | 1           | 12.5        | 1           | 16.7        | 0           | 0           |
| 2 times                      | 7           | 87.5        | 6           | 75          | 3           | 50          |
| 3 times                      | 0           | 0           | 1           | 16.7        | 3           | 50          |
| Recurrence                   |             |             |             |             |             |             |
| Yes                          | 1           | 12.5        | 2           | 33.3        | 2           | 33.3        |
| No                           | 7           | 87.5        | 4           | 66.7        | 4           | 66.7        |
| Complications                |             |             |             |             |             |             |
| Yes                          | 6           | 75          | 4           | 66.7        | 5           | 83.3        |
| No                           | 2           | 25          | 2           | 33.3        | 1           | 16.7        |
| Severity of pleural effusion |             |             |             |             |             |             |
| Moderate                     | 2           | 25          | 1           | 16.7        | 3           | 50          |
| Massive                      | 6           | 75          | 5           | 83.3        | 3           | 50          |

### Table II. Frequency and percentages in cases with and without recurrence

| No. of followed up cases = 20 | Recurrence | No recurrence |
|------------------------------|------------|---------------|
|                              | Frequency  | %             | Frequency  | %             |
| Gender                       |            |               |            |               |
| Male                         | 5          | 100           | 11         | 73.3          |
| Female                       | 0          | 0             | 4          | 26.7          |
| Previous thoracocentesis     |            |               |            |               |
| 2 times                      | 0          | 0             | 1          | 6.7           |
| 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          |
| 2 times                      | 2          | 40            | 12         | 80            |
| 3 times                      | 3          | 60            | 1          | 6.7           |
| Complications                |            |               |            |               |
| Yes                          | 5          | 100           | 8          | 53.3          |
| No                           | 0          | 0             | 7          | 46.7          |
| Severity of pleural effusion |            |               |            |               |
| Moderate                     | 0          | 0             | 6          | 40            |
| Massive                      | 5          | 100           | 9          | 60            |
The time needed to remove the chest tube ranged from 4 to 17 days with a mean of 9.8 ±2.3 days (in bovoiodine the range was 5-9 days with a mean of 8.1 ±2 days, in Vibramycin the range was 6-15 days with a mean of 9.4 ±4.3 days and in talc slurry the range was 4-17 days with a mean of 10.3 ±3.6 days). Post-procedure hospital stay ranged from 5 to 18 days.

**Early post-procedure results**

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%) who suffered from surgical emphysema, 2 patients (9.1%) with minimal left side pleural effusion which disappeared spontaneously after a few days, 2 patients (9.1%) with superficial wound infection, 1 patient (4.5%) with mild thoracic pain, another single patient (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 patient (4.5%) who developed pre-hepatic coma 4 days after the procedure, cured by medical therapy and associated with no recurrence of hepatic hydrothorax.

**Late post-procedure results**

However, during the follow-up period 2 out of 19 patients (10.5%) developed late complications. A patient treated with bovoiodine suffered from tense ascites 2 months after the procedure (3 l were tapped) but with no associated recurrence of hepatic hydrothorax. The second patient 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 (Table III).

**Discussion**

Despite numerous reports describing clinical features, pathogenesis and treatment for 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 is 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 just 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].

In contrast to ascites, which becomes massive (< 10 l) while presenting mild symptoms in most patients, relatively small volumes of fluid (< 1 l) 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 dyspnoea secondary to massive pleural effusion associated with hepatic hydrothorax, it carries the risk of substantial protein depletion without preventing fluid re-accumulation, especially if repeated thoracocentesis is required [7]. Pleural drainage by chest tube thoracotomy can be very dangerous in patients with massive ascites and pleural effusion. Runyon et al. [10] reported 2 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].

Out of the 20 cases that have been followed up during this work we used Vibramycin in 6 cases, with no recurrence in 4 cases (66.7%). The reported adverse effects are pain and fever with tetracycline and pain with doxycycline [12]. In our work the number of patients was small. Pain and fever were not reported with the use of Vibramycin. However, recurrence occurred in 2 patients; 1 suffered from encysted effusion and the other from minimal right side pleural effusion. Also, surgical emphysema, left side pleural effusion and hepatic precoma were each found in a single case.

