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Early Effective Drainage in the Treatment of Loculated Tuberculous Pleurisy

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ABSTRACT

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

Sixty-four consecutive patients with TB pleurisy subjected to anti-TB treatment and pigtail drainage were divided into three groups: (1) 20 free-flowing effusions irrigated with saline (free-flowing group); (2) 22 loculated effusions irrigated with streptokinase (streptokinase group); and (3) 22 loculated effusions irrigated with saline (saline group). Pleural irrigation was performed for three consecutive days and effusion was 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 (RPT).

The total effusions removed were significantly greater in free-flowing (2.36 ± 1.62 L) and streptokinase groups (2.59 ± 1.77 L) than in saline group (1.28 ± 1.21 L). Compared to saline group, free-flowing and streptokinase groups had significant improvement in radiological scores and forced vital capacity at different time points during follow-up and had significantly lower occurrence of RPT. All outcome variables were comparable between streptokinase and free-flowing groups.

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

Key words: loculated pleural effusion, pigtail drainage; pleural effusion; pleural thickening; tuberculosis

Introduction

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 have been tried to rapidly relieve dyspnea caused by effusions and to decrease the occurrence of RPT. However, contradictory results are reported without clear elucidation [2-5].

Pleural involvement by TB may increase vascular permeability of the pleura, leading to pleural fluid accumulation. This pleural fluid is enriched in proteins, inflammatory cells, and various proinflammatory 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].

Loculation of pleural effusion is not uncommon at the 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 the patients with loculated TB pleurisy treated with intrapleural urokinase developed less RPT than did those with no drainage or those treated with simple drainage [10,11]. The results implicate that

intrapleural administration of fibrinolytic agents with effective drainage of pleural effusion may be promising in the treatment of loculated TB pleurisy. To the best of our knowledge, there are no controlled studies addressed on the clinical significance of early effective drainage in patients with loculated and free-flowing TB pleurisy.

Our 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. In this randomized, double-blinded, placebo-controlled study, we intended to investigate the usefulness of early effective drainage of pleural effusion in the treatment of TB pleurisy and 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-center, double-blinded, randomized, 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 [ClinicalTrials.gov]) and all patients gave written informed consent.

Patient selection

Patients with pleural effusions of unknown causes admitted to Taipei Medical University Hospital between October 2003 and December 2005 were included if TB pleurisy was diagnosed by the demonstration of granulomatous pleuritis on closed pleura biopsy specimens with or without the presence of acid-fast bacilli. Exclusion criteria were as follows: history of invasive procedures directed into the pleural cavity; recent severe trauma, hemorrhage, or stroke; bleeding disorder or anticoagulant therapy; use of streptokinase in the previous 2 years; and lack of dyspnea caused by effusions.

Study Protocol

All patients were subjected to routine chest radiography (CXR, frontal and lateral views), lateral decubitus view with the lesioned side down, real-time chest ultrasonography (US) and/or thoracic computed tomography (CT) to determine the free-flowing or loculated pleural effusion. Standard anti-TB medications in addition to pigtail drainage were administered once TB pleurisy was diagnosed. Intrapleural injection therapy started on the following day, and was done once daily for three

continuous days. Patients with free-flowing effusion (free-flowing group) underwent intrapleural injection with 50 ml normal saline. Patients with loculated effusions were randomly assigned to receive intrapleural injection with solutions containing 50 ml normal saline with (streptokinase group) or without (saline group) 250,000 IU of dissolved streptokinase (Aventis, Marburg, Germany) by a computer-generated random number. After injection, the pigtail tube was clamped for 2 hours and then 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 the net drainage was less than 50 ml during the previous 24 hours.

Outcome measures

The effectiveness of treatment was primarily assessed by: (*1*) CXR; *(2)* daily monitoring of the volume of fluid drained from the pigtail tube; and (*3*) clinically, the time needed for resolution of fever and dyspnea.

Secondary end points included total amounts of fluid drained, the length of chest drainage and hospitalization. CXR and pulmonary function testing with spirometry were performed at discharge and at 2, 4, 6, and 12 months, respectively. 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 largest

linear width of 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 ≥ 10 mm shown on CXR at the end of 12-month follow-up.

