Early use of intrapleural fibrinolytics in the management of postpneumonic empyema. A prospective study

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Abstract

Objective: A prospective randomized study was conducted in order to analyze the role of fibrinolytics in the treatment of complicated parapneumonic effusion. Methods: From 2001 to 2004, 127 consecutive patients were managed for thoracic empyema. In all cases the cause was bacterial pneumonia. Seventy patients were managed with sole tube thoracostomy (group A) and 57 with combination of tube thoracostomy and streptokinase instillation (group B). Groups were statistically compared for the age, gender, duration of symptoms, quality of pleural fluid, chest imaging, complete drainage, length of hospital stay and mortality. Multivariate analysis was used in order to define the factors that affect outcome. Results: Tube thoracostomy was successful in 47 (67.1%) cases (group A), while fibrinolysis led to a favorable outcome in 50 cases (87.7%) (P < 0.05). The length of stay in thoracic surgical department was significantly longer for group A (P < 0.001). Mortality rate in group A was significantly higher (P < 0.001). Multiple regression analysis disclosed as sole independent favorable factor for pleural drainage, the use of fibrinolysis during the course of chest tube drainage (P = 0.006, odds ratio 4.29, 95% CI 1.51–12.14). Conclusions: Fibrinolytic agents are a useful adjunct in the management of complicated parapneumonic effusions. Intrapleural fibrinolytics, if used early in the fibrinopurulent stage of a parapneumonic effusion, decrease the rate of surgical interventions (VATS or open decortication) and the length of hospital stay with minor associated morbidity.

Keywords: Thoracic empyema; Chest tube thoracostomy; Fibrinolysis

1. Introduction

Despite the advances in antibiotic therapy during the last decades, thoracic empyema remains a common clinical entity with significant associated morbidity and mortality. This should be attributed to the rise of antibiotic-multi-resistant infections, to the increased frequency of nosocomial pneumonias and to the treatment of a wider population with immune deficiencies. Primary thoracic empyema is defined as all complicated pleural effusions after pleuropulmonary infection and accounts for about half of all empyema cases. Traditionally, Light and co-workers have classified primary thoracic empyema in three stages [1]. Secondary thoracic empyema includes pleural empyemas after lung resections, thoracic trauma and extension of a suppurative process. Treatment of thoracic empyema includes three basic principles: (a) drainage of complicated parapneumonic effusion, (b) full expansion of the underlying lung and (c) elimination of the pleuropulmonary infection with antimicrobial agents. The optimal method for thoracic empyema management defined by the stage of thoracic empyema remains controversial [2]. The decision of the type of treatment is usually empiric, sometimes guided by the failure of another treatment modality [3]. Antimicrobial treatment (sometimes with thoracentesis) is the treatment of choice for stage I with good results, while in stage III a more aggressive open surgical drainage and decortication is needed.

Chest tube thoracostomy is required for stage II, sometimes in conjunction with fibrinolytic agents. Although chest tube thoracostomy is considered the appropriate treatment modality for stage II thoracic empyema, not infrequently (25–35%) chest tube thoracostomy proves to be inadequate for definite thoracic empyema treatment and more invasive modalities are required, such as VATS or open thoracotomy decortication. Intrapleural administration of fibrinolytic agents has provided an option of managing these patients without subjecting them to surgical procedures. This therapeutic modality helps to break the loculations by virtue of its fibrinolytic property is still controversial. Prospective studies during the last decade have come to contradictory conclusions [4-7].

The authors conducted a prospective randomized study that compared intrapleural streptokinase administration with simple tube drainage for the treatment of patients with complicated parapneumonic pleural effusions (stage II).
2. Patients and methods

From July 2001 to July 2004, out of 147 consecutive patients that were assessed for eligibility, 135 met the inclusion criteria. The major inclusion criterion was patients with primary bacterial postpneumonic thoracic empyema. The stage of empyema was not a point for evaluation for inclusion in the study.

