A study of loculated tuberculous pleural effusions treated with intrapleural urokinase

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Summary

Aim: To assess the effect of intrapleural urokinase, vis-à-vis simple pleural drainage, on residual pleural thickening in a series of patients suffering from loculated tuberculous pleural effusion.

Patients and method: Twenty-nine patients (21 males and 8 females) with loculated pleural effusion were studied. These patients were randomly allocated to one of two groups: one group received intrapleural urokinase (n = 12) and the other was treated by simple drainage with suction (n = 17). The urokinase (125,000 UI) was administered into the pleural cavity via an intrathoracic tube. This procedure was repeated every 12 h until the quantity of pleural fluid obtained was less than 50 cm3, at which point the intrathoracic tube was removed.

Results: In both groups, the biochemical analysis of the pleural fluid was an exudate and the fluid had a serous appearance. Pleural thickening when the drainage tube was removed was 8.09 ± 3.36 mm for the group treated with urokinase, and 14.78 ± 17.20 mm (P > 0.05) for the control group. Residual pleural thickening measured upon completion of medical treatment at 6 months was 1.45 ± 0.89 mm for the group treated with urokinase and 7.47 ± 10.95 mm for the control group (P < 0.05). In the control group, only two patients presented over 10 mm of residual pleural thickening. The mean quantity of fluid drained in the two groups was 1,487 ± 711 ml for the patients with urokinase, and 795 ± 519 ml for the control group (P < 0.01).

Conclusion: Our study shows that patients with loculated tuberculous pleural effusion treated with urokinase suffered less from residual pleural thickening, as measured after six months, than those treated by simple drainage. It is therefore

Abbreviation: PE, pleural effusion.

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suggested that the administration of intrapleural urokinase is a safe and effective treatment for those patients who drain a larger quantity of pleural fluid. © 2006 Elsevier Ltd. All rights reserved.

Introduction

In Spain, up to 23% of all patients with tuberculosis present tuberculous pleural effusion, and tuberculosis is the most frequent cause of pleural effusion (PE) in patients under 35.¹,² Current treatment for tuberculosis has a high clinical efficacy rate,³ however, it frequently results in different degrees of residual pleural thickening. In a series of 45 patients with tuberculous PE, Soler et al.⁴ found that 72.6% of them presented pleural thickening, of which 8.1% were in excess of 15 mm, always on the lower side of the affected hemithorax. This complication of treatment for tuberculous PE has been addressed, with no clear benefits, by adding corticoids both systemically and locally⁵,⁶ and with repeated thoracocentesis⁷.

Urokinase, for its part, has been successfully used since the 1960s⁸ to treat purulent pleurisy and complicated pleural effusions. Intrapleural fibrinolytic agents provide a safe and effective treatment for loculated PE, reducing morbidity and the need for surgery.⁹–¹¹ There are in fact several studies that assess the use of intrapleural urokinase to treat encapsulated PE.¹²–¹⁴ However, in spite of the high frequency of encapsulated tuberculous pleural effusions, we found only one recent study that attempted to assess the use of intrapleural urokinase in tuberculous effusions with signs of pleural loculation.¹⁵

The purpose of our randomised prospective study was to compare the impact on residual pleural thickening and on the amount of pleural fluid drained of either administering intrapleural urokinase to, or treating by simple pleural drainage, patients with loculated tuberculous PE.

Patients and procedure

From 1993 to 2003, we studied a total of 97 tuberculous pleural effusions in patients older than fourteen years old. Of these, 29 (28.3%) corresponded to patients (21 men and 8 women, mean age of 31) with loculated PE (Table 1). Diagnosis of loculated PE in these patients had been established from the findings of chest X-ray examinations, which showed a lack of layering on decubitus view. This was subsequently confirmed by the presence of loculations in the thorax ultrasound examination, which was performed on all the patients prior to the insertion of a pleural drainage tube. In those cases in which a thoracoscopia was needed to obtain biopic samples, the presence of pleural adhesions was confirmed through such direct thoracoscope examination. The initial PE was subdivided into three groups according to radiologic size: it was defined as small when it occupied less than 1/3 of the affected hemithorax, as medium when it occupied less than two-thirds of the hemithorax, and as large when it occupied up to 2/3 of the hemithorax. Diagnosis of pleural tuberculosis was established by the presence of one or more of the following findings: the presence of necrotising granulomas in the pleural biopsy; pleural fluid, or biopsy that was positive to Ziehl staining or Löwenstein–Jensen medium. For 6 months all patients were treated with isoniazid and rifampicin, together with pyrazinamide during the first 2 months. In no case were corticoids added to the treatment.