Statistical analysis

Data were expressed as mean ± SD or frequency (%), where appropriate and were analyzed with one-way analysis of the variance (ANOVA) followed by Scheffẻ test for multiple comparisons among means of the three groups. Categorical variables between groups were examined using χ^2 method and/or Fisher's exact test, when appropriate. A p value < 0.05 was considered to be statistically significant. Analysis was performed using a statistical software package (Statistica for Window, version 5.5, StatSoft Inc, Tulsa, OK, USA).

Results

Patient characteristics

During the study period, there were 70 patients with TB pleurisy. Six patients were excluded based on the reasons as follows: recent stroke in one, recent gastrointestinal bleeding in two, and no informed consent in three cases, respectively. Finally, 64 patients who met the inclusion criteria were enrolled in this study (Figure 1). After evaluation of pleural fluid status, 20 patients with free-flowing effusions were pooled as

free-flowing group. The patients with loculated effusions were randomly divided into streptokinase group (n = 22) and saline group (n = 22). Clinical data and pleural fluid characteristics of the patients divided into three groups are shown in Table 1. No statistical differences among the three groups were found in terms of age, gender, preexisting risk factors, duration of illness before treatment, characteristics of acute illness, the 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 injections are summarized in Table 2. Following the 3-day treatment of intrapleural instillation, resolution of pleural effusion as shown on CXR and the number of patients with complete drainage of pleural effusion were significantly greater in free-flowing group than in saline group. Compared to saline group, streptokinase group had significantly greater improvement in CXR scores after three days of streptokinase irrigation, though there was no significant difference in the rate of total resolution of effusions between the two groups. Fever and dyspnea improved in all patients. The time needed to relieve dyspnea was significantly shorter in free-flowing and streptokinase groups than in saline group, but was

comparable between streptokinase and free-flowing groups. There was no significant difference in the time for defervescence among the three groups.

Secondary Outcome

The amounts of effusion removed were significantly greater in free-flowing group than in saline group for the initial drainage, after first injection, and in total (Table 2). Initial amount of fluid drained was comparable between streptokinase and saline groups. However, the patients treated with intrapleural injection of streptokinase had significantly greater amounts of pleural fluid removed after first injection, during treatment period and in total. Furthermore, there was no significant difference in the amounts of pleural effusion removed during irrigations and in total between streptokinase and free-flowing groups. Since significantly greater amounts of effusions could be drained out in free-flowing and streptokinase groups, the length of pigtail tube insertion was significantly longer as compared with saline group. However, the mean duration of hospital stay was significantly longer in saline group than in 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 of liver cirrhosis and six patients were lost to follow up (Figure 1). The remaining 57 patients who finished the 6-month anti-TB medications were followed up continuously for another 6 months, and all these patients improved clinically over time, showing no recurrence of the disease. The improvement of pleural effusions as evidenced by CXR and forced vital capacity (FVC) were significantly greater in free-flowing group than in saline group, irrespective of different time points (Table 3 and Figure 2A-C). Compared to saline group, streptokinase group had significantly greater improvement in CXR scores and FVC at different time points during follow up. In addition, CXR scores and the values of FVC were comparable between streptokinase and free-flowing groups. Six months after completion of anti-TB treatment, RPT developed less frequently in free-flowing and streptokinase groups than in saline group, and there was no significant difference in the occurrence of RPT between streptokinase and free-flowing groups (Table 3).

Discussion

Our 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 had better short-term and long-term outcomes as evidenced by more pleural fluid removed, rapid resolution of pleural effusions, less occurrence of RPT and greater FVC during 12-month follow up. To our knowledge, this is the first randomized study to show that early evacuation of inflammatory exudates as complete as possible 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 indwelling intercostal drain experienced significant symptomatic improvement and did not have pleural fluid reaccumulation after initial complete drainage. It is not surprising that thoracoscopy is useful for lysis of pleural adhesion bands and facilitating the drainage of loculated effusions. However, thoracoscopy is not universally available and its routine use is out of reach for the majority of health care 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.

