Treating tuberculous pleurisy with effusion
by artificial pneumothorax

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Summary. - The efficacy of artificial pneumothorax therapy was evaluated in subjects with tuberculous pleurisy with effusion. The patients (57 cases) were divided into two groups at random: 30 cases in the control group and 27 cases in the group under treatment. They were all given standard treatment with antituberculous drugs drawing liquid accumulated and injecting antituberculous drugs and corticosteroids into their intrapleural cavity. In addition, the treating group received artificial pneumothorax to enhance the treatment efficacy. The frequency and amount of liquid drawn in the treating group were obviously less than those in the control group, Time necessary to draw all the liquid was substantially shortened in the former case with a higher degree of efficiency (92.59%) than that of the latter (83.33%). We also found that the artificial pneumothorax could raise the intrapleural pressure of 2 to 4 cm H₂O, reduce leakage in parietal pleura and evidently increase the absorption in visceral pleura. The results suggest that artificial pneumothorax can reduce the liquid leakage and accelerate absorption of the liquid in thorax. As the two layers of pleura can be isolated by the air in thorax, the occurrence rate of pleural adhesion can be cut down. Hence, it is an effective assistant therapy for tuberculous pleurisy with effusion.

Key words: tuberculous pleurisy with effusion, pneumotorax, artificial treatment.

Riassunto (La terapia con pneumotorace artificiale della pleurite tubercolare effusiva). - L'efficacia della terapia con pneumotorace artificiale è stata valutata in soggetti affetti da pleurite tubercolare effusiva. I pazienti (57 soggetti) sono stati suddivisi in due gruppi con distribuzione casuale, e precisamente 30 soggetti nel gruppo di controllo e 27 soggetti nel gruppo in trattamento. A tutti è stata applicata una terapia con farmaci antitubercolari basata sull'aspirazione del liquido accumulato ed iniezione dei farmaci antitubercolari e dei corticosteroidi nella cavità intrapleurale. Inoltre, il gruppo in trattamento è stato sottoposto a pneumotorace artificiale per aumentare l'efficacia della terapia. La frequenza di aspirazione del liquido e la quantità aspirata nel gruppo in trattamento sono state ovviamente minori di quelle nel gruppo di controllo. Il tempo necessario per completare l'assorbimento del liquido è risultato essere sostanzialmente più breve nel primo gruppo, con una percentuale totale effettiva (92.59%), chiaramente superiore a quella del secondo caso (83.33%). È stato anche riscontrato che il pneumotorace può elevare la pressione intrapleurale di 2-4 cm di colonna d'acqua, ridurre la perdita nelle pareti della pleura ed evidentemente aumentare l'assorbimento nella pleura viscerale. Questi risultati fanno ritenere che il pneumotorace artificiale possa ridurre l'effusione di liquido ed accelerare l'assorbimento nel torace. Poche i due strati della pleura possono essere isolati dall'aria nel torace, la frequenza di insorgenza dell'adesione pleurica viene minimizzata. Ne deriva che la terapia proposta è efficace quale coadiuvante per il trattamento della pleurite tubercolare effusiva.

Parese chiave: pleurite tubercolare effusiva, pneumotorace, trattamento artificiale.

Introduction

Tuberculous pleurisy with effusion is a common disease in China and is the most common cause of pleural disorders in persons of young and middle age. After treating it with antituberculous drugs (chemotherapy), the curative effect has been obviously improved. In addition, by drawing the pleural effusion time and again, especially when a large amount of fluid is drawn in one run, and then by injecting chemotherapy drugs and corticosteroids into pleural cavity, it was possible to increase the speed of absorption of the fluid and to lower the complication of pleural membrane adhesion. But there are many drawbacks in these therapies, such as: the duration of treatment is still a bit too long, the frequency of liquid drawing is rather high, and the pleural membrane adhesion occurs in some patients. The aim of the present study is to treat tuberculous pleurisy with effusion by artificial pneumothorax based on standard chemotherapy in order to further enhance the curative effect and clarify the action mechanism of the therapy.
Methods

Subjects

The study was performed in accordance with the Declaration of Helsinki and all patients gave written or oral informed consent. Fifty-seven patients (31 men, 26 women) with tuberculous pleurisy with effusion, between 14 and 68 years of age (mean 32.7 years) were studied. The diagnoses were established by one of the following standards: 1) 2 out of 57 cases were diagnosed by detecting tubercle bacilli in pleural fluid; 2) tuberculous tissue alterations in 11 out of 57 patients were found on their pleura by pleural biopsy through thoracoscopy; 3) tubercle bacilli DNA detected by PCR were positive twice per person in 23 subjects and accounted for 40%; 4) 21 cases (37%) were diagnosed according to the clinical diagnostic standards which were: a) some tuberculous toxemia symptoms are shown; b) the character of the effusion is exudative; c) after chemotherapy the symptoms were obviously relieved and the fluid was evidently absorbed 15 days later. The subjects were all treated for the first time and had only unilateral pleurisy and no encystment of effusions. Of 57 patients showed complications by pulmonary tuberculosis but none had tuberculosis out of lungs. Cases of nontuberculous pleurisy were all excluded. The heart and pulmonary vessel disorders, as well as liver and renal chronic diseases were also excluded.

