Spontaneous Pneumothorax*
Long-term Results With Tetracycline Pleurodesis

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The aim of this prospective study was to determine the rate of recurrence for spontaneous pneumothorax (SP) after tetracycline pleurodesis (TCP), using that of observation, tube thoracostomy alone, and thoracotomy as references. From 1985 to the end of 1991, 78 patients were treated with tetracycline pleurodesis and 135 patients served as control subjects. Pleurodesis was induced by instillation of tetracycline and ascorbic acid through the pleural drain. The indication was any SP treated with tube thoracostomy, without active pulmonary infection. Follow-up period was from 13 to 95 months (mean, 45 months); follow-up rate was 94 percent. Post-therapy surgery was necessary for eight patients in whom pleurodesis failed due to presence of a persistent air leak. The ipsilateral recurrence rate of patients treated with TCP was 9 percent (6/66) and recurrence time ranged from 2 days to 9 months. The recurrence rate for patients treated with observation was 36 percent, 35 percent for those having chest tube alone, and none for those undergoing surgery. No death occurred as a direct result of this procedure and all patients could be released from the hospital. Eleven subjects died during the follow-up period; the mean follow-up until death was 37 months (range, 2 to 87 months). Five deaths were due to respiratory causes and six were due to extrapulmonary causes. Tetracycline pleurodesis has been shown to be a good alternative for the prevention of recurrence of SP. Its recurrence rate is lower than that of tube drainage but higher than that of surgical treatment. (Chest 1994; 106:347-50)

Key words: pneumothorax prevention; pneumothorax, secondary; pneumothorax, spontaneous; prospective studies; recurrence; tetracycline pleurodesis

The incidence of spontaneous pneumothorax (SP) is about 8.6/100,000/year. Spontaneous pneumothorax may occur in subjects with no history of lung disease (primary spontaneous pneumothorax [PSP]) or in those with preexisting lung disease (secondary spontaneous pneumothorax [SSP]). Basic therapeutic goals are resolution of symptoms by evacuating air from the pleural space, reexpansion of the lung, and preventive methods to avoid recurrence. The ipsilateral recurrence rate for patients with primary SP treated with tube thoracostomy varies from 25 percent to 52 percent and the rates are similar for SSP. However, recurrence depends on patient selection. Treatment of SP includes observation, pleural drainage, pleurodesis produced by different agents, and thoracotomy either with cyst resection or with pleurodesis induced by brushing the pleural surface, or both. The choice of treatment is influenced by pneumothorax size, clinical symptoms, technical possibilities, and presumed recurrence rate.

The aim of the present study was to evaluate the effectiveness of tetracycline pleurodesis (TCP) in preventing the recurrence of spontaneous pneumothorax, using that of observation, tube thoracostomy

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a history of ipsilateral SP. Twenty-nine of these 38 cases were of PSP and 9 were of SSP (1 had pneumonia, 2 pneumonia and COPD, 2 COPD, 1 active tuberculosis, 2 asthma, 1 residual tuberculosis).

In group 3, 68 episodes in 66 patients (63 men and 3 women; aged from 16 to 77 years) were treated by chest tube alone. Included in this group were patients with active pulmonary or pleural infections and those who refused other types of treatment. Two patients of this group had a history of ipsilateral SP. Forty-seven of these 68 cases were of PSP and 21 were of SSP (2 had active tuberculosis, 1 mesothelioma, 6 COPD, 3 pneumonia with COPD, and 9 pneumonia with AIDS).

In group 4, 29 patients (28 men and 1 woman; aged from 16 to 75 years) were treated by thoracotomy. The criterion for this treatment was failure of lung expansion after tube placement along with important pulmonary-pleural air leak, or hemopneumothorax, or simultaneous lung biopsy, or patient's preference for this kind of treatment. Nine patients of this group had history of ipsilateral SP. Sixteen of these 29 cases were of PSP and 13 were of SSP (6 COPD, 2 histicycosis, 1 asthma, 1 active tuberculosis, and 3 residual inactive tuberculosis).

**Tetracycline Pleurodesis Procedure**

For drainage, a No. 20 or 24 Argyle catheter was inserted in all patients, usually through the sixth intercostal space in the midaxillary line and attached to a water-seal system. The patient was premedicated with atropine and analgesics in anticipation of significant discomfort. Drugs were used were intravenous buprenorphine and ketamine administered in the intensive care unit. Intrapleural instillation of 200 mg of lidocaine hydrochloride was carried out prior to tetracycline instillation at the discretion of the physician. Pleurodesis was induced with 5 g of ascorbic acid and tetracycline hydrochloride dissolved in a 150-ml sterile saline solution (prepared in our hospital's pharmacy) administered at doses of 20 mg/kg until 1988 and after that date at a total dose of 2 g regardless of the size of the patient (total volume of fluid, 150 ml). The solution was instilled through the drain. The patient was repositioned frequently so that the tetracycline could make contact with all pleural surfaces. After tetracycline instillation, the drain was clamped for 2 h, after which suction of 20 to 30 cm H2O was applied. Pleural drainage was continued until total lung expansion, no air had escaped for 24 h, and fluid drainage volume was less than 50 to 100 ml in 24 h. This procedure was carried out once on 71 patients and twice on the other 7 patients who had persistent air leaks.