Recently, a randomized study [5] reported that pigtail drainage in addition to anti-TB drugs improved dyspnea 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 fibrinolytic agent, pigtail drainage alone may not be sufficient enough to clear loculated effusions [12,13], which may lessen the effect of early complete drainage in TB pleurisy in which loculation of pleural effusion is not uncommon [8]. Therefore, the studies on the usefulness of pigtail drainage between loculated and free-flowing TB pleurisy and the role of intrapleural fibrinolytic agent in loculated TB pleurisy are mandatory. In the present study, 44 of 64 (69%) consecutive patients with TB pleurisy presented with loculated effusions. Compared with saline group, simple drainage was more effective to evacuate pleural effusion in free-flowing group, and intrapleural streptokinase treatment significantly increased drainage of loculated pleural effusions in streptokinase group (Table 2). The more efficient drainage did improve dyspnea 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 to resolve pleural inflammation in TB pleurisy, whereas early and effective pleural drainage, either with or without streptokinase instillation, did improve the respiratory function but did not affect the intensity of pleural inflammation.

Most patients in the present study (57 of 64 patients, 89%) completed the follow-up for 12 months. All the patients improved clinically over time and recurrence of the disease did not occur. CXR scores and FVC gradually improved in all groups and statistically significant differences were observed between free-flowing and saline groups and between streptokinase and saline groups at any time points (Table 3 and Figure 2A-C). Our results demonstrated that more effective drainage of pleural effusions did translate into more rapid resolution of pleural opacity and quicker recovery of pulmonary function in patients with TB pleurisy. To the best our knowledge, this is the first prospective randomized controlled study to demonstrate long-term benefits of early effective pigtail drainage in the treatment of loculated and/or free-flowing TB pleurisy.

RPT more than 10 mm may cause significant functional disturbance [14]. 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 yet 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 in those treated with simple drainage [10,11]. In the present study, 10 of 22 patients (45%) in saline group developed RPT. In

contrast, only 2 patients each in free-flowing and streptokinase groups had RPT at the end of follow up. Our results confirm that loculated effusion at initial presentation is a significant predictor for RPT in TB pleurisy and pigtail drainage with intrapleural streptokinase irrigation may decrease the occurrence of RPT in such patients. These can be explained by that retention of inflammatory exudate in the pleural space in TB pleurisy may perpetuate pleural inflammation and cause fibrin formation and deposition in 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 streptokinase group than in saline group, the difference in mean FVC at 12 months between two groups (79.7 vs. 78.0 % of predicted, $p < 0.05$) was minimal (Table 3). This finding is in line with the previous report [14] and may suggest that the functional impairment caused by RPT is usually mild. More precise functional assessment and image measurement of RPT are needed to investigate the clinical impact of RPT in patients with TB pleurisy.

The limitation of the present study was 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, we retrospectively reviewed 20 patients with free-flowing TB pleurisy

treated with anti-TB drugs alone at our institute as a historic control (free-flowing controls) for free-flowing group (unpublished data). The results showed that occurrence of RPT was comparable between the two groups (5/20 vs. 2/20, p = 0.41), despite that free-flowing group had 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 that in the treatment of loculated TB pleural effusions. Accordingly, distinguishing loculated from free-flowing effusion in the treatment of TB pleurisy is of utmost importance in determining whether early pigtail drainage with fibrinolytic agents is required or not. Further studies are needed 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 less than 35 years [15]. 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 [16]. Moreover, Epstein et al demonstrated a rise in the median age (56 years) at presentation of TB pleural effusions with 19% of patients having reactivation disease [17]. In addition, the studies on TB pleurisy in Taiwan revealed that the mean or median age of the patients studied

were greater than 55 years [5,18]. Taken together, the relatively older age (mean age of 63 to 65 years) of patients in this study is in line with other reports [5,17-19] and may suggest that a higher prevalence of TB pleurisy is due to reactivation of previous disease in Taiwan, an endemic region of TB infection.