Groups and treatment protocols

All patients were divided into two groups at random. There were 30 cases in the control group (16 men, 14 women) between 16 and 65 years of age (mean 33.5 years) and the duration of their illness before treatment averaged 30.5 days. They all received shortened course of chemotherapy such as first two months of isoniazid (H), rifampicin (R), streptomycin (S), and secondary 4 months of H, R (abbreviated to 2HRS/4HR) or 2HRS/4HRP (abbreviated pyrazinamide to P. Their pleural effusions were drawn at two-days interval. When tolerable to the patient, the liquid was drawn to the possible extent and 0.1 g isoniazid (INH) and 5 mg dexamethasone were injected into the pleural cavity. There were 27 cases in treating group (15 men, 12 women) between 14 and 68 years (mean 32 years) and the duration of their illness before treatment averaged 32.3 days. Apart from artificial pneumothorax, the other treatment protocols were the same as the control group. After the fluid was drawn out and chemotherapy drugs injected, 60-100 ml filtered air were injected into the pleural cavity. The proper volume of injected air was determined by the pressure of the pleural cavity. The suitable air volume was to make the pleural cavity pressure group 2 to 4 cm H₂O after injecting air, with no discomfort for the patient. The patients of two groups were divided again into three subgroups, respectively: the first subgroup included patients with fewer fluid and the top of the fluid below the down edge of the fourth prior rib; the second group, patients with middle quantity effusion and the top of the fluid between the down edges of the second and the fourth prior rib; the third group included patients with a large amount of effusion and the top of the fluid above the down edge of the second prior rib. The two groups were similar in age, sex and duration of illness before treatment.

Criteria for the assessment of the therapeutic effect

The effect was evaluated on the speed of absorption of the pleural fluid and on the thickening or adhesion of the pleural membranes appearing in X-ray chest film two months later. In this context "cure" means that the fluid was absorbed entirely in two weeks and had not pleural membranes thickening or adhesion. "Evident effect" is that the fluid was essentially absorbed (only the obliterated costophrenic angle is still there) between two and four weeks and kept this state over two months. "Effectiveness" is that the major part of the fluid was absorbed and the top of the fluid fell below the down edge of the fifth prior rib in one month and the pleural membranes adhesion and thickening had taken place (1-2 cm thickness at the exterior zone of the lung two months later). "No effect" means that the fluid was not absorbed or had encystment for a long time and serious adhesion or thickening in pleural membrane two months later (over 2 cm thickness at the exterior zone).

Measure items and methods

Routine pleura effusion, and biochemical and cytological tests were carried out as appropriate.

Tubercle bacilli were detected on the smear of the deposit of pleural fluid by Ziehl-Neelsen's staining.

Detection of DNA of Mycobacterium tuberculosis in the fluid by PCR: 2 ml pleural fluid was centrifuged and allowed to deposit. The DNA genes of tubercle bacilli in the fluid were then extracted by D. de Wit method [1]. The DNA reagent box was purchased from the Institute of Inheritance of Shanghai Fudan University. The series of introductive materials were INS-1, 5'-CGTGAAGGCCATCGAGGTGCG and INS-2, 5'-GGCTAGACGCCTCGGTGACAAA. The amplified products of the DNA were analyzed by agarose gel electrophoresis on the DNA amplified meter (PCR-90AD model, Institute of Inheritance of Chinese Academy of Sciences).

The pleural membrane biopsy was performed by thoracoscopy (replaced by Olympus BF-20 model of optic-fiber bronchoscope) based on an improvement of the Chen's methods [2]. The optic-fiber bronchoscopy device was inserted into the patients' thoracic cavity through the incision on the chest wall, the fluid was drawn, and then 3-4 patches of the pleura showing
pathological changes such as congestion, edema, and coarse, white nodular plaques were excised and sent to pathology inspection.

The average pressure of thoracic cavity balanced between the pressures of inspiratory and expiratory phases was measured by water pressure manometer.

**Observation items**

The following items were measured: the total of the fluid drawn out; the frequency of fluid drawing; the air volume injected into the pleural cavity; the pressure changes in the cavity which were measured before and after drawing fluid and after injecting air; chest Roentgenography before and after drawing the liquid in order to ascertain the level of this last and whether the amount of injected air was sufficient (a separation of 0.5-1.0 cm between the two layers of pleura was acceptable). X-ray chest film was given when necessary and after two months following-up.

