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The Effects of Urokinase Instillation Therapy via Percutaneous Transthoracic Catheter in Loculated Tuberculous Pleural Effusion: A Randomized Prospective Study

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The purpose of this study was to propose that intrapleural urokinase (UK) instillation could reduce pleural thickening in the treatment of loculated tuberculous pleural effusion. Forty-three patients who were initially diagnosed as having loculated tuberculous pleural effusion were assigned at random to receive either the combined treatment of UK instillation including anti-tuberculosis agents (UK group, 21 patients) or strictly the unaccompanied anti-tuberculous agents (control group, 22 patients). The UK group received 100,000 IU of UK dissolved in 150 ml of normal saline daily, introduced into the pleural cavity via a pig-tail catheter. The control group was treated with anti-tuberculous agents, excepting diagnostic thoracentesis. After the cessation of treatment, residual pleural thickening (RPT) was compared between the two groups. Clinical characteristics and pleural fluid biochemistry were also evaluated. The RPT (4.59 ± 5.93 mm) of the UK group was significantly lower than that (18.6 ± 26.37 mm) of the control group ($p<0.05$). The interval of symptoms observed prior to treatment of patients with RPT $\geq$ 10 mm (6.0 ± 3.4 wks) was detected to be significantly longer than in those with RPT $<$ 10 mm (2.1 ± 1.2 wks) in the control group ($p<0.05$). However, there were no discernible differences were seen in the pleural fluid parameter in patients with RPT $\geq$ 10 mm, as compared to patients with RPT $<$ 10 mm in the UK group. These results indicate that the treatment of loculated tuberculous pleural effusion with UK instillation via percutaneous transthoracic catheter can cause a successful reduction in pleural thickening.

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INTRODUCTION

Residual pleural thickening of tuberculous effusion after anti-tuberculous agents is inconsistent and has been reported at levels from 10% to 72%, depending on various researchers.[1-5] Therapeutic trials, including corticosteroids[6-8] and therapeutic thoracentesis,[9] have been added to anti-tuberculous agents in order to reduce pleural thickening corresponding to the treatment of tuberculous effusion. No satisfactory results have yet been reported. The loculation of tuberculous pleural effusion, when diagnosed, may possibly show an increased incidence of pleural thickening subsequent to the completion of therapy using anti-tuberculous agents. Severe pleural thickening could cause respiratory difficulty and occasionally requires future surgical intervention.

Since urokinase (UK) was first introduced as a fibrinolytic agent,[10] its clinical utility in the treatments of multiloculated empyema, complicated parapneumonic effusion, and loculated pleural effusion was tested in an attempt to reduce pleural thickening andavoid surgical interventions. Studies were completed with good results.[11-17]

The object of our study was the identification of the effects of the intrapleural UK instillation via pigtail catheter on the reduction of residual pleural thickening in the treatment of loculated tuberculous pleural effusion in a randomized prospective manner. The clinical characteristics and biochemical parameters of pleural fluid were evaluated in order to assess residual pleural thickening.

MATERIALS AND METHODS

Patients

Over a 3-year period, 43 potential patients with loculated tuberculous pleural effusion were evaluated. These patients were randomly assigned to either the UK group (21 patients) or the control group (22 patients). All patients with tuberculous effusion were diagnosed both by pleural biopsy and by a total pleural fluid analysis, which included acid-fast bacillus stain, as well as chemical analysis. All patients received isoniazid, rifampin, ethambutol and pyrazinamide for the two preliminary months, followed by an additional four months of treatment with isoniazid, rifampin and ethambutol.

Loculated tuberculous effusion was defined pleural effusion having not shifted on decubitus film and/or loculated on chest ultrasonography after diagnostic thoracentesis with pleural biopsy. The patients of the control group were treated with only anti-tuberculous medication. The patients of the UK group, however, were treated with UK instillation via pigtail catheter in addition to anti-tuberculous medication. The patients in the UK group received a solitary radiographically-guided percutaneous catheter ranging in size from 10 to 12 French. Initially, the pleural fluid was drained naturally, normally 12 hours following natural drainage. The catheter was connected to a water seal suction chamber with negative pressure measuring 20 cm H_2O. The amount of pleural fluid drainage was assessed. When pleural fluid drainage was less than 100 ml/day, 100,000 IU of UK, dissolved in 150 ml of normal saline, was then infused daily using a percutaneous catheter. Subsequent to instillation of UK, the suction tube was clamped for 2 hours, after which fluid was drained naturally. When the amount of pleural fluid drainage fell below 50 ml/day after UK instillation, UK infusion was discontinued and the percutaneous catheter was then removed. This protocol was sanctioned by the committees of ethics in our hospital.