In the first thoracocentesis, samples of pleural fluid were taken for biochemistry, cell count, microbiology and inflammation markers (Table 1). All patients were fitted with an 18–20 F intercostal drainage tube which was connected to a graduated container with a water seal. The patients were then randomised into two groups: one of them received intrapleural urokinase (n = 12) and the other was treated with simple drainage with suction (n = 17). The urokinase was prepared in a solution of 125,000 UI of urokinase with 50 ml of saline. This solution was administered into the pleural cavity via an intrathoracic tube. The tube was subsequently sealed for two hours and then connected to suction of up to −25 cm of H₂O. This procedure was repeated every 12 h until the amount of pleural fluid extracted was less than 50 cm³, at which point the intrathoracic tube was removed. The average dosage administered to each patient was 3.5 ± 2 (range 2–8).

The main variable of interest to our study was pleural thickening, as assessed at the end of pleural drainage and after completion of treatment. Pleural thickening was measured on the lower side of a posteroanterior chest X-ray and recorded in millimetres. Other variables were also evaluated, including the quantity of drained fluid, the duration...
of the drainage process, and the length of hospitalisation.

The results below are recorded as the mean ± standard deviation from the mean. A Student’s t-test and a \( \chi^2 \) test were conducted to determine the statistical significance of the differences and relationships between variables observed between the two groups, respectively. The level of statistical significance was set at \( P < 0.05 \).

## Results

The quantity of PE as determined by the initial X-ray findings was similar in the two groups (Table 1). Table 1 also shows the characteristics of the pleural fluid, including the total number of leukocytes, the percentage of lymphocytes, the levels of glucose, proteins, lactic acid dehydrogenase (LDH) and inflammation markers resulting from the first thoracocentesis. No significant differences were found between the biochemical parameters of the two groups, except for pleural proteins. Neither were differences found between the cell count and percentage of lymphocytes, or the inflammation markers, adenosine deaminase (ADA) and interferon \( \gamma \). In both groups, the biochemical analysis of the pleural fluid was an exudate and the fluid had a serous appearance. Glucose in the pleural fluid was significantly lower than blood glucose (group treated with urokinase: \( 63 \pm 17 \) and \( 101 \pm 18 \), \( P < 0.05 \); control group: \( 70 \pm 24 \) and \( 99 \pm 9 \), \( P < 0.05 \)), and no difference was found between glucose in pleural fluid in the two groups. The pH of the pleural fluid was low in the two groups (\( 7.23 \pm 0.07 \) and \( 7.24 \pm 0.07 \)), and no difference was found between glucose in pleural fluid in the two groups. The pH of the pleural fluid was low in the two groups (\( 7.23 \pm 0.07 \) and \( 7.24 \pm 0.08 \), respectively, \( P > 0.05 \)). None of the patients presented local complications at the point of insertion of the intrathoracic tube, nor were systemic complications observed during drainage.

Pleural thickening when the drainage tube was removed was \( 8.09 \pm 3.36 \) mm for the group treated with urokinase and \( 14.78 \pm 17.20 \) mm for the control group (\( P > 0.05 \)). Residual pleural thickening measured upon completion of the medical treatment at six months was \( 1.45 \pm 0.89 \) mm for the group treated with urokinase and \( 7.47 \pm 10.95 \) mm for the control group (\( P < 0.05 \)). Only two patients in the control group presented over 10 mm of pleural thickening. The mean quantity of fluid drained was \( 1.487 \pm 711 \text{ cm}^3 \) for the patients treated with urokinase and \( 795 \pm 519 \text{ ml} \) for the control group (\( P < 0.01 \)). Table 2 compares the hospitalisation times for the two groups, the time between admission and drainage placement, and the duration of drainage. No significant differences were found regarding any of these parameters.

### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>With urokinase (n = 12)</th>
<th>Control (n = 17)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (males/females)</td>
<td>12 (8/4)</td>
<td>17 (13/4)</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>29</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>22–39</td>
<td>15–51</td>
<td></td>
</tr>
<tr>
<td><strong>Radiologic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Large</td>
<td>4</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Analysis of pleural fluid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>( 7.23 \pm 0.07 )</td>
<td>( 7.24 \pm 0.07 )</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>( 63 \pm 17 )</td>
<td>( 70 \pm 24 )</td>
<td>NS</td>
</tr>
<tr>
<td>Proteins (gr/dl)</td>
<td>( 5.42 \pm 0.5 )</td>
<td>( 4.92 \pm 0.71 )</td>
<td>( &lt;0.02 )</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>( 1081 \pm 436 )</td>
<td>( 1260 \pm 616 )</td>
<td>NS</td>
</tr>
<tr>
<td>LDH p/s</td>
<td>( 4.07 \pm 2.64 )</td>
<td>( 3.50 \pm 2.62 )</td>
<td>NS</td>
</tr>
<tr>
<td>ADA (U/l)</td>
<td>( 68.83 \pm 15.02 )</td>
<td>( 82.63 \pm 23.46 )</td>
<td>NS</td>
</tr>
<tr>
<td>INF-( \gamma ) (pg/ml)</td>
<td>( 3955 \pm 3073 )</td>
<td>( 5344 \pm 3711 )</td>
<td>NS</td>
</tr>
<tr>
<td>Total cells ( ( \times 10^3 )/ml)</td>
<td>( 3.4 \pm 3.9 )</td>
<td>( 2.5 \pm 2.5 )</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>( 89 \pm 10 )</td>
<td>( 88 \pm 13 )</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD.

ADA, adenosine deaminase; INF-\( \gamma \), interferon \( \gamma \); LDH, lactic acid dehydrogenase; NS, not significant.
No patient required surgery and there were no fatalities. Urokinase was tolerated well by all twelve patients and no bleeding was observed in these patients.

Discussion

Our results show that the treatment of loculated tuberculous pleural effusion with drainage plus urokinase leads to less residual pleural thickening than treatment with simple pleural drainage. Residual pleural thickening is a relatively frequent complication in cases of tuberculous PE. In order to reduce the severe inflammatory reaction that patients with tuberculous PE experience, past studies have administered corticoids. Such a treatment, however, has failed to reduce pleural thickening in the affected patients. Corticoids were not used in our study, and all the patients received tuberculosis medical treatment in addition to pleural drainage. Urokinase has also been used to try to reduce pleural thickening in cases of complicated parapneumonic effusions. Urokinase activates plasminogen, converting it into plasmin, a non-specific proteolytic enzyme. Plasmin is capable of degrading fibrinogen and fibrin clots, thus reducing pleural walls and facilitating drainage of the pleural cavity. We have only found one study conducted by Ding et al. on a series of tuberculous pleural effusions in which urokinase was added to prevent the development of pleural thickening. Ding et al.’s study is however different from ours in that, in theirs, urokinase was used in cases that did not show pleural loculation. Recently, Kwak et al. conducted a similar study to ours, in which they treated patients with loculated PE with urokinase. The results of Kwak et al.’s study were similar to ours, albeit that their monitoring period was shorter than ours.

Another variable that is usually assessed in studies which use intrapleural fibrinolytic agents is the amount of fluid that can be drained. Our findings show that those patients with tuberculous PE who were treated with urokinase drained more pleural fluid than those in the control group. This result coincides with the findings in Bouros et al. in which the amount of fluid drained in non-tuberculous pleural effusions was significantly greater in the urokinase group than in the control group. Both Kwak et al. and Bouros et al. studies on tuberculous pleural effusion coincide in this respect. Since in our study the quantity of fluid drained was greater in the group treated with urokinase, we believe this was due to the effect of the urokinase, which produced lysis of the pleural adhesions. Lysis contributed to diminishing pleural thickening, whereas according to Bouros et al. rupture of the adhesions would not diminish residual pleural thickening. It is also possible that the increase in the amount of drained fluid in the group treated with urokinase was due to the amount of saline fluid administered with the urokinase. However, since the latter was significantly lower than the amount of fluid drained, we believe that it had no consequence on the total volume of drained fluid that was obtained.