In our study we selected asbestos-free talc slurry to be used in 6 patients to avoid the claims associated with the hazards of asbestos. We reported no recurrence in 4 patients (66.7%). The reported complications with talc pleurodesis include fever, chest pain, empyema, incomplete expansion of the lung, pneumonia, wound infection [7, 13-16] and ARDS [17]. In our cases 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 each noticed in 1 patient. Also, the only mortality in our work was in a patient treated with talc slurry; it occurred 14 days after the procedure due to rapid increase of bilirubin and creatinine followed by hepatic coma and death, and this can be attributable to the course of the disease since the patient’s medical status necessitated thoracocentesis 5 times before our procedure.

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 1 patient (12.5%). There were complications in the form of surgical emphysema
| No. of cases | Age [year] | Sex | Ascites | Pleural effusion | Previous thoracocentesis | Sclerosing agent | No. of sessions | Length of stay | Complications | Follow-up/3 months |
|--------------|------------|-----|---------|----------------|-------------------------|----------------|----------------|----------------|--------------|-----------------|
| 1            | 50         | F   | Moderate| Rt Massive    | 2                       | Bovoiodine       | 1              | 7              | _            | No recurrence   |
| 2            | 53         | M   | Mild    | Rt Massive    | 3                       | Bovoiodine       | 2              | 14             | Wound infection | Recurrence with encysted effusion |
| 3            | 62         | F   | Moderate| Rt Moderate   | 4                       | Vibramycin       | 2              | 12             | _            | No recurrence   |
| 4            | 70         | M   | Mild    | Rt Massive    | 3                       | Vibramycin       | 1              | 4              | _            | No recurrence   |
| 5            | 51         | F   | Moderate| Rt Moderate   | 3                       | Talc             | 2              | 11             | _            | No recurrence   |
| 6            | 63         | M   | Moderate| Rt Massive    | 3                       | Talc             | 3              | 15             | Pain          | Recurrence of minimal effusion |
| 7            | 68         | M   | Mild    | Rt Massive    | 4                       | Vibramycin       | 2              | 13             | Hepatic precoma (4 days after thoracoscopy) | No recurrence |
| 8            | 65         | M   | Moderate| Rt Massive    | 3                       | Vibramycin       | 2              | 9              | Minimal left pleural effusion | Recurrence of minimal effusion |
| 9            | 57         | M   | Mild    | Rt Massive    | 5                       | Talc             | 3              | 16             | Patient had rapid increase of bilirubin and creatinine and patient had hepatic coma and died 14 days after thoracoscopy | |
| 10           | 50         | M   | Mild    | Rt Massive    | 4                       | Bovoiodine       | 2              | 11             | _            | No recurrence   |
| 11           | 52         | M   | Mild    | Rt Moderate   | 3                       | Bovoiodine       | 2              | 11             | Failure of the lung to expand and lung expanded by –ve suction | No recurrence |
| 12           | 43         | M   | Moderate| Rt Massive    | 5                       | Talc             | 1              | 7              | _            | Follow-up of patient failed |
| 13           | 56         | M   | Moderate| Rt Massive    | 3                       | Bovoiodine       | 2              | 10             | Wound infection | No recurrence   |
| 14           | 51         | M   | Moderate| Rt Massive    | 3                       | Bovoiodine       | 2              | 8              | *Surgical emphysema |
|              |            |     |         |                |                         |                 |                |                | *Tense ascites 2 months after procedure (tapping of 3 l) | No recurrence |
| 15           | 68         | M   | –       | Rt Massive    | 4                       | Bovoiodine       | 2              | 10             | _            | No recurrence   |
Chemical pleurodesis in hepatic hydrothorax

in 2 patients (25%), wound infection in 2 patients (25%), failure of the lung to expand which was treated by negative suction with complete expansion of the lung in 1 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, although these 2 complications were the most reported in the literature [18, 19]. 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 [20], can and will produce intense pleuritic pain and a vasovagal reaction if analgesia and anaesthesia are inadequate, and the control of pain should be individualized.

