

Tetracycline Pleurodesis for Malignant Pleural Effusions

A 10-Year Retrospective Study

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We retrospectively examined the use of tetracycline pleurodesis for the palliative treatment of malignant pleural effusions. Twenty-five patients (32 procedures) were identified for study. In contrast to higher success rates in prior reports, 13 procedures (40.6%) failed as repeated pleural drainage was required. Only five procedures (15.6%) achieved complete resolution of pleural fluid. In 14 procedures (43.8%) pleural effusions recurred but were not treated. In some of these cases the effusion may have been reduced sufficiently to relieve symptoms, while in others the high short-term mortality rate (29% in 30 days) and the development of loculated effusions (34%) may have led to the decision not to treat. Instillation of a larger dose of tetracycline (≥ 1 g) was associated with a better outcome. Although adequate pleural drainage and proper technique were used, other factors such as the presence of pleural masses, atelectasis, loculations, and patient performance status were not uniformly controlled. Greater attention to these factors and use of a larger dose of tetracycline (≥ 1 g) may increase the likelihood of a successful pleural symphysis.

Cancer 59:1973-1977, 1987.

PLEURAL EFFUSIONS caused by malignancy occur commonly and are generally a manifestation of advanced disease.¹⁻³ Regardless of the underlying tumor type or whether there is direct carcinomatous involvement of the pleura, 30-day mortality has been reported to be as high as 50%.² Respiratory insufficiency often demands palliative management of the effusion. Rapidly accumulating effusions may not be controlled by repeated thoracentesis, and surgical pleurectomy may not be considered appropriate for terminal patients. Chemical pleurodesis has therefore been suggested as achieving the best balance between efficacy and acceptability for the terminally ill.

Tetracycline is currently recommended as the agent of choice for chemical pleurodesis.^{3,4} Several prospective studies have estimated the efficacy of tetracycline pleurodesis to be 70% to 100%.⁵⁻⁹ However, there were significant differences among these studies in the criteria for a successful pleurodesis, as well as patient selection and technique of the procedure. In the current study we sought to determine if our experience with tetracycline pleurodesis compared favorably with previous reports, and to

look for factors that may improve the effectiveness of the procedure.

Methods

All patient records with diagnosis codes of malignant pleural effusion and tube thoracostomy or pleurodesis dating from January, 1975 through September, 1985 were reviewed. Thirty-nine patients were identified who underwent tetracycline pleurodesis. Fourteen patients were excluded only because information was inadequate to establish the outcome of the procedure. The remaining 25 patients (32 procedures) constituted the study group. Clinical information, as well as the dose of tetracycline, and the duration and method of pleural drainage, were reviewed.

Procedures were categorized by outcome according to the following scheme: (1) A pleurodesis was deemed a "complete response" (CR) when no subsequent drainage procedure was performed and reaccumulation of pleural fluid was not evident on chest radiographs; (2) a "partial response" (PR) was defined by a reaccumulation of pleural fluid which was not treated by repeated drainage; and (3) a procedure was deemed a "failure" (F) when a subsequent drainage procedure was performed. The chest radiographs were reviewed jointly (T.G., R.S., and B.G.) and the size of the effusion classified by consensus without knowledge of the outcome category of the procedure. "Small" pleural effusions were defined as those that did not extend above

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Accepted for publication January 12, 1987.

TABLE 1. Study Population

Patient	Age (yr)	Sex	Primary malignancy	Dyspnea	Outcome*	Duration of follow-up (days) after procedure†
1	49	F	Breast	+	CR	1535
2	61	M	Mesothelioma	+	CR	127
3	35	F	Ovary	-	CR	60
4	59	F	Breast	+	CR	8
5	47	F	Endometrium	+	CR	40
6	38	F	Breast	-	PR	63
7	73	F	Ovary	+	PR	58
8	61	F	Adeno CA ? origin	+	F	86
1st (R)				+	PR	227
2nd (R)				+	F	11
3rd (L)				+	F	88
4th (L)				+	F	143
9	57	F	Breast	-	F	98
1st (L)			Breast	+	PR	51
2nd (R)			Breast	-	PR	163
10	64	F	Adeno CA ? origin	+	PR	159
11	88	F	Lung	-	F	31
12	60	F	Lung	-	PR	15
13	77	F	Cervical CA	+	PR	287
14	49	F	Breast	+	PR	5
15	54	F	Breast	+	PR	191
16	26	F	Hodgkin's	+	PR	3
1st (L)				-	F	87
2nd (R)				-	F	33
3rd (R)				-	F	4
17	60	M	Melanoma	+	F	13
18	69	M	Lung	-	F	37
19	56	F	Breast	+	F	16
20	67	M	Lung	+	F	8
21	22	M	Neurofibrosarcoma	-	F	198
22	71	M	Melanoma	+	PR	65
23	53	F	Cervical CA	+	PR	15
24	71	F	Lung	+	PR	
25	60	M	Lymphoma	+	F	

+: positive; -: negative.