The effectiveness of this study was evaluated through the assessment of: (1) residual pleural thickening, (2) an improved amount of loculated pleural effusion when compared to initial chest radiography after diagnostic thoracentesis. The pleural thickening was measured by calculating the longest transverse distance between visceral pleura and parietal pleura on the lateral-inferior portion of the posteroanterior chest radiography. In order to appraise the radiographic improvement of loculated pleural effusion in both groups, the amount of pleural effusion improvement was evaluated by three specialists; two chest physicians and one radiologist. The first chest radiography following diagnostic thoracentesis was compared with the chest radiography taken at the termination of follow-up in both the UK and the control group. The improved pleural effusion was ranked as follows: more than 75% improvement, 50 - 75% improvement, 25 - 50% improvement, and less than 25% improvement. In cases of inter-observer disagreement, the lowest perceived improvement was used.

Follow-up

Patients were followed for a mean period of eight months (range, 6 to 15 months) in the UK group and 8.1 months (range, 6 to 13 months) in the control group. The follow-up interval consisted of clinical examination and chest radiography.

Statistical analysis

The data are expressed as the mean ± standard deviation. The pleural fluid protein, LDH, and glucose levels and the ratios of the pleural fluid to serum protein, LDH, and glucose levels in all patients of the UK and the control group were compared using the unpaired t test. A value of $p < 0.05$ was regarded to be significant.

RESULTS

The clinical characteristics of the UK group and the control group were quite similar (Table 1). The mean age of both groups was about 30 years old. The UK group consisted of 15 men and 6 women, while the control group was comprised of 12 men and 10 women. The duration of symptoms of the UK group was slightly longer than that of the control group, but it was not seen to be statistically significant. No clinically significant difference in the fraction of patients with chest pain, cough, fever and dyspnea was established. The amounts of diagnostic thoracentesis in the UK and control group were 545 and 644 ml, respectively. In the UK group, the initial pleural fluid drainage subsequent to insertion of percutaneous transthoracic catheter was 470 ml. The number of UK instillations (mean ± SD) in the UK group was 3.8 ± 3.1 (range, 1 to 12) and the mean volume of pleural fluid drainage after instillation of UK was 936 ± 724 ml.

In both groups, pleural fluid analysis on initial thoracentesis showed an exudate when analyzed using Light's criteria. The WBC count, pH, LDH, glucose, proteins, and ADA did not differ significantly between the UK group and the control group, nor did the ratios of pleural fluid to serum protein and LDH (Table 2).

The width of residual pleural thickening of the UK group was determined to be 4.59 ± 5.93 mm. This was significantly lower than that (18.6 ± 26.37 mm) of the control group ($p < 0.05$) (Table 3). According to the depth of residual pleural thickening (RPT), eight (38.1%) in the UK group and eight (36.4%) in the control group had minimal RPT, with RPT of less than 2 mm (Table 3); 11 (52.4%) in the UK group and four (18.1%) in the control group had moderate RPT, with RPT between 2 and 10 mm (Table 3); and two (9.5%) in the UK group and 10 (45.5%) in the control group had severe RPT, with RPT measuring more than 10 mm (Table 3).

All of the 21 patients in the UK group showed considerably marked improvement, with pleural effusion improvements of more than 75%. Out of

Table 1. General Characteristics of the UK Group and the Control Group

	UK group* (N=21)	Control group† (N=22)
Age (years)	30.6 ± 7.8	29.9 ± 10.0
Sex (male : female)	15 : 6	12 : 10
Duration of symptoms (weeks)‡	3.8 ± 3.6	3.3 ± 2.7
Symptom		
Chest pain	17 (81%)	18 (82%)
Cough	16 (76%)	17 (77%)
Fever	16 (76%)	14 (64%)
Dyspnea	11 (52%)	13 (59%)
Volume of diagnostic Thoracentesis (ml)	545 ± 531	644 ± 565
Volume of pleural fluid drainage After insertion of percutaneous Transthoracic catheter (ml)	470 ± 466	
Volume of pleural fluid drainage After instillation of urokinase via Percutaneous transthoracic catheter (ml)	936 ± 724	

*Combined treatment of urokinase instillation via percutaneous transthoracic catheterization and anti-tuberculous medication.
†Anti-tuberculous medication only.
‡Duration of symptoms before admission.

Table 2. Fluid Characteristics of Diagnostic Thoracentesis in the UK Group and the Control Group

	UK group (N=21)	Control group (N=22)	*p*-value
WBC (/uL)	3058 ± 2379	3582 ± 3148	NS*
PH	7.44 ± 0.16	7.40 ± 0.30	NS
LDH (U/L)	670 ± 266	466 ± 186	NS
Ratio of LDH (serum/pleura)	3.19 ± 1.44	2.93 ± 1.06	NS
Glucose (mg/dL)	96.1 ± 46	81.7 ± 17.8	NS
Proteins (g/L)	6.1 ± 0.46	6.3 ± 0.32	NS
Ratio of protein (serum/pleura)	0.74 ± 0.06	0.75 ± 0.08	NS
Adenosine Deaminase (U/L)	69.6 ± 14.9	67.9 ± 20.8	NS

*Non-significant.