We used somatostatin in all of our patients to reduce the drainage volume and shorten the duration of chest tube removal. Somatostatin reduces splanchnic and hepatic blood flow as well as the portosystemic pressure gradient. Therefore, we used it in our patient instead of TIPS, as in contrast to TIPS, somatostatin has few, mostly minor side effects [21, 22]. The only drawback is that it is expensive. Our data revealed that using the 3 sclerosing agents there was no recurrence in 15 patients (75%) (bovoiodine 87.5%, Vibramycin and talc slurry 66.7% each) and the rates of recurrence and complications of the 3 sclerosing agents used were almost comparable.

In conclusion, in our case series, we used 3 sclerosing agents with a convenient outcome and minimal complications. The medical decision in such patients should be individualized and the balance between treating hepatic hydrothorax and the deterioration of the hepatic condition and ascites should be weighed.

References

1. Xiol X, Guardiola J. Hepatic hydrothorax. Curr Opin Pulm Med 1998; 4: 239-42.
2. Albais WM, Salem AI, Solomon DA, et al. Hepatic hydrothorax: cause and management. Arch Intern Med 1991; 151: 2383-8 (Abstract).
3. Algjakrishnan K, Patel PJ. Left sided hepatic hydrothorax with ascites. Int J Clin Pract 1999; 53: 225-6.
4. Strauss RM, Martin LG, Kaufman SL, et al. Transjugular intrahepatic portal systemic shunt for the management of symptomatic cirrhotic hydrothorax. Am J Gastroenterol 1994; 94: 1520-2.
5. Mouroux J, Perrin C, Venissac N, et al. Management of pleural effusion of cirrhotic origin. Chest 1996; 109: 1093-6.
6. Zenda T, Miyamoto S, Murata S, et al. Detection of diaphragmatic defect as the cause of severe hepatic hydrothorax with magnetic resonance imaging. Am J Gastroenterol 1998; 93: 2288-9.
7. Milanez de Campos JR, Filho LA, Webre EC, et al. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. Chest 2000; 118: 13-7.
8. Cardenas A, Kelleher T, Chopra S. Review article: hepatic hydrothorax. Aliment Pharmacol Ther 2004; 20: 271-9.
9. Kiafar C, Gilani N. Hepatic hydrothorax: current concepts of pathophysiology and treatment options. Ann Hepatol 2008; 7: 313-20.
10. Runyon BA, Greenblatt M, Ring MH. Hepatic hydrothorax is a relative contraindication to chest tube insertion. Am J Gastroenterol 1986; 81: 566-7.
11. Borchart J, Smirnov A, Metchnik L, et al. Treating hepatic hydrothorax. BMJ 2003; 326: 751-2.
12. Richard W, Light MD. Pleurodesis: what agent should be used? J Pneumol 2003; 29: 23-7.
13. Vargas FS, Milanez JR, Filomeno LT, et al. Intrapleural talc for the prevention of recurrent in benign or undiagnosed pleural effusions. Chest 1994; 106: 1771-5.
14. Glazer M, Berkman N, Lafair JS, et al. Successful talc slurry pleurodesis in patients with nonmalignant pleural effusion. Chest 2000; 117: 1404-9.
15. Yim AB, Izzat MB. Talc slurry versus talc insufflation revisited. Ann Thorac Surg 1997; 64: 285-5.
16. Yim AP, Chan AT, Lee TW, et al. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg 1996; 62: 1655-6.
17. Light RW. Talc should not be used for pleurodesis. Am Rev Respir Crit Care Med 2000; 162: 2024-6.
18. Morales-Gomez J, Tellez-Becerra JL, Martinez-Ormeño JE. Pleurodesis conyodopovidona en el derrame pleural neoplásico. Rev Int Nal Enf Resp Mex 1993; 6: 71-4.
19. Olivares-Torres CA, Laniado-Laborín R, Chavez-Garcia C, et al. Iodopovidone pleurodesis for recurrent pleural effusions. Chest 2002; 122: 581-3.
20. Brant A, Eaton T. Serious complications with talc slurry pleurodesis. Respiratory Care 2001; 6: 181-5.
21. Nevens F. Resource analysis of somatostatin in the treatment of bleeding esophageal varices. Digestion 1999; 60 (Suppl 3): 35-7.
22. Patel NH, Chalasani N, Jindal RM. Current status of transjugular intrahepatic portosystemic shunts. Postgrad Med J 1998; 74: 716-20.