Data were analyzed with the statistical computing software issued by Huaxi Medical University of China. The various parameters obtained during the trial were compared by means of the t-test between the two subgroups. The significant statistical borderline is considered to be as \( P < 0.05 \).

**Results**

The frequency of fluid drawing (the fluid was drawn every two days and the total number of drawings during two months was recorded), the total fluid quantities drawn and the overall fluid absorption picture are listed in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>no.</th>
<th>Mean frequency of liquid drawing</th>
<th>Mean total quantity of the fluid drawn (ml)</th>
<th>Time of complete absorption (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fewer</td>
<td>10</td>
<td>1.5 ± 0.52</td>
<td>1270 ± 347.3</td>
<td>15.6 ± 5.76</td>
</tr>
<tr>
<td>middle</td>
<td>10</td>
<td>2.8 ± 0.78</td>
<td>2550 ± 377.09</td>
<td>31.9 ± 9.84</td>
</tr>
<tr>
<td>large</td>
<td>10</td>
<td>3.3 ± 0.82</td>
<td>3397.5 ± 498.61</td>
<td>42.1 ± 10.42</td>
</tr>
</tbody>
</table>

| Treating group  |     |                                 |                                            |                                  |
| fewers          | 7   | 1.00                            | 625.7 ± 302.26 (5)                         | 10.14 ± 5.24 (5)                |
| middle          | 11  | 1.64 ± 0.67 (5)                 | 1579 ± 528.96 (5)                         | 21.82 ± 5.38 (5)               |
| large           | 9   | 2.0 ± 0.71 (5)                  | 2102.2 ± 569.16 (5)                       | 29.30 ± 10.14 (5)              |

(1)Values and SD. (a) \( P < 0.01 \), for the comparison with changes in the control group. (b) \( P < 0.05 \), for the comparison with changes in the control group.
Fewer: the subgroup of patients who had fewer fluid in the cavity and the top of the fluid below the down edge of the fourth prior rib in the X-ray film; middle: the subgroup of patients with middle quantity effusion and the top of the fluid between the down edges of the second and the fourth prior rib; large: the subgroup patients with a large amount of effusion and the top of the fluid above the down edge of the second prior rib.

The comparison between the therapeutic effects reached in the two groups is set forth in Table 2.

We can see from Table 2 that the total efficacy in the treating group (92.39%) was clearly higher than in the control group (83.33%).

The relationship between the changes of pressure in pleural cavity before and after injecting air and the changes of exudative and absorptive power in treating group is given in Table 3.

The effusion in pleural cavity is exuded from parietal pleura and is reabsorbed from visceral pleura. The changes of exudative and reabsorbed forces are calculated by the formula: capillary pressure + (intrapleural pressure + intrapleural colloid osmotic pressure) - plasma colloid osmotic pressure. Under normal conditions, the exudative and absorbed forces are probably equal, so there is no free fluid in the pleural cavity but as a latent cavity. The plasma colloid osmotic pressure of each patient is equal both before and after drawing fluid. Great changes have not taken place in capillary pressure of general and pulmonary circulation. Heart and pulmonary vessel disorders, liver and renal chronic diseases had been excluded from the patients selected, so that one can calculate the exudative and reabsorbed force of the patients referring to the capillary pressure and plasma colloid osmotic pressure of the normal persons. Although the intrapleural colloid osmotic pressure in the patients slightly increased due to increase in the fibrin exudation, drawing fluid did not influence intrapleural colloid osmotic pressure. Hence, the only alteration before and after drawing is the intrapleural pressure. The changes of the exudative and reabsorbed force are calculated according to the standards of normal persons: intrapleural colloid osmotic pressure is 8 cm H2O, plasma colloid...
osmotic pressure is 34 cm H₂O, capillary pressure in
general circulation is 30 cm H₂O and in pulmonary
circulation is 11 cm H₂O. According to the formula
mentioned above, the exudative force (in cm H₂O) in
parietal pleura was 30 + (measured intrapleural pressure
+ 8) - 34; the reabsorption force (in cm H₂O) in visceral
pleura was 11 + (measured intrapleural pressure + 8) - 34.
Results are listed in Table 3.