Table 3. Residual Pleural Thickening (RPT) in the UK Group and the Control Group

	UK group (N=21)	Control group (N=22)	
RPT (mean ± SD (mm))	4.59 ± 5.93	18.6 ± 26.37	*p*=0.017
≥ 10 mm	2 (9.5%)	10 (45.5%)	
2 - 10 mm	11 (52.4%)	4 (18.1%)	
< 2 mm	8 (38.1%)	8 (36.4%)	

Table 4. Improved Pleural Effusion (IPE) in the UK Group and the Control Group

IPE *	UK group (N=21)	Control group (N=22)
> 75%	21 (100%)	17 (77.3%)
50 - 75%	0	3 (13.7%)
25 - 50%	0	1 (4.5%)
< 25%	0	1 (4.5%)

*Improved amount of pleural effusion after complete treatment compared to initial treatment.

Table 5. Comparison of Pleural Fluid Biochemical Markers and Symptom Duration before Admission between the Patients with Residual Pleural Thickening (RPT) ≥ 10 mm) and Those with RPT < 10 mm in Control Group

	RPT ≥ 10 (N=10)	RPT < 10 mm (N=12)	*p*-value
Duration of symptoms (weeks)*	6.0 ± 3.4	2.1 ± 1.2	*p*=0.012
Pleural fluid			
PH	7.38 ± 0.31	7.44 ± 0.20	NS†
LDH (U/L)	501 ± 238	520 ± 215	NS
Ratio of LDH (serum/pleura)	3.07 ± 1.03	3.01 ± 1.01	NS
Glucose (mg/dL)	89 ± 51	88 ± 24	NS
Proteins (g/L)	5.0 ± 0.6	5.3 ± 0.4	NS
Ratio of protein (serum/pleura)	0.83 ± 0.05	0.76 ± 0.06	NS
Adenosine Deaminase (U/L)	66 ± 18	63 ± 19	NS

*Duration of symptoms before admission (weeks).
†Non-significant.

22 patients in the control group, 17 patients saw considerably marked improvement with improved pleural effusion more than 75%; three had noticeable improvement with improved pleural effusion between 50 and 70%; one experienced moderate improvement with improved pleural effusion between 25 and 50%; one saw minimal improvement with improved pleural effusion of less than 25% (Table 4).

Out of 22 patients in the control group, 12 patients had RPT of less than 10 mm, and 10 patients had RPT of more than 10 mm after the completion of treatment. Pleural fluid biomarkers were not substantially different between patients with RPT ≥ 10 mm and patients with RPT < 10 mm. However, the duration of symptoms before admission in the patients with RPT < 10 mm had been 2.1 ± 1.2 months, which was significantly shorter in comparison to those (6.0 ± 3.4 months) patients with RPT ≥ 10 mm (Table 5).

DISCUSSION

UK was first introduced to treat loculated pleural effusion in 1989.[10] UK, which acts as a direct plasminogen activator, is synthesized in the kidney and excreted in the urine. The clinical use of UK as a fibronolytic agent is being tested in the treatment of empyema, complicated parapneumonic effusion, and loculated pleural effusion, including tuberculous effusion. All reports suggest that the effect of UK on pleural disease is significant due to the fibrinolysis of loculations, which promotes the drainage of pleural fluid. Though most patients do not experience respiratory dysfunction after treatment, pleural thickening still a major hindrance of tuberculous effusion following treatment with anti-tuberculous agent.[1-5] A few patients with severe pleural thickening, however would require surgical intervention, including decortication. Patients experiencing loculated tuberculous pleural effusion are especially likely to have severe residual pleural thickening.

In a randomized, double-blind study in which the efficacy of UK versus normal saline was compared, Bouros and coworkers[18] showed that UK is effective in the treatment of loculated pleural effusions, due to lysis of pleural adhesions, not the volume effect. Furthermore, as compared to normal saline on clinical and chest radiographic improvement, including duration of hospitalization and amount of pleural drainage, the effects of UK were considerable.

A reported UK success rate ranging from 63% to 100% has been observed.[10-17] In a previous study of UK in the management of patients with loculated tuberculous pleural effusion and loculated empyema,[19,20] the drainage brought about by UK was effective in 77% of patients with partial expansion of pleural effusion. Our study, in contrast, showed an absolute success rate of UK in loculated tuberculous effusion of 100%. The efficacy of fibrinolytic agents is dependent upon the injection time. Several previous reports have suggested that early use of intrapleural UK proved more effective[21-23] than unsuccessful chest tube drainage.

