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Early effective drainage in the treatment of loculated tuberculous pleurisy

C-L. Chung*,#, C-H. Chen*, C-Y. Yeh*, J-R. Sheu¶ and S-C. Chang+,§

ABSTRACT: The role of early effective drainage in loculated tuberculous (TB) pleurisy treatment remains unclear.

Consecutive patients with TB pleurisy subjected to anti-TB treatment and pigtail drainage (n=64) were divided into three groups: 1) patients with free-flowing effusions irrigated with saline (free-flowing group; n=20); 2) patients with loculated effusions irrigated with streptokinase (streptokinase group; n=22); and 3) patients with loculated effusions irrigated with saline (saline group; n=22). Pleural irrigation was performed for 3 days consecutively and the effusion drained as completely as possible. Outcomes were assessed for 12 months by clinical symptoms, effusion removed, radiological scores for effusion amount, lung function and occurrence of residual pleural thickening.

The total effusion volumes removed were significantly greater in the free-flowing (2.36±1.62 L) and streptokinase groups (2.59±1.77 L) than in the saline group (1.28±1.21 L). Compared with the saline group, the free-flowing and streptokinase groups showed significant improvement in radiological scores and forced vital capacity at different time-points during follow-up, and a significantly lower occurrence of residual pleural thickening. All outcome variables were comparable between the streptokinase and free-flowing groups.

In summary, early effective drainage and complete anti-tuberculosis treatment may hasten clearance of pleural effusion, reduce residual pleural thickening occurrence and accelerate pulmonary function recovery in patients with symptomatic loculated tuberculous pleurisy.

KEYWORDS: Loculated pleural effusion, pigtail drainage, pleural effusion, pleural thickening, tuberculosis

Tuberculous (TB) pleurisy can cause clinical symptoms and pleural fibrosis with resultant residual pleural thickening (RPT) [1]. Therapeutic thoracentesis or initial complete drainage in addition to anti-TB drugs has been tried in order to rapidly relieve dyspnoea caused by effusions and decrease the occurrence of RPT. However, contradictory results have been reported without clear elucidation [2–5].

Pleural TB involvement may increase the vascular permeability of the pleura, leading to pleural fluid accumulation. This pleural fluid is enriched in proteins, inflammatory cells, and various pro-inflammatory and profibrotic cytokines [6]. Delayed diagnosis and/or treatment of TB pleurisy may cause disordered fibrin turnover in the pleural cavity with subsequent fibrin deposition and loculation of pleural fluid, and may impair uneventful resolution of pleural effusion [7, 8].

Pleural effusion loculation is not uncommon on initial presentation of TB pleurisy, and may be of value in predicting the occurrence of RPT after completion of anti-TB medications [8, 9]. Recent studies have shown that patients with loculated TB pleurisy treated with intrapleural urokinase developed less RPT than those with no drainage or those treated with simple drainage [10, 11]. These results imply that intrapleural administration of fibrinolytic agents with effective drainage of the pleural effusion may be promising in the treatment of loculated TB pleurisy. To the best of the present authors' knowledge, there are no controlled studies addressing the clinical significance of early effective drainage in patients with loculated and free-flowing TB pleurisy.

The present hypothesis is that, in addition to anti-TB medications, early effective evacuation of inflammatory exudates with or without fibrinolytic agents may hasten resolution of pleural effusion, reduce the occurrence of RPT and accelerate recovery of pulmonary function in patients with TB pleurisy. The aim of the present randomised double-blinded placebo-controlled study was to investigate the usefulness of early

AFFILIATIONS
*Dept of Chest Medicine, Taipei Medical University Hospital,
#Graduate Institute of Clinical Medicine, and
¶Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University,
+Chest Department, Taipei Veterans General Hospital, and
§Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan.

CORRESPONDENCE
S-C. Chang
Chest Department
Taipei Veterans General Hospital
No. 201
Section 2
Shih-Pai Road
Shih-Pai
Taipei 112
Taiwan
Fax: 886 228752380
E-mail: scchang@vghtpe.gov.tw

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This study is a registered clinical trial on ClinicalTrials.gov (identifier No. NCT00524147).

STATEMENT OF INTEREST
None declared.