**Discussion**

In theory, if the capillary pressure of two layers of
parietal and visceral pleura, the plasma colloid osmotic
pressure and the intrapleural colloid osmotic pressure
remain constant, the small change of intrapleural pressure
can lead to greater change in exudative and reabsorbed
force. The research results show that when intrapleural
pressure increases to 3.14 cm H₂O, the exudative force of
parietal pleura will reduce from 9.48 cm H₂O to 6.34 cm
H₂O to 12.66 cm H₂O (absolute value). Consequently,
the exudation will be reduced and the reabsorption of
the fluid will be clearly increased. The frequency and total
quantity of fluid drawn in the treating group are notably
less than those in the control group (P < 0.05). We
compared two subgroups of fewer fluid respectively in
treating group and control group and found that the
frequency of drawing in treating group was less than that
in control group, but there were no marked differences
between them on statistics (P > 0.05). The reasons may
be related to the less fluid and less cases in these two
fewer fluid subgroups.

A small amount of air in the intrapleural cavity can
isolate two layers of pleura from each other and therefore
the chance of adhesion between them will be reduced.
Thorough liquid drawing in the pleural cavity can
eliminate into the pleural cavity in due course. Corticosteroids act as anti-inflammatory substances, thus

**Table 2.** - Comparison of the cure efficacy in two groups (%)

<table>
<thead>
<tr>
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<td>%</td>
<td>%</td>
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<tr>
<td>Control group</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>fewer</td>
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<td>1</td>
<td>10</td>
<td>5</td>
<td>3</td>
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<tr>
<td>middle</td>
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<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>2</td>
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<tr>
<td>large</td>
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<td>0</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>3</td>
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<td>30</td>
<td>1</td>
<td>3.33</td>
<td>12</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Treating group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fewer</td>
<td>7</td>
<td>2</td>
<td>28.57</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>middle</td>
<td>11</td>
<td>2</td>
<td>18.8</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>large</td>
<td>9</td>
<td>1</td>
<td>11.11</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>total count</td>
<td>27</td>
<td>5</td>
<td>18.52</td>
<td>13</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

Fewer: the subgroup of patients who had fewer fluid in the capacity and the top of the fluid below the down edge of the fourth prior rib in the X-ray film; middle: the subgroup of patients with middle quantity effusion and the top of the fluid between the down edges of the second and the fourth prior rib; large: the subgroup patients with a large amount of effusion and the top of the fluid above the down edge of the second prior rib.

**Table 3.** - The changes of the intrapleural pressure, the forces of exudation and absorption in the treating group

<table>
<thead>
<tr>
<th></th>
<th>Mean intrapleural pressure (cm H₂O)</th>
<th>Exudative force of parietal pleura (cm H₂O)</th>
<th>Absorption force of visceral pleura (cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injecting air</td>
<td>- 5.48 ± 1.3</td>
<td>9.48</td>
<td>- 9.52</td>
</tr>
<tr>
<td>After injecting air</td>
<td>- 2.34 ± 0.7</td>
<td>6.34</td>
<td>- 12.66</td>
</tr>
</tbody>
</table>

(a) Values and SD.
(b) The values were calculated only on the basis on the mean values of intrapleural pressure.
reducing the permeability of capillary vessels and alleviating fibrin exudation. Due to the actions mentioned above, the possibility of pleura adhesion can dramatically drop.

The incidence of pleura fibrous adhesion in the artificial pneumothorax group is notably lower than in the control group, so that the cure rate in the former (18.5%) is evidently higher than in the latter (3.33%). Total efficacy in the former is also much higher than in the latter. Dynamic measurements revealed that 60-100 ml of air could be adsorbed basically in 2-4 days; hence, injecting air after drawing fluid every two-three days can maintain the two layers of pleura separated without adherence to each other. However, pleural thickening and adhesion occurred in a few patients in the treating group; enhance 7.41%. The reason may be due to pleural adhesions or encystments occurred before hospitalization, gone unnoticed because of the large amount of liquid until the first drawing. In addition, the longer was the history of the disease before hospitalization, the greater was the possibility of adhesion. Therefore, a medical check and an early treatment are the key steps to increase the cure expected effects.

After injecting 60-100 ml of air into the pleural cavity the intrapleural pressure decreased momentarily above 2-4 cm H₂O. It was however still lower than that before drawing of the liquid.

No drawbacks for the patients were observed. The air injected had been filtered through sterilized gauze and none of the patients had treatment-induced infection. This method can be thus considered safe and feasible.

The artificial pneumothorax method takes advantage of physics principles and makes the intrapleural pressure increase, thus achieving the goals of lessening exudation, increasing reabsorption, decreasing adhesion and accelerating recovery. The method is safe and feasible and no side effects have been found. The treatment is simple and affords a good success rate, but it is only an auxiliary therapy of tuberculous pleurisy with effusion and cannot replace etiology treatment.

We deem that the treatment based on drawing of liquid and injection of antituberculous drugs along with corticosteroids into the intrapleural cavity in combination with the artificial pneumothorax results in an effective therapy for tuberculous pleurisy with effusion and has a potential for routine applications. Finally, this treatment shows promise for effusion pleurisies of other etiology.

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