Patients being medically contraindicated to surgery or the ones with endstage underlying diseases or tuberculous empyema were excluded from the study. Furthermore, exclusion criteria also included the existence of a bronchopleural fistula, the occurrence of lung abscess, a known sensitivity to streptokinase, and contraindication to thrombolytic therapy. Twelve patients were excluded from the study.

There were 96 men (71%) and 37 women (29%). Their age ranged from 19 to 77 years (mean 46 ± 12 years). In all cases the primary infection was bacterial pneumonia.

Clinically, all patients had prolonged fever, cough, dyspnea, and sputum production despite antibiotic therapy. All patients were previously managed with antibiotic treatment and thoracentesis and were referred to the Thoracic Surgical Department with the diagnosis of complicated parapneumonic effusion, which was defined as any parapneumonic effusion with one or more of the following characteristics: (1) grossly purulent pleural fluid; (2) positive effusion gram stain or culture for bacteria; (3) pH < 7.2; (4) glucose level < 40 mg/dl; (5) lactate dehydrogenase (LDH) level > 1000 IU/l.

The study design included two modes of management: solely chest tube thoracostomy drainage (group A, control group) or combination of chest tube thoracostomy and streptokinase intrapleural instillation (group B). The patients were randomly allocated to groups A and B by inserting the patients with odd last digit of their hospital code number in group A and with even one in group B for a certain duration of time (July 2001-July 2004).

The indications for chest tube thoracostomy±fibrinolysis were the following findings. Freely aspirated large quantity ((0.4 l) of turbid fluid or frank pus with pH < 7.2 or/and glucose level < 40 mg/dl, or/and LDH > 1000 IU/l, or/and positive cultures.

All patients initially had a closed intercostal drainage with a size 28- to 32-Fr Argyle chest tube attached to a water seal system with suction at —20 cm H2O. Proper chest tube position for successful drainage was defined as the one within the most dependent part of the effusion. For the patients assigned to receive fibrinolitics, streptokinase was used at a dose of 250,000 IU dissolved in 60 ml of normal saline, that was instilled in the pleural cavity through the chest tube during the first day of thoracostomy. After instillation, the tube was clamped for 4 h and the patient asked to repeatedly change position so that streptokinase could thoroughly spread in the pleural cavity. At the end of 4 h, the clamp was opened. One cycle of streptokinase of 250,000 IU was given every day, for three successive days. Complete drainage for group B was assessed after completion of the 3-day treatment with streptokinase.

The surgical team kept the data of which patient was in group A or B. The evaluation of outcome for every patient was performed by a doctor of the Pulmonology Department who was not informed for the mode of treatment that has been followed. It was his/her evaluation that led to the decision of whether or not to continue chest tube thoracostomy ± fibrinolytic therapy or to proceed to surgery. The end point criteria were strictly set: Successful drainage was defined as the almost complete evacuation of the pleural space as evidenced at chest radiograph or CT scan. This must be followed by near total lung re-expansion and clinical improvement (of dyspnea, debilitation, and discomfort) of the patient’s condition. Drainage was left in place until daily fluid output was less than 50 ml and the satisfactory radiographic image remained unchanged. Criteria to proceed to surgery (VATS or open thoracotomy decortication) consisted of progressive or persistent septic course in the presence of substantial residual pleural fluid.

The following data were prospectively collected for each patient: age, gender and the onset and duration of the infectious disease. The recorded pleural fluid’s characteristics included: Gross appearance; Cell count; Glucose level; LDH level; pH; Protein level; Gram stain and culture results. After chest imaging with CT scan, data for existence of multiple loculations were also recorded.

Groups were statistically compared for the duration of symptoms, quality of pleural fluid, chest imaging findings, hospital stay duration, outcome and mortality. Duration of symptoms, quality of pleural fluid, chest imaging findings and treatment modalities were entered in multivariate analysis in order to