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effective drainage of pleural effusion in the treatment of TB pleurisy. The role of intrapleural streptokinase in the treatment of loculated TB pleurisy was also explored.

MATERIALS AND METHODS

Study design

The present study was a single-centre, double-blind, randomised placebo-controlled trial to assess the effect of early effective drainage in the treatment of loculated TB pleurisy. Ethics approval was obtained from the Institutional Review Board of Taipei Medical University (Taipei, Taiwan), the study was registered on ClinicalTrials.gov (NCT00524147) [12] and all patients gave written informed consent.

Patient selection

Patients with pleural effusions of unknown cause admitted to the Taipei Medical University Hospital between October 2003 and December 2005 were included if TB pleurisy was diagnosed by the demonstration of granulomatous pleuritis in closed pleural biopsy specimens in the presence or absence of acid-fast bacilli. Exclusion criteria were as follows: a history of invasive procedures directed into the pleural cavity; recent severe trauma, haemorrhage or stroke; a bleeding disorder or anticoagulant therapy; use of streptokinase in the previous 2 yrs; and lack of dyspnoea caused by the effusions.

Study protocol

All patients were subjected to routine chest radiography (CXR; frontal, lateral and lateral decubitus views), with the lateral decubitus view with the lesioned side down, real-time chest ultrasonography and/or thoracic computed tomography in order to determine whether the pleural effusion was free-flowing or loculated. Standard anti-TB medications in addition to pigtail drainage were administered once TB pleurisy was diagnosed. Intrapleural injection therapy was started on the following day, and was performed once daily for 3 days consecutively. Patients with free-flowing effusions (free-flowing group) underwent intrapleural injection with 50 mL normal saline. Patients with loculated effusions were randomly assigned (using a computer-generated random number) to undergo intrapleural injection with solutions containing 50 mL normal saline with (streptokinase group) or without (saline group) 250,000 IU dissolved streptokinase (Aventis, Marburg, Germany). After injection, the pigtail tube was clamped for 2 h and subsequently opened for free drainage. CXR was performed after the third day of treatment. Complete drainage was defined as no or minimal pleural effusion on CXR. The pigtail tube was removed when net drainage was $<$50 mL in the previous 24 h.

Outcome measures

The effectiveness of treatment was assessed primarily by: 1) CXR; 2) daily monitoring of the volume of fluid drained from the pigtail tube; and 3) the time required for clinical resolution of fever and dyspnoea.

Secondary end-points included total amounts of fluid drained, and the duration of chest drainage and hospitalisation.