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

References

1. Light RW. Tuberculous pleural effusions. In: Light RW, ed. Pleural diseases, 4th Ed. Lippincott Williams & Wilkins, Philadelphia, 2001; pp. 182-195.
2. Wyser C, Walzl G, Smedema JP, Swart F, van Schalkwyk EM, van de Wal BW. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind placebo-controlled randomized study. *Chest* 1996; 110: 333-338.
3. Large SE, Levick RK. Aspiration in the treatment of primary tuberculous pleural effusion. *BMJ* 1958; 30: 1512–1514.
4. Morrone N, Lombardi MC, Machado O. Prevention of pleural thickening through pleural aspiration in patients with tuberculous effusion. *J Pneumo (Sao Paulo)* 1989; 15: 180-184.
5. Lai YF, Chao TY, Wang YH, Lin AS. Pigtail drainage in the treatment of tuberculous pleural effusions: a randomised study. *Thorax* 2003; 58: 149-152.

6. Antony VB. Immunological mechanisms in pleural disease. *Eur Respir J* 2003; 21: 539-544.
7. Idell S, Zwieb C, Kumar A, Koenig KB, Johnson AR. Pathways of fibrin turnover of human pleural mesothelial cells *in vitro*. *Am J Respir Cell Mol Biol* 1992; 7: 414-426.
8. Chung CL, Chen CH, Sheu JR, Chen YC, Chang SC. Proinflammatory cytokines, transforming growth factor-β1, and fibrinolytic enzymes in loculated and free-flowing pleural exudates. *Chest* 2005; 128: 690-697.
9. Han DH, Song JW, Chung HS, Lee JH. Resolution of residual pleural disease according to time course in tuberculous pleurisy during and after the termination of antituberculosis medication. *Chest* 2005; 128: 3240-3245.
10. Kwak SM, Park CS, Cho JH, Ryu JS, Kim SK, Chang J, Kim SK. The effects of urokinase instillation therapy via percutaneous transthoracic catheter in loculated tuberculous pleural effusion: A randomized prospective study. *Yonsei Med J* 2004; 45: 822–828.
11. Cases Viedma E, Lorenzo Dus MJ, González-Molina A, Sanchis Aldás JL. A study of loculated tuberculous pleural effusions treated with intrapleural urokinase. *Resp Med* 2006; 100: 2037-2042.

12. Pollak JS, Passik CS. Intrapleural urokinase in the treatment of loculated pleural effusions. *Chest* 1994; 105: 868–873.

13. Bouros D, Schiza S, Tzanakis N, Chalkiadakis G, Drositis J, Siafakas N. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema . A randomized, double-blind study. *Am J Respir Crit Care Med* 1999; 159: 37-42.

14. Candela A, Andujar J, Hernandez L, Martin C, Barroso E, Arriero JM, Romero S. Functional sequelae of tuberculous pleurisy in patients correctly treated. *Chest* 2003; 123: 1996-2000.

15. Valdes L, Alvarez D, San Jose E, Penela P, Valle JM, Garcia-Pazos JM, Suarez J, Pose A. Tuberculous Pleurisy: A Study of 254 Patients. *Arch Intern Med* 1998; 158: 2017-2021.

16. Liam CK, Lim KH, Wong MM. Tuberculous pleurisy as a manifestation of primary and reactivation disease in a region with a high prevalence of tuberculosis. *Int J Tuberc Lung Dis* 1999; 3: 816-822.

17. Epstein DM, Kline LR, Albelda SM, Miller WT. Tuberculous pleural effusions. *Chest* 1987; 91: 106-109.

18. Lin FC, Chen YC, Chen FJ, Chang SC. Cytokines and fibrinolytic enzymes in tuberculous and parapneumonic effusions. *Clin Immunol* 2005; 116: 166-173.

19. Baumann MH, Nolan R, Petrini M, Lee YCG, Light RW, Schneider E. Pleural tuberculosis in the United States: incidence and drug resistance. *Chest* 2007; 131: 1125-1132.