* CR: complete response; PR: partial response; F: failure; L: left hemithorax; R: right hemithorax.

† Interval to death, loss of follow-up, repeat ipsilateral pleurodesis, or ipsilateral drainage procedure.

the dome of the hemidiaphragm. "Moderate" effusions were those extending above the dome of the hemidiaphragm but below the level of the hilum. "Large" effusions were those extending above the level of the hilum. In addition, the radiographs were examined for evidence of loculated pleural fluid.

Statistical Analysis

Comparisons of means between groups were performed with Student's *t* test, or where appropriate, a one-way analysis of variance. Intergroup comparisons of frequency distribution were performed using Fisher's exact test.¹⁰

Results

Study Population

A summary of the study population is shown in Table 1. There were 18 women and seven men, ranging in age

from 22 to 88 years (mean age, 57 years). Carcinoma of the breast was the most common primary malignancy, occurring in eight patients. Bronchogenic carcinoma occurred in four, and there were two patients each with adenocarcinoma of unknown primary, lymphoma, and ovarian carcinoma. Excluded patients showed a similar distribution of age and tumor type. Four patients had either bilateral procedures or repeated pleurodesis on the same hemithorax. When procedures were repeated, duration of follow-up was then determined as the interval to a subsequent ipsilateral pleurodesis. All but three of the patients were followed until their deaths; Patients 23 to 25 were lost to follow-up 15 to 198 days after pleurodesis. Of the 32 procedures, the length of follow-up after tetracycline instillation ranged from 3 to 1535 days (≤ 30 days in ten, 31 to 60 days in seven, 61-90 days in five, and >90 days in ten). Dyspnea was specifically noted in the medical records as the indication for attempting pleurodesis in 22 of the 32 procedures. In the remainder, no specific indication for pleurodesis was described.

Outcome

When all procedures are included in the analysis, regardless of duration of follow-up, the overall response rate was 59%. Complete responses to tetracycline pleurodesis occurred in only five of the 32 procedures (15.6%). One of these patients died 8 days after tetracycline was instilled. Fourteen procedures (43.8%) resulted in a partial response, and 13 (40.6%) were failures (Fig. 1). These groups could not be distinguished by age or type of malignancy. Also, there were no significant relationships between the outcome of the procedure and either the total survival time after the effusion was recognized or the concomitant administration of chemotherapy. Twenty-nine percent of the patients died within 30 days of the first tetracycline instillation, and 58% died within 60 days. To determine if the high failure rate for pleurodesis resulted from including patients who died soon after a failed procedure, the outcome categories were also tabulated for procedures after which the patients survived for 30 or 60 days. As shown in Figure 1, the proportion of failures, partial responses, and complete responses were identical to those of the entire study group. The failure group was examined to determine the length of time between the attempted pleurodesis and the subsequent drainage procedure. As shown in Figure 2, pleural drainage had to be repeated within 2 weeks in 70% of the failure group.

Radiographic Findings

Complete x-ray files were available for review in 11 patients (14 procedures). Among these, there were two complete responses, five partial responses, and seven failures. In the two complete responses, one effusion was large and the other moderate before pleurodesis. After the procedure neither showed significant loculation or reaccumulation of fluid. In the partial responses, all the effusions were moderate in size before pleurodesis. All decreased in size after the procedure, but only one of the five effusions was reduced sufficiently to be reclassified as a small effusion. Of the seven failures, five effusions were moderate and two were large before pleurodesis. All moderate effusions increased in size after the procedure, three being reclassified as large effusions. One large effusion remained stable and the other increased after the attempted pleurodesis.