In most cases, we conducted a thorax ultrasound examination prior to insertion of the drainage tube in order to locate the best drainage point. In no case was it necessary to use a CT scan or multiple catheterisation. With regards to catheter size, we used a medium grade size catheter in both groups, which allowed for the drainage of dead tissue that is so common in this type of complicated pleural effusion. No differences were found between the groups as regards either the patients’ characteristics, the quantity of PE or the analysis of their initial pleural fluid. Both groups presented a similar degree of pleural inflammation based on LDH values and inflammation markers, as well as similarly low glucose and pH values. In both groups, the

<table>
<thead>
<tr>
<th>Parameters (range)</th>
<th>With urokinase (n = 12)</th>
<th>Control (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial PT (mm)</td>
<td>8.09 ± 3.36</td>
<td>14.78 ± 17.20</td>
<td>NS</td>
</tr>
<tr>
<td>Final PT (mm)</td>
<td>1.45 ± 0.89</td>
<td>7.47 ± 10.95</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Drainage quantity (ml)</td>
<td>1487 ± 711 (150–3000)</td>
<td>795 ± 519 (150–1500)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of hospitalisation (days)</td>
<td>14.72 ± 4.22 (7–20)</td>
<td>16.85 ± 6.24 (7–26)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of fever after drainage placement (days)</td>
<td>3.63 ± 2.06 (1–6)</td>
<td>4.50 ± 2.88 (1–8)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of pleural drainage (days)</td>
<td>2.66 ± 1.72 (2–8)</td>
<td>2.42 ± 0.78 (2–4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Pleural drainage and clinical parameters. Values expressed as mean ± so (range).

NS, not significant; PT, pleural thickening.
LDH p/s ratio was over 2.1, which led us to predict pleural thickening as a complication of these pleural effusions. The doses of urokinase administered was 250,000 UI every 24 h. This dose, which is retained in the pleural cavity for 2 or 3 h before connecting the drainage, is that most frequently used in the bibliography consulted.\(^{10,12,15}\) Drainage time was similar in both groups, as was the time that it took for the fever to disappear after starting pleural drainage, irrespective of urokinase. Drainage time, therefore, does not appear to affect residual pleural thickening which, as we have reported, was significantly lower in the group treated with urokinase. However, the time taken to inject the fibrinolytic agent does appear to have an impact on residual pleural thickening; the sooner treatment is started, the smaller the collagen deposits, which in turn favours disappearance of the PE.\(^{12}\) In our study, there was no time difference between the groups vis-à-vis either urokinase administration or pleural drainage. Bouros et al. found a reduction in the length of hospitalisation and the number of days of pleural drainage required in patients with purulent pleurisy treated with urokinase.\(^{12}\) We found no such difference, although the length of hospitalisation in days for the group treated with urokinase in our study was similar to that found by these authors. Other studies that have used streptokinase have found no differences between the treatment and the control groups as regards these parameters compared.\(^{23,24}\)

We believe that this could be due to factors such as early start of treatment, the dose and type of fibrinolytic agent used, or the size of the drainage tube.

In our opinion, the use of urokinase is justified in those patients who show loculation of the pleural cavity and when factors predicting that residual pleural thickening will be over 10 mm can be identified. Indeed, we found two patients in the control group with over 10 mm of pleural thickening and none in the group treated with urokinase. Our belief is based on: firstly, that pleural thickening is reduced between removal of the drainage tube and completion of treatment (as described by De Pablo et al.\(^{25}\) who found a reduction in pleural thickening and even normalisation after a one-year period; and secondly, that functional sequelae in patients with tuberculous residual pleural thickening of up to 2 mm are irrelevant (although in patients with pleural thickening over 10 mm there appears to be a reduction in pulmonary volume\(^{26}\)).

To conclude, our study showed that patients with loculated tuberculous pleural effusion treated with urokinase had less residual pleural thickening, as measured after 6 months, than those treated with simple drainage. Administration of intrapleural urokinase is therefore a safe treatment for those patients with loculated tuberculous PE. Although functional sequelae in this type of PE are both common and irrelevant, we believe that administration of urokinase in patients with loculated effusion is nevertheless to be recommended.

**Acknowledgments**

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**Reference**