TABLE 1.CLINICAL DATA AND PLEURAL FLUID CHARACTERISITCS*

Characteristics	Free-flowing (n = 20)	Loculated		p Value
		Streptokinase (n = 22)	Saline (n = 22)	
Mean age, yr	65 ± 20	65 ± 19	63 ± 24	0.914
Male, n (%)	15 (75)	17 (77)	19 (86)	0.632
Patients with risk factors, n (%) †	6 (30)	4(18)	8 (36)	0.409
Days from onset of symptoms to treatment, d	12 ± 6	13 ± 8	14 ± 14	0.849
Dyspnea grade (NYHA) ‡	2.2 ± 0.6	2.1 ± 0.7	2.1 ± 0.7	0.946
Fever > 38.5□, n (%)	5 (25)	5 (23)	6 (27)	0.990
Pleuritis combined with pulmonary tuberculosis, n (%)	6 (30)	7 (32)	7 (32)	0.990
Chest radiograph, pa				
Area of effusion shadowing, %	59.7 ± 22.3	54.2 ± 27.3	54.9 ± 19.5	0.719
Pleural effusion variables				
pH value	7.36 ± 0.06	7.33 ± 0.13	7.33 ± 0.05	0.321
Glucose, mg/dL	108 ± 30	106 ± 40	109 ± 40	0.958
LDH, IU/dL	429 ± 247	456 ± 295	581 ± 862	0.633
Leukocyte count, cells/μL	1748 ± 1676	1937 ± 1962	1710 ± 1220	0.888

Definition of abbreviations: NYHA = New York Heart Association; pa = posteroanterior; LDH = lactate dehydrogenase.

* Values are presented as mean ± SD unless specified.

† Risk factors including alcoholism, diabetes mellitus, liver cirrhosis and subtotal gastrectomy.

‡ Dyspnea grading I-IV according to New York Heart Association classification.

TABLE 2. CLINICAL OUTCOME AFTER INTRAPLEURAL INJECTION TREATMENT*

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

* Values are presented as mean ± SD unless specified.

† $p < 0.05$ compared to free-flowing group.

‡ $p < 0.05$ compared to streptokinase group.

§ $p < 0.01$ compared to free-flowing group.

ll $p < 0.01$ compared to streptokinase group.

TABLE 3.LONG-TERM OUTCOME AFTER INTRAPLEURAL INJECTION TREATMENT*

Parameter	Free-flowing (n = 20)	Loculated		p Value
		Streptokinase (n = 22)	Saline (n = 22)	
Follow-up				
Area of effusion shadowing on CXR pa, %				
Discharge	8.5 ± 10.3	12.7 ± 9.8	19.9 ± 10.0 §‡	0.002
12 mo	0.3 ± 0.6	0.6 ± 1.9	4.2 ± 6.8†‡	0.009
Lateral effusion thickness on CXR pa, mm				
Discharge	48.0 ± 44.8	72.7 ± 34.1	93.2 ± 28.6 ll ‡	< 0.001
12 mo	3.6 ± 7.2	4.7 ± 11.3	19.2 ± 15.9 ll ¶	< 0.001
Residual pleural thickening > 10 mm, n (%)	2 (10)	2 (9)	10 (45) †‡	0.003
FVC, % predicted				
Discharge	75.8 ± 5.1	73.7 ± 4.9	70.0 ± 5.0 §‡	0.002
12 mo	79.8 ± 0.3	79.7 ± 1.0	78.0 ± 3.3†‡	0.012

Definition of abbreviations: pa = posteroanterior; FVC = forced vital capacity.

* Values are presented as mean ± SD unless specified.

† $p < 0.05$ compared to free-flowing group.

‡ $p < 0.05$ compared to streptokinase group.

§ $p < 0.01$ compared to free-flowing group.

ll $p < 0.001$ compared to free-flowing group.

¶ $p < 0.01$ compared to streptokinase group.