Pleurodesis Procedure

Pleural drainage was achieved by placement of a thoracostomy tube before instillation of tetracycline in 30 of the 32 procedures. In two patients, tetracycline was instilled after the effusion was removed by thoracentesis, and both procedures were failures. Tube thoracostomy drainage was maintained for an average of 3 days before

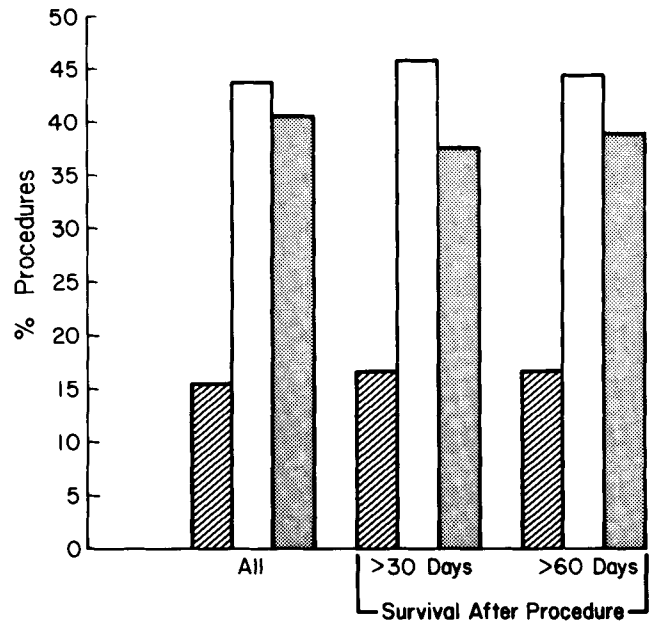


FIG. 1. Outcome of tetracycline pleurodesis. The proportion of procedures in each outcome category is shown for all procedures in the study group and those after which the patient survived for at least 30 or 60 days. The high percentage of failures and low percentage of complete responses was virtually identical in the three groups. ■: Complete response; □: partial response; ▨: failure.

tetracycline instillation, and 2.3 days afterwards. There were no differences among the outcome categories in the mean duration of tube drainage either before or after tetracycline was instilled. The dose of tetracycline appeared to be an important determinant of the outcome of the procedure (Fig. 3). Four of the five complete responses

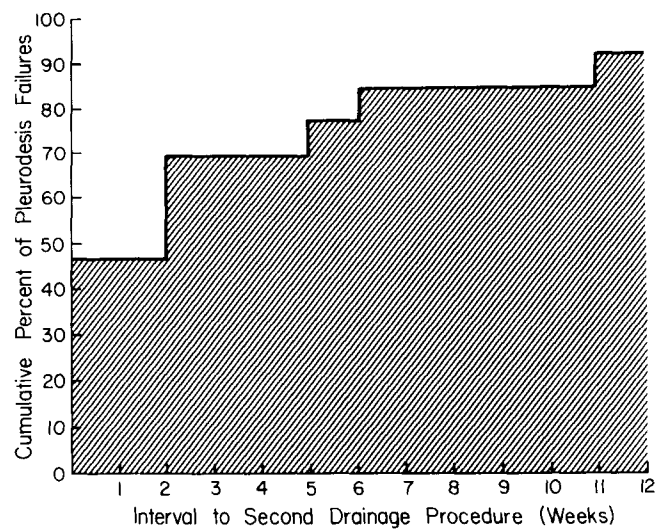


FIG. 2. Pleurodesis failures. The cumulative percentage of failed tetracycline pleurodesis is shown in relationship to the time elapsed to performance of a repeated drainage procedure; 70% of failed procedures were followed by another drainage procedure within 2 weeks.

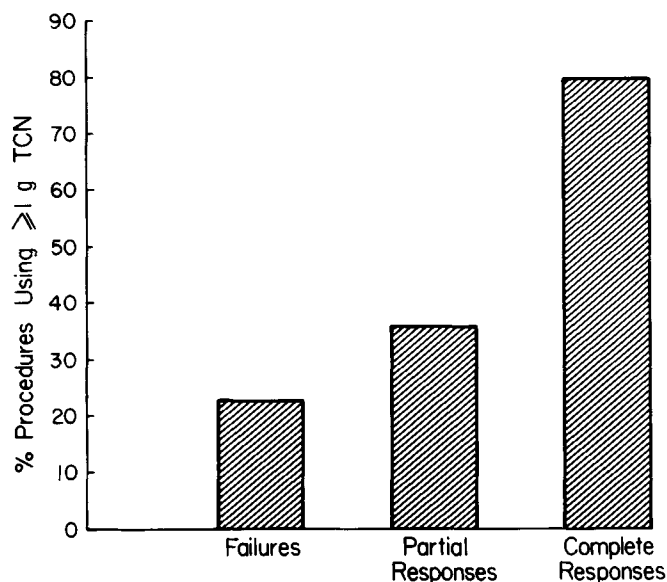


FIG. 3. Relationship between dose of tetracycline instilled and outcome of the procedure. A significantly greater proportion of procedures in the complete response group were performed with ≥ 1 g tetracycline, compared with failures ($P < 0.05$).

were given ≥ 1 g of tetracycline in a single dose, compared with only three of 13 in the failure group ($P < 0.05$). In two procedures, 500 mg doses were instilled twice over 72 hours, resulting in one partial response and one failure.