**Evaluation of Results**

Recurrence of SP was defined as the occurrence of a new event of SP in the same hemithorax. If the patient had a persistent air leak after tetracycline administration, the procedure was considered to be unsuccessful, and the patient was excluded from the final data analysis.

**Follow-up**

In December 1992, all patients were contacted. Each follow-up visit included clinical evaluation, physical examination, and chest radiography. Patients who could not come to hospital were interviewed by telephone. Patients were followed up for at least 1 year or until recurrence of pneumothorax or death occurred. In the group of patients treated by TCP, four subjects were not located (follow-up rate of 94 percent); hence, they were excluded from the final data analysis. The follow-up for the patients who did not have a recurrence, did not die, and were not procedure failures was from 13 to 95 months (mean, 45 months). The follow-up rate of the group of patients treated by observation and thoracotomy was 74 percent and 90 percent, respectively (ten and three patients not located). The follow-up for the patients who did not have a recurrence and did not die was from 12 to 91 months (mean, 47 months) for the group of patients treated by observation, and from 15 to 96 months (mean, 42 months) for the patients treated by thoracotomy. Among the patients treated by chest tube alone, 15 patients were not located and two patients had died during the episode (follow-up rate was 75 percent); the follow-up for the patients who did not have recurrence and did not die was from 12 to 89 months (mean, 58 months).

**Variable distribution of age and days of hospital stay did not follow a normal (gaussian) distribution and treatment comparisons were made using the Wilcoxon two-sample test. Data are expressed as mean ± SD unless otherwise noted. Treatment comparisons for qualitative variables (recurrence of SP) were made using the χ2 test. Differences were statistically significant at p<0.05.**

**RESULTS**

There were no significant differences in age among the patient group treated by TCP (mean, 39 ± 21 years) and the patient group treated by chest tube alone (mean, 34 ± 17 years) or the patient group treated by thoracotomy (mean, 34 ± 17 years); however, the patient group treated by means of observation was significantly younger (30 ± 17 years, p = 0.04). Mean hospital stay of the patient group treated by TLP was 10 days (8 days for primary SP and 12 days for secondary SP) and the mode was 6 days. The hospital stay was significantly longer for the TCP group than for either the group treated by means of observation (4 ± 6 days, p<0.01) or for those

<table>
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<tr>
<th>Group</th>
<th>Tetracycline</th>
<th>Observation</th>
<th>Chest Tube Alone</th>
<th>Thoracotomy</th>
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<td>29</td>
<td>47</td>
<td>16</td>
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<td>Total</td>
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**Table 1—Distribution of 213 Episodes of Spontaneous Pneumothorax According to Etiology and Treatment**

**Table 2—Treatment of 78 Patients With Tetracycline Pleurodesis**

*Patients excluded of final analysis.*
treated by chest tube alone (8 ± 8 days, p<0.01).

The results of treatment by TCP are summarized in Table 2. In the group treated by TCP, 20 patients of the total of 78 had pulmonary-pleural air leak from the chest tube at the time of tetracycline application. Of these, the procedure failed to achieve pleurodesis in 8 patients with persistent pulmonary-pleural air leak (8/20, 40 percent of the patients with pulmonary-pleural air leak); therefore, surgery was necessary for these patients. Although these eight patients (procedure failures) were treated by TCP and thoracotomy, they were not included in the thoracotomy group, since during this same episode, they were treated by two different kinds of treatment). Thus, these patients were excluded from the final analysis.

After TCP, six patients had ipsilateral recurrent SP. Excluding procedure failures (8 patients) and follow-up losses (4 patients), the ipsilateral recurrence rate was 9 percent (6/66). Recurrence time ranged from 2 days to 9 months (4 within the first month). In the six patients who had ipsilateral SP recurrence, a second TCP was performed on one patient, thoracotomy on three patients, and observation was prescribed for two patients who developed a small apical pneumothorax. No subsequent recurrences have been observed in these patients.

No patient died as a direct result of TCP and all were discharged from the hospital. Infection of the pleural cavity was not observed in our study. At the beginning of our study, pain during the procedure was reported by all patients, but once we standardized the analgesic, only occasional slight discomfort was described. Six patients had transitory fever, and seven had muscular rigidity and nausea attributed to premedication. One elderly man underwent ventricular tachycardia that was resolved with treatment. At follow-up, patients reported no pain and none who had TCP presented with obliteration of lateral costophrenic angle on the chest radiography or severe pleural thickening.

The recurrence rate for all groups is summarized in Table 3; the global rate for patients treated with observation was 36 percent; 35 percent for those having thoracic drainage alone and none for those undergoing surgery. In the group of patients treated with observation, recurrence time ranged from 22 days to 17 months (7 within the first year). Recurrence time was from 8 days to 50 months in the patients treated by chest tube alone (11 within the first year and 7 in the first month).