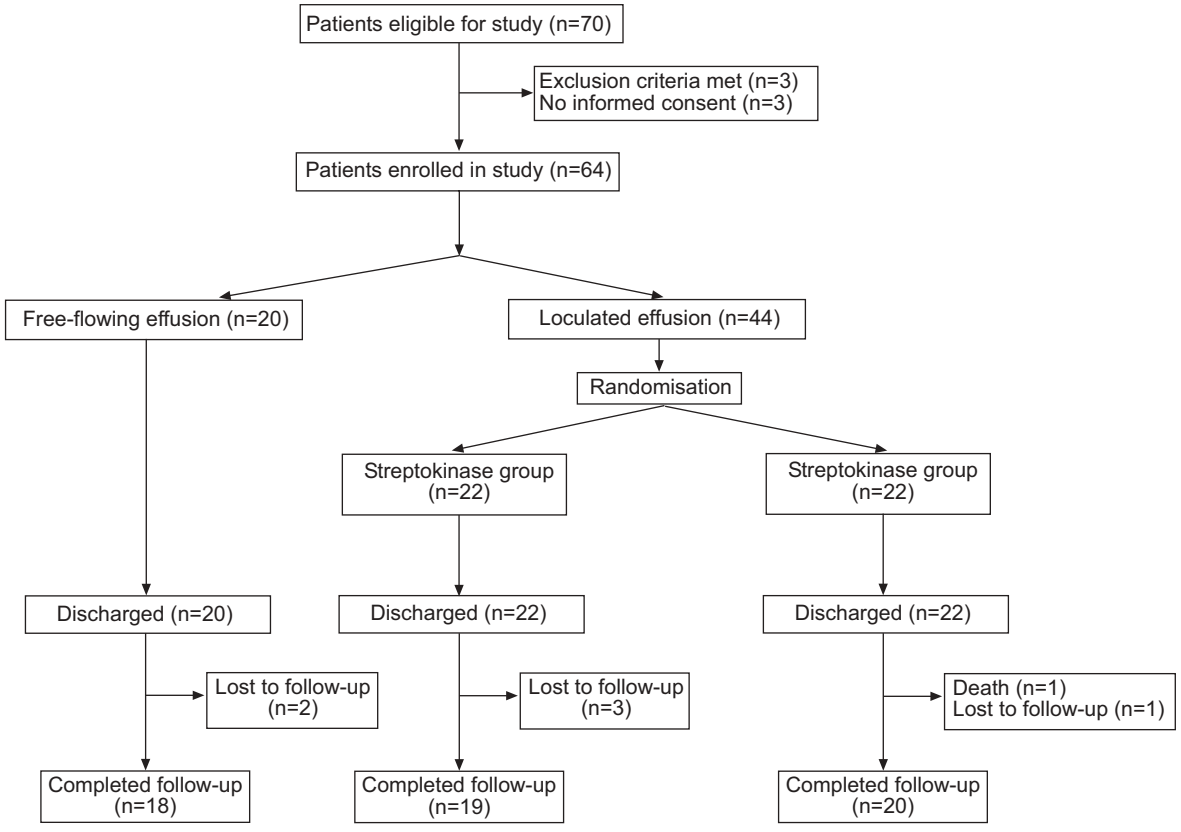

FIGURE 1. Enrolment of patients and completion of the study.

CXR and pulmonary function testing with spirometry were performed at discharge and after 2, 4, 6 and 12 months. Radiographs were read and scored by a senior radiologist blinded to any clinical information. For CXR scoring, erect posteroanterior CXR films were used to determine: 1) the greatest linear width of the pleural opacity; and 2) the estimated overall percentage of pleural shadowing in the hemithorax. RPT was measured and defined as a lateral pleural thickening of $\geqslant$10 mm shown on CXR at the end of 12 month's follow-up.

Statistical analysis

Data are expressed as mean±SD or n (%), as appropriate, and were analysed using one-way ANOVA followed by Scheffé's test for multiple comparisons among the means of the three groups. Categorical variables between groups were examined using the Chi-squared method and/or Fisher's exact test, as appropriate. A p-value <0.05 was considered significant.

RESULTS

Patient characteristics

During the study period, there were 70 patients with TB pleurisy. Six patients were excluded on the basis of the following reasons: recent stroke in one, recent gastrointestinal bleeding in two, and no informed consent in three. Finally, 64 patients who met the inclusion criteria were enrolled into the present study (fig. 1). After evaluation of pleural fluid status, 20 patients with free-flowing effusions were pooled as the free-flowing group. The patients with loculated effusions were randomly divided into the streptokinase group (n=22) and saline group (n=22). The clinical data and pleural fluid characteristics of the patients in the three groups are shown in table 1. No differences were found between the three groups in terms of age, sex, pre-existing risk factors, duration of illness before treatment, characteristics of acute illness, rate of associated pulmonary TB, initial amount of effusion, area of effusion shadowing on CXR and pleural effusion variables.

Primary outcome

The clinical outcomes of intrapleural injection are summarised in table 2. Following the 3-day intrapleural instillation treatment, the number of patients showing resolution of pleural effusion on CXR and complete drainage of the pleural effusion was significantly greater in the free-flowing group than in the saline group. Compared with the saline group, the streptokinase group showed significantly greater improvement in CXR scores after 3 days of streptokinase irrigation, although there was no significant difference in the rate of total resolution of effusions between the two groups. Fever and dyspnoea improved in all patients. The time required to relieve dyspnoea was significantly shorter in the free-flowing and streptokinase groups than in the saline group, but was comparable between the streptokinase and free-flowing groups. There was no significant difference in the time for defervescence between the three groups.