Complications

Complications of tetracycline pleurodesis for all patients are shown in Table 2; loculation of pleural fluid (34%), pain (31%), and fever (28%) were common. Sixty-six percent of the procedures were associated with at least one complication. The frequency of these complications was virtually identical among the outcome categories (data not shown).

Discussion

The clinical features of malignant pleural effusions in this series are consistent with those described in previous studies.^{3,4} Specifically, we note that carcinomas of the

breast and lung, adenocarcinoma of unknown primary, and lymphoma constitute the majority of the primary tumors. The overall prognosis was poor, with 29% and 58% cumulative mortality at 1 and 2 months after pleurodesis was first attempted.

We found only five of 32 procedures (15.6%) yielded complete responses, while 14 (43.8%) were partial responses, and 13 (40.6%) were failures. We defined two of the outcome categories to minimize subjective interpretations. Our complete response category satisfied the definition of the ideal outcome, a complete pleural symphysis with no reaccumulation of effusion. Similarly, reaccumulation of pleural fluid sufficient to warrant a repeated drainage procedure should be generally accepted to represent a failed pleurodesis. The rapid reaccumulation of effusion requiring drainage within 2 weeks in 70% of procedures is similar to the rates of recurrence after thoracentesis,¹¹ and argues against the contention that these pleurodesis attempts may at least have forestalled the recurrence of a symptomatic effusion.

The procedures most difficult to evaluate are those we designated as partial responses. Several observations indicate that factors other than adequate relief of symptoms may have mitigated against repeating a drainage procedure. First, in four of the five partial responses with available radiographs the reaccumulated effusion was only modestly smaller than before the pleurodesis. Second, the high short-term mortality rate suggests that some patients were terminal when the effusions returned and a second procedure was not deemed appropriate. Finally, the lack of symptoms before the pleurodesis attempt or the appearance of loculations afterwards may have been factors dissuading physicians from draining a reaccumulated effusion. Only a prospective study can reliably distinguish between these factors. Currently, we can only place the overall success rate of tetracycline pleurodesis between 15% and 59%, in contrast to the 70% to 100% described previously.⁵⁻⁹ This discrepancy does not result from differences in duration of follow-up after the procedure, as the outcomes of procedures followed for 30 or 60 days were identical to those of the entire study population (Fig. 1).

The technique used in these procedures was generally in keeping with standard recommendations.³ In particular, efforts were made to evacuate pleural fluid as completely as possible, as well as positioning the patient to distribute the tetracycline uniformly over the pleural surfaces. Drainage of the effusion was accomplished by tube thoracostomy in 30 of the 32 procedures. The duration of pleural drainage either before or after tetracycline instillation did not appear to affect the outcome of the procedure. Tetracycline was instilled in doses of 500 mg in 20 procedures, and doses of 1 g or more were used in 12. There was a direct and significant relationship ($P < 0.05$)

TABLE 2. Complications After Pleurodesis

Complication	Number of procedures	% of total procedures
Loculated pleural effusion	11	(34%)
Pain	10	(31%)
Fever ($>38^{\circ}\text{C}$)	9	(28%)
Persistent hydropneumothorax	2	(6%)
Two or more complications	9	(28%)
Total procedures associated with complications	21	(66%)

between the success of the procedure and the use of 1 g of tetracycline (Fig. 3). This observation agrees well with animal studies that have shown a better pleural symphysis can be obtained with higher doses (30 mg/kg) of tetracycline.^{12,13} Earlier clinical studies have generally used 500 mg doses, and have not sought to determine a relationship between dose and outcome.⁵⁻⁹

In summary, our retrospective study has demonstrated a low success rate for tetracycline pleurodesis that cannot be explained by duration of follow-up or improper technique. Several factors are thought to bear on the success of a pleurodesis, including performance status, incomplete apposition of the pleural surfaces (due to atelectasis, masses, or loculations), and the drainage rate and pH of pleural fluid.³ In many of the subjects in the current study, it is likely that some of these factors were not ideally suited to a successful pleurodesis. Nevertheless, clinicians may conclude that attempting chemical pleurodesis may be their best treatment alternative even when optimal conditions for success do not obtain. Therefore, the outcomes described in this study may be more representative than prospective studies of what can be expected in common clinical practice. Additional studies will be necessary to identify factors that will improve our ability to select patients to undergo tetracycline pleurodesis. Based on the current study, we conclude that a minimum of 1 g of

tetracycline should be used with adequate thoracostomy tube drainage to ensure the best possible results.

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