In the group of 78 patients treated by TCP, there were 11 deaths during the follow-up period (2 of these patients were procedure failures). Three patients died in the first year of follow-up (at 2, 5, and 8 months after the procedure, respectively) without recurrence of SP. The mean follow-up until death was 37 months (range, 2 to 87 months). The deaths were due to respiratory causes in five patients (all patients were elderly with COPD) and to extrapulmonary causes in the remaining six (three neoplasias, two cirrhosis of the liver, one suicide). There were no deaths in the group of patients treated by observation. In the group of patients treated by thoracotomy, there were two deaths (at 16 and 83 months); the cause of death was pulmonary neoplasia in one patient and unknown in the other. In the group of patients treated by chest tube alone, five patients died: two patients at the time of SP (one had advanced active tuberculosis and the other had pneumococcal pneumonia and COPD); two patients died at 2 and 5 months after SP (one had AIDS and the other had a mesothelioma); and the remaining patient died of extrapulmonary neoplasia at 12 months after SP.

**DISCUSSION**

Achieving effective pleurodesis is the therapeutic goal in the treatment of pneumothoraces. When surgical procedures such as thoracotomy with scrubbing of the pleural surface or parietal pleurectomy have been performed, a recurrence rate of 0.4 to 2.3 percent has been reported. If pleurodesis is carried out, the recurrence rate ranges from 4 to 28 percent; this depends on the etiology of the SP (primary or secondary) as well as the substances used. New alternatives such as thoracoscopy allow a complete evaluation of pleural lesions as well as treatment in many cases; it has a recurrence rate after 2 years of 7 percent (5 percent for primary SP). Among the agents employed to produce pleurodesis, tetracycline has not been associated with significant side effects and has been found to be highly effective in both animals and man. Although the low pH of tetracycline hydrochloride was initially thought to be a factor in producing pleuritis and subsequent pleural fibrosis, intrapleural instillation of this substance effectively produces pleural fibrosis by stimulating mesothelial cells to release a growth-factor-like activity for fibroblasts.
manufacturer in the United States of injectable tetracycline hydrochloride used in pleurodesis, has discontinued production of this agent, but in Spain as well as other European countries, it is still produced. Alternatives such as minocycline are available for pleurodesis and Light et al have reported this agent to give better results in rabbits.

All patients who died during follow-up had secondary SP; therefore, the recurrence rate of secondary SP treated by TCP is lower than for primary SP, probably due to a shorter follow-up period. Our global recurrence rate of 9 percent is somewhat lower than the 16 percent reported by Olsén and Andersen and the 25 percent previously reported by Light et al. Due to the small size (less than 20 percent) and the presence of pleural adhesions in the rest of the pleural cavity, thoracic drainage was not necessary in two of the six patients suffering recurrence. A possible cause for these improved results could be that we employed a higher dose of tetracycline than that used by other authors who prescribed 1 g or 1.5 g. Although the addition of ascorbic acid to tetracycline could produce pleural irritation, studies with multivitamin solutions did not find that these had a great capacity to create pleural fibrosis. In our series, the overall failure rate of this procedure was 19 percent (14/74), including not only the six patients with SP recurrence but also the other eight patients who required surgery, due to persistent air leak.

The eight subjects in whom the procedure failed had large pneumothoraces (greater than 80 percent of the hemithorax) with persistent air leak and lung reexpansion was incomplete, therefore impeding pleural adhesion. A reevaluation of these cases indicated nonsuitability for pleurodesis. To avoid this error, a thoracoscopic examination should be performed to search for cysts or blebs, for those greater than 2 cm in size are presumed to be implicated in SP recurrence. This technique, however, is not available in all hospitals and according to Olsen and Andersen, there is a recurrence rate of 4 percent since it is often performed by inexperienced personnel under emergency conditions. As an alternative method to search for cysts or blebs greater than 2 cm, a computed tomographic scan of the reexpanded lung could be obtained.

Due to the high rate of procedure failure in the performance of pleurodesis on patients with air leaks (40 percent in our series), we prefer to wait until air leaks cease before tetracycline is instilled. Waiting for the air leaks to stop may have influenced the length of our patients' hospital stays, which were somewhat longer than those referred to by other authors such as Olsen and Andersen and Light et al. Pleurodesis through the drainage tube itself is an easy method to perform that does not require anesthesia; if tetracycline instillation is done after air leak stops, the results are more satisfactory. The only precaution necessary is the administration of a strong analgesia at instillation and, following the procedure, no more than the usual analgesic care. Because a fair number of patients with primary spontaneous pneumothoraces never develop a recurrence, definitive surgical treatment should not be regarded as the treatment of choice for all patients. Tetracycline pleurodesis has been shown to be a realistic alternative with a lower recurrence rate than that of tube drainage although higher than that of surgical treatment.

In countries in which tetracycline is available, this agent should be indicated for the treatment of any patients with SP (primary or secondary), without pulmonary or pleural infection, in which a chest tube is inserted, complete lung reexpansion is achieved, and air leak stops if present.

REFERENCES
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