Secondary outcome

The amounts of effusion removed were significantly greater in the free-flowing group than in the saline group for the initial drainage, after the first injection and in total (table 2). The initial amount of fluid drained was comparable between the streptokinase and saline groups. However, the patients treated with intrapleural streptokinase injection had significantly greater amounts of pleural fluid removed after the first injection, during the treatment period and in total. Furthermore, there was no significant difference in the amounts of pleural effusion removed during irrigations and in total between the streptokinase and free-flowing groups. Since significantly greater amounts of effusion could be drained out in the free-flowing and streptokinase groups, the

TABLE 1 Clinical data and pleural fluid characteristics

	Group			p-value
	Free-flowing	Streptokinase	Saline	
Subjects n	20	22	22	
Mean age yrs	65±20	65±19	63±24	0.914
Males n	15 (75)	17 (77)	19 (86)	0.632
Patients with risk factors#	6 (30)	4 (18)	8 (36)	0.409
Symptom onset to treatment days	12±6	13±8	14±14	0.849
Dyspnoea grade¶	2.2±0.6	2.1±0.7	2.1±0.7	0.946
Fever >38.5°C	5 (25)	5 (23)	6 (27)	0.990
Pleuritis combined with PTB	6 (30)	7 (32)	7 (32)	0.990
Area of effusion shadowing+ %	59.7±22.3	54.2±27.3	54.9±19.5	0.719
Pleural effusion				
pH	7.36±0.06	7.33±0.13	7.33±0.05	0.321
Glucose mg·dL^{-1}	108±30	106±40	109±40	0.958
LDH IU·dL^{-1}	429±247	456±295	581±862	0.633
Leukocyte count cells·μL^{-1}	1748±1676	1937±1962	1710±1220	0.888

Data are presented as n (%) or mean±SD, unless otherwise indicated. PTB: pulmonary tuberculosis; LDH: lactate dehydrogenase. #: including alcoholism, diabetes mellitus, liver cirrhosis and subtotal gastrectomy; ¶: I–IV, according to the New York Heart Association classification; +: on posteroanterior chest radiography.

TABLE 2 Clinical outcome after intrapleural injection treatment

	Group			p-value
	Free-flowing	Streptokinase	Saline	
Subjects n	20	22	22	
Clinical outcome				
CXR improvement at 3 days %	81.8±21.7	75.2±16.0	60.8±23.1*,#	0.011
Complete drainage at 3 days n (%)	12 (60)	2 (9)**	0 (0)**	<0.001
Time to dyspnoea relief days	3±2	3±2	5±3**,##	0.018
Time to defervescence days	3±2	2±2	3±2	0.219
Pleural drainage L				
Initial	1.26±0.69	0.77±0.49*	0.72±0.56*	0.009
After first injection (24 h)	0.58±0.39	0.58±0.45	0.28±0.36*,#	0.024
After second injection (24 h)	0.41±0.62	0.27±0.29	0.14±0.25	0.114
After third injection (24 h)	0.15±0.36	0.20±0.29	0.10±0.19	0.527
Total after three injections (72 h)	1.13±1.18	1.05±0.86	0.57±0.67	0.104
Total	2.36±1.62	2.59±1.77	1.28±1.21*,##	0.016
Duration of drainage days	5±1	5±2	4±1*,#	0.012
Time from treatment to discharge days	7±3	7±2	10±6*,#	0.022

Data are presented as mean±SD, unless otherwise indicated. CXR: chest radiography. *: $p<0.05$ and **: $p<0.01$ *versus* free-flowing group; #: $p<0.05$ and ##: $p<0.01$ *versus* streptokinase group.

length of pigtail tube insertion was significantly longer than for saline group. However, the mean duration of hospital stay was significantly longer in the saline group than in the free-flowing and streptokinase groups.

Follow-up period

All patients were successfully treated with anti-TB medications and intrapleural instillation of normal saline or streptokinase, and were discharged uneventfully. During the first 4 months, one patient died due to liver cirrhosis and six patients were lost to follow-up (fig. 1). The remaining 57 patients who finished the 6-month anti-TB medication course were followed-up continuously for a further 6 months, and all of these patients improved clinically over time, showing no recurrence of the disease. The improvement in pleural effusions, as evidenced by CXR and forced vital capacity (FVC), was significantly greater in the free-flowing group than in the saline group, regardless of time-point (table 3; fig. 2). Compared with the saline group, the streptokinase group showed significantly greater improvement in CXR scores and FVCs at different time-points during follow-up. In addition, CXR scores and FVCs were comparable between