Our results showed that intrapleural UK instillation is effective in moderating pleural thickening. All patients in the UK group experienced striking improvements with pleural effusion levels increasing more than 75%. Five of 22 patients in the control group, however, suffered significant residual pleural thickening, some of which might necessitate surgical intervention in the future.

The pleural thickening of tuberculous effusion after treatment with anti-tuberculous agents was reported at ranges of 10% to 72%, dependent on investigators.[1-3] This suggests a lack of uniformity in the approach to the concept of residual pleural thickening (RPT). In the control group of this particular analysis, 10 (45.5%) had RPT > 10 mm and 14 (63.5%) had RPT > 2 mm., These show a relatively high incidence of RPT when compared to the findings of de Pablos and coworkers,[4] who reported that 19.6% had RPT > 10 mm and 42.8% had RPT > 2 mm in tuberculous effusion without loculation. However, they advised further controlled study in order to determine the possible effect of the loculation of tuberculous effusion on pleural thickening.

No correlation was found in the control group between the pleural fluid parameters and development of RPT more than 10 mm. Examinations of the connection between pleural fluid findings and the development of pleural thickening in

tuberculous effusion were reported. Haro and coworkers[5] evaluated factors relating to pleural thickening in pleural tuberculosis in 99 patients. It was determined that pleural thickening had no connection to pleural fluid analysis. In another study, Barbas et al.[1] treated 44 patients with pleural tuberculosis and reported that no correlation was found tying pleural fluid findings to pleural thickening. These previous findings reinforce our findings. They are, however, inconsistent with findings that the development of RPT ≥ 10 mm was linked to lower glucose concentrations and pH and higher concentrations of lysozyme and tumor necrosis factor-alpha in pleural fluid. Cases examined in our research concerned tuberculous pleural effusion with loculation, which might account for some of the discrepancies in pleural fluid parameter.

It was determined in this study that a longer duration of symptoms of clinical characteristics is associated with RPT ≥ 10 mm. We also found out that intrapleural UK instillation in patients with loculated tuberculous pleural effusion prior to admission showed significant different symptom durations between the success group with more than 50% expansion of pleural effusion (11.8 days) and failure group (26.6 days) showing less than 50% expansion of pleural effusion. Also, UK was ineffective in patients whose pleural fluid exhibited a honeycomb appearance on ultrasonography or whose parietal pleura were thicker than 5 mm on chest CT scans. This suggests that the duration of symptoms is associated with residual pleural thickening. It is also indicated that the chronic process of tuberculous effusion without immediate treatment could contribute to the formation of loculation and fibrosis of pleural effusion, which results in continued pleural thickening. Generally, fibrinolytics provide more benefit if used early, prior to the deposit of extensive collagen in pleural space.[21-24]

UK is safer than streptokinase because urokinase is not antigenic. Adverse reactions are rarely observed , tend to be of the allergic type, and are more frequent when streptokinase is used.[19,25] Intrapleural UK treatment does not appear to have an adverse effect on bleeding and systemic coagulation.[20,21] The usual daily dose ranges from 50,000 U to 250,000 U diluted in 30 - 150 ml of normal saline via chest tube or pigtail catheter. No recommendations for optimal dosage and dilution technique have yet been made. We have used 100,000 U of UK in 150 ml of normal saline via pigtail catheter daily. The pig-tail catheter, easily manipulated and less invasive than a chest tube,[14,16] was chosen for drainage of the loculated pleural effusion. All patients in our study tolerated the procedure well. The only complications observed were mild fever and chest pain in a few patients.

In conclusion, treatment of loculated tuberculous pleural effusion with urokinase instillation via percutaneous transthoracic catheter at a daily dose of 100,000 IU was effective in causing the inhibiting of pleural thickening. Our study shows that longer symptom duration is directly related to residual pleural thickening. Urokinase has proven to be safe and effective in the treatment of loculated tuberculous effusion. The use of urokinase may make surgical intervention due to pleural thickening avoidable.

The natural time course of RPT in the tuberculous pleural effusion is not yet well-known. De Pablo et al.[4] radiologically reevaluated 13 patients 1 year post-treatment and found that 10 patients had experienced RPT reduction of 3 to 28 mm. RPT change subsequent to our study period must be observed in order to reevaluate the natural decrease of RPT.

Although our study showed that urokinase instillation therapy via percutaneous transthoracic catheter in loculated tuberculous effusion is a potentially effective method in preventing pleural thickening, it is uncertain whether this is a gold standard treatment of loculated tubeculous pleural effusion. Further, more in-depth studies with a greater number of cases is necessary in the future. Future studies must also be planned over a longer duration of time.

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