Figure 1. Enrollment of patients and completion of the study

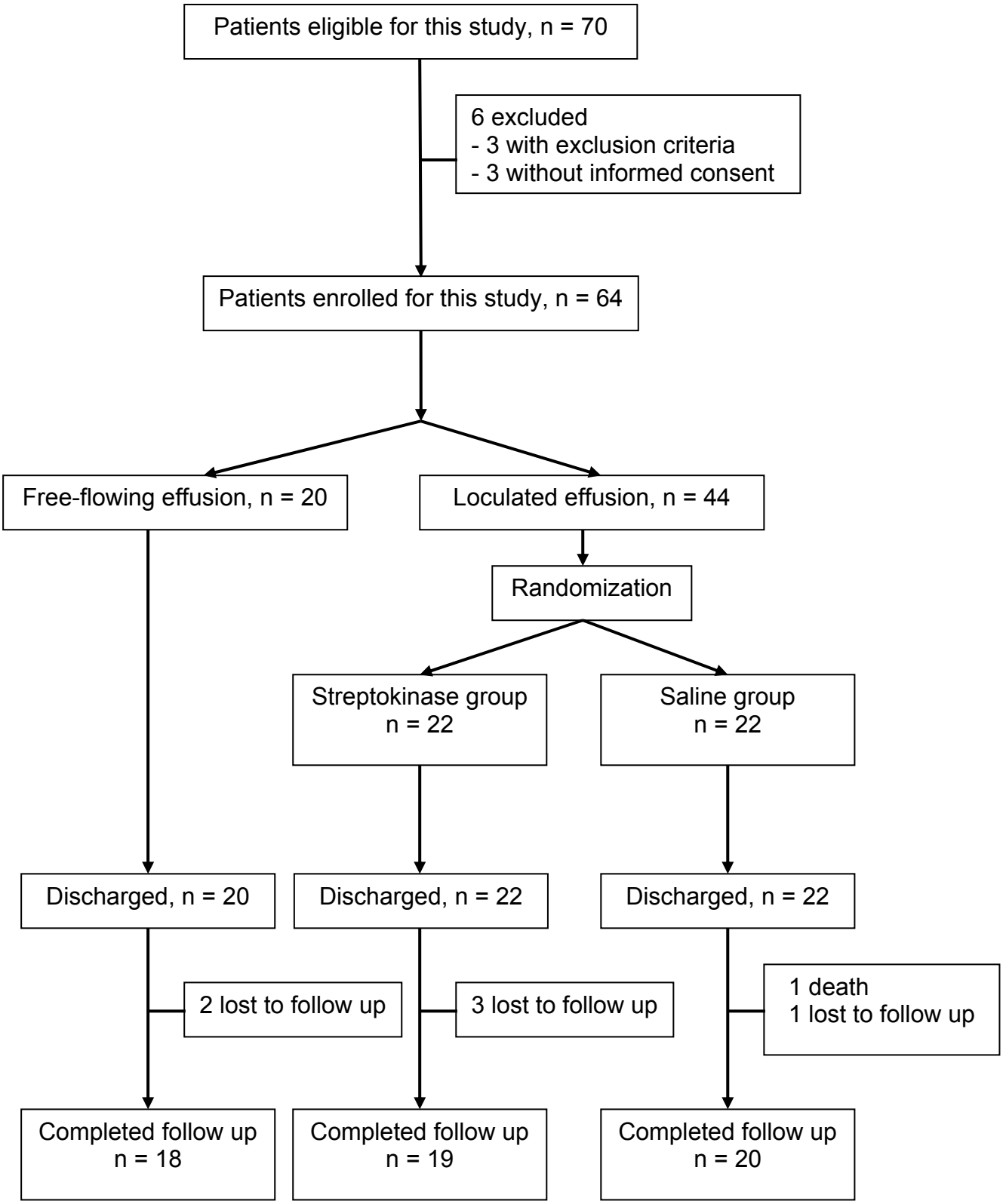

Figure 2.