TABLE 3 Long-term outcome after intrapleural injection treatment

	Group			p-value
	Free-flowing	Streptokinase	Saline	
Subjects n	20	22	22	
Area of effusion shadowing¶ %				
On discharge	8.5±10.3	12.7±9.8	19.9±10.0**,#	0.002
At 12 months	0.3±0.6	0.6±1.9	4.2±6.8*,#	0.009
Lateral effusion thickness¶ mm				
On discharge	48.0±44.8	72.7±34.1	93.2±28.6***,#	<0.001
At 12 months	3.6±7.2	4.7±11.3	19.2±15.9***,##	<0.001
RPT of >10 mm n (%)	2 (10)	2 (9)	10 (45)*,#	0.003
FVC % pred				
On discharge	75.8±5.1	73.7±4.9	70.0±5.0**,#	0.002
At 12 months	79.8±0.3	79.7±1.0	78.0±3.3*,#	0.012

Data are presented as mean±SD, unless otherwise indicated. RPT: residual pleural thickening; FVC: forced vital capacity; % pred: % predicted. ¶: on posteroanterior chest radiography. *: $p<0.05$, **: $p<0.01$ and ***: $p<0.001$ *versus* free-flowing group; #: $p<0.05$ and ##: $p<0.01$ *versus* streptokinase group.

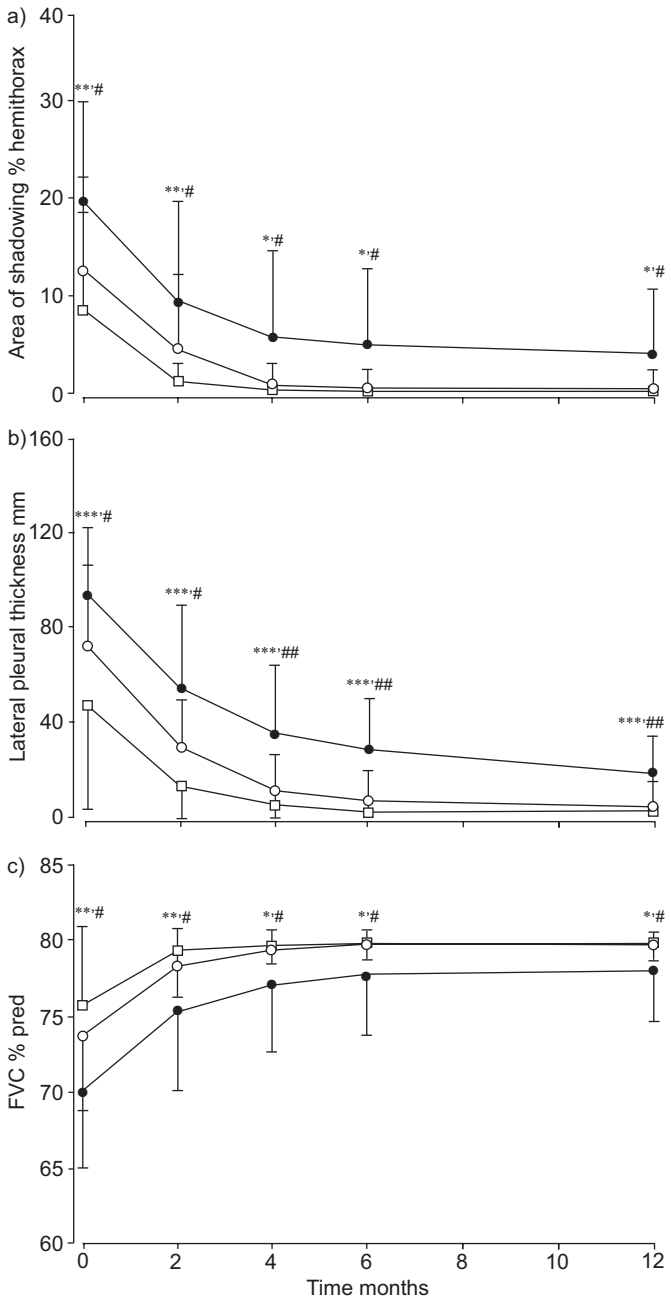

FIGURE 2. a, b) Chest radiography (CXR) scores; and c) forced vital capacity (FVC) in the free-flowing (□), streptokinase (○) and saline (●) groups during follow-up. Data are presented as mean±SEM. CXR scores and FVC gradually improved in all groups, and significant differences were noted between the free-flowing and saline groups and between the streptokinase and saline groups at all time-points. 0 months: discharge; % pred: % predicted. *: $p<0.05$, **: $p<0.01$ and ***: $p<0.001$ for saline *versus* free-flowing group; #: $p<0.05$ and ##: $p<0.01$ for saline *versus* streptokinase group.

the streptokinase and free-flowing groups. RPT developed less frequently in the free-flowing and streptokinase groups than in the saline group, and there was no significant difference in the occurrence of RPT between the streptokinase and free-flowing groups 6 months after completion of anti-TB treatment (table 3).

DISCUSSION

The present results demonstrate that initial effective pleural drainage may hasten resolution of pleural effusion, reduce the occurrence of RPT and accelerate recovery of pulmonary function in patients with symptomatic loculated TB pleurisy. Compared to patients with loculated effusions treated with simple drainage, those with free-flowing effusions treated with simple drainage and those with loculated effusions treated with pigtail drainage and streptokinase irrigation exhibited better short- and long-term outcomes, as evidenced by greater pleural fluid removal, rapid resolution of pleural effusions, less occurrence of RPT and higher FVCs during the 12-months follow-up. To the best of the present authors' knowledge, this is the first randomised study to show that an as complete as possible early evacuation of inflammatory exudates may be of clinical benefit in patients with loculated and/or free-flowing TB pleurisy.

Early complete drainage of pleural fluid had been advocated for the treatment of TB pleurisy [2, 3]. WYSER *et al.* [2] reported that 70 patients with TB pleurisy who underwent thoracoscopy and insertion of an indwelling intercostal drain experienced significant symptomatic improvement and did not show pleural fluid reaccumulation after the initial complete drainage. It is not surprising that thoracoscopy is useful for the lysis of pleural adhesion bands and facilitates the drainage of loculated effusions. However, thoracoscopy is not universally available and its routine use is out of reach for the majority of healthcare systems worldwide. Moreover, the previous study [2] lacked a control group to document the usefulness of early complete drainage in the treatment of TB pleurisy.

In 2003, a randomised study [5] reported that pigtail drainage in addition to anti-TB drugs improved dyspnoea but did not decrease the incidence of RPT and other clinical symptoms. However, the study [5] reported neither the number of patients presenting with loculated effusions nor the effectiveness of pigtail drainage of the pleural fluid. Without the use of a fibrinolytic agent, pigtail drainage alone may be insufficient to clear loculated effusions [13, 14], which may lessen the effect of early complete drainage in TB pleurisy, in which loculation of pleural effusions is not uncommon [8]. Therefore, studies comparing the usefulness of pigtail drainage in loculated and free-flowing TB pleurisy and on the role of intrapleural fibrinolytic agent in loculated TB pleurisy are mandatory. In the present study, 44 (69%) out of 64 consecutive patients with TB pleurisy presented with loculated effusions. Compared with the saline group, simple drainage was more effective for the evacuation of pleural effusion in the free-flowing group, and intrapleural streptokinase treatment significantly increased drainage of loculated pleural effusions in the streptokinase group (table 2). This more efficient drainage improved dyspnoea more rapidly, but did not shorten the duration of fever. These findings are in line with previous studies [5, 10, 11], and strongly suggest that anti-TB medication is the mainstay of treatment for the resolution of pleural inflammation in TB pleurisy, whereas early and effective pleural drainage, with or without streptokinase instillation, improves respiratory function but does not affect the intensity of the pleural inflammation.

Most (57 out of 64; 89%) of the patients in the present study completed the 12-month follow-up. All of the patients

improved clinically over time, and recurrence of the disease did not occur. CXR scores and FVC gradually improved in all groups, and significant differences were observed between the free-flowing and saline groups and between the streptokinase and saline groups at all time-points (table 3; fig. 2). The present results demonstrate that more effective drainage of pleural effusions translates into more rapid resolution of pleural opacity and quicker recovery of pulmonary function in patients with TB pleurisy. To the best of the present authors' knowledge, this is the first prospective randomised controlled study to demonstrate long-term benefits of early effective pigtail drainage in the treatment of loculated and/or free-flowing TB pleurisy.