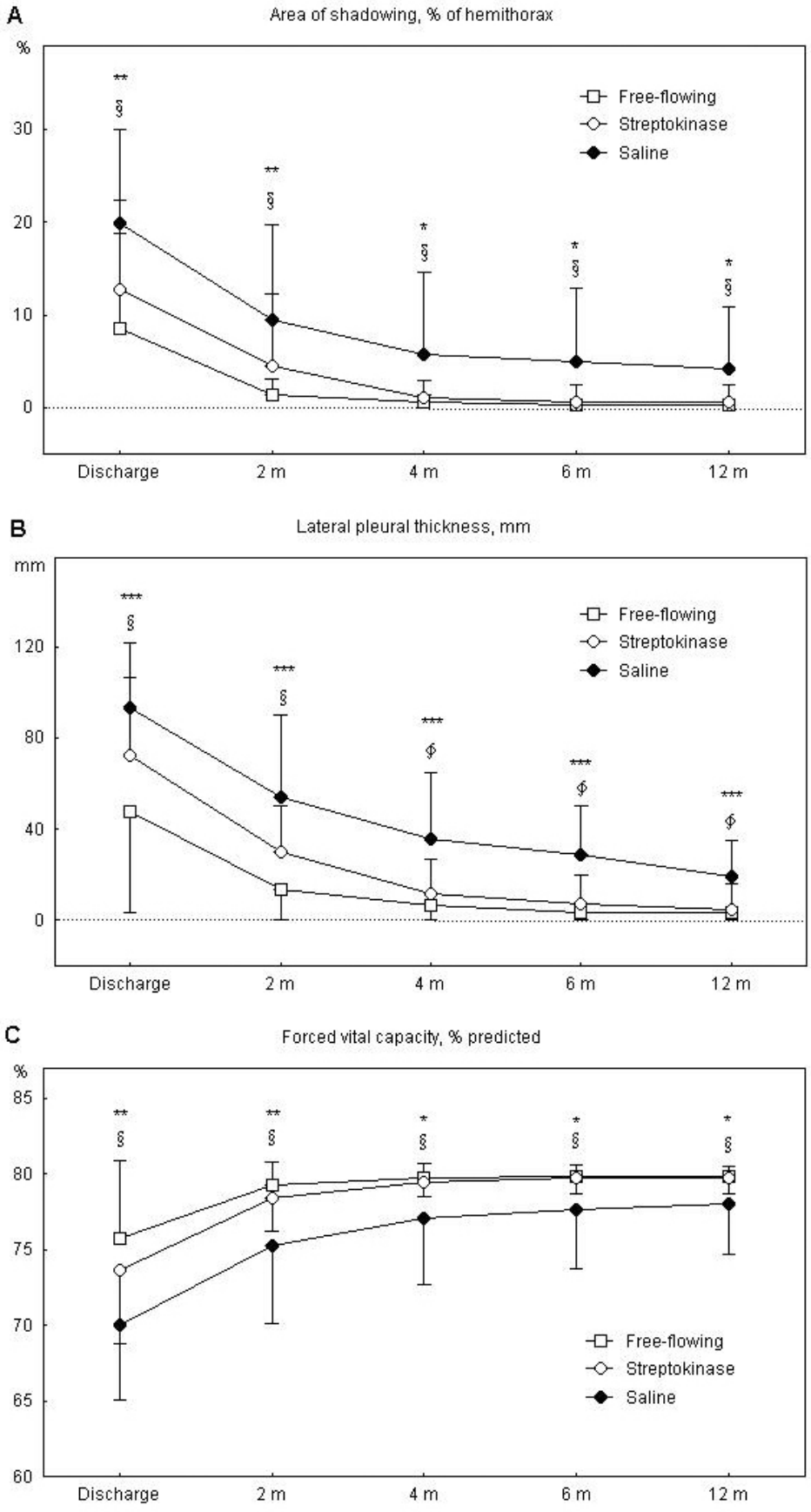
A
Area of shadowing, % of hemithorax
%
30
20
10
0
Free-flowing
Streptokinase
Saline
Discharge
2 m
4 m
6 m
12 m
B
Lateral pleural thickness, mm
mm
120
80
40
0
Free-flowing
Streptokinase
Saline
Discharge
2 m
4 m
6 m
12 m
C
Forced vital capacity, % predicted
%
85
80
75
70
65
60
Free-flowing
Streptokinase
Saline
Discharge
2 m
4 m
6 m
12 m

Figure 2. Chest radiograph scores (A and B) and forced vital capacity (C) during follow up. CXR scores and forced vital capacity gradually improved in all groups and statistically significant differences were noted between free-flowing and saline groups and between streptokinase and saline groups at any point of time. Values represent means and error bars represent standard deviations. m = month.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (comparisons between free-flowing and saline groups)

§ $p < 0.05$; □ $p < 0.01$ (comparisons between streptokinase and saline groups)