RPT of >10 mm may cause significant functional disturbance [15]. Fluid loculation at initial presentation may be of value in predicting the development or occurrence of RPT in TB pleurisy following completion of anti-TB medication [8, 9]. The influence of therapeutic thoracentesis on the development of RPT has not been verified by previous studies [2–5]. However, two recent studies indicated that RPT occurred less frequently in patients with loculated TB pleurisy treated with intrapleural urokinase than in those with no drainage or those treated with simple drainage [10, 11]. In the present study, 10 (45%) out of 22 patients in the saline group developed RPT. In contrast, only two patients each from the free-flowing and streptokinase groups showed RPT at the end of follow-up. The present results confirm that loculated effusion at initial presentation is a significant predictor for RPT in TB pleurisy, and that pigtail drainage with intrapleural streptokinase irrigation may decrease the occurrence of RPT in such patients. These results can be explained by the retention of inflammatory exudate in the pleural space in TB pleurisy possibly perpetuating pleural inflammation and causing fibrin formation and deposition in the pleural cavity with subsequent development of pleural fibrosis and RPT. Accordingly, early and effective evacuation of pleural fluid may decrease the occurrence of RPT in loculated and/or free-flowing TB pleurisy. However, although the occurrence of RPT was significantly lower in the streptokinase group than in the saline group, the difference in mean FVC at 12 months between the two groups (79.7 *versus* 78.0% of the predicted value; $p<0.05$) was minimal (table 3). This finding is in line with a previous report [15], and may suggest that the functional impairment caused by RPT is usually mild. More precise functional assessment and image measurement in RPT are required in order to investigate the clinical impact of RPT in patients with TB pleurisy.

The limitation of the present study was the lack of inclusion of patients with free-flowing TB pleurisy treated with anti-TB drugs alone. Accordingly, the role of early complete drainage in the treatment of free-flowing TB pleurisy remains unknown. Nonetheless, 20 patients with free-flowing TB pleurisy treated with anti-TB drugs alone at Taipei Medical University Hospital were retrospectively reviewed as a historic control (free-flowing controls) for the free-flowing group (data not shown). The results showed that the occurrence of RPT was comparable between the two groups (five out of 20 *versus* two out of 20; $p=0.41$), despite the free-flowing group showing significantly faster resolution of pleural effusion during follow-up. It is suggested that early effective drainage in the treatment of free-flowing TB pleurisy may not be as beneficial as in the treatment of loculated TB pleural effusions. Accordingly, distinguishing loculated from free-flowing effusions in the treatment of TB pleurisy is of the utmost importance in determining whether or not early pigtail drainage with fibrinolytic agents is required. Further studies are required to verify these issues.

TB pleurisy can occur as a primary infection, especially in young adults and adolescents, and has been considered to be a disease of younger patients with a mean age of <35 yrs [16]. However, with the reduced prevalence of TB in developed countries, TB pleurisy is now commonly a result of reactivation of previous infections, and patients with pleurisy due to reactivation TB are significantly older than those with pleurisy as a sequel of primary TB infection [17]. Moreover, EPSTEIN *et al.* [18] demonstrated a rise in the median age at presentation (56 yrs) of patients with TB pleural effusions, with 19% of patients having reactivation disease. In addition, the studies on TB pleurisy in Taiwan revealed that the mean or median age of the patients studied was >55 yrs [5, 19]. Taken together, the relatively older age (mean 63–65 yrs) of patients in the present study is in line with other reports [5, 18–20], and may suggest that a higher prevalence of TB pleurisy is due to reactivation of previous disease in Taiwan, a region of endemic TB infection.

In conclusion, the results of the present study support pigtail drainage with streptokinase irrigation being safe and effective for the evacuation of loculated tuberculous effusions. Effective pigtail drainage adjuvant to complete anti-tuberculosis treatments may hasten resolution of pleural effusion, reduce the incidence of residual pleural thickening and accelerate recovery of pulmonary function in patients with symptomatic loculated tuberculous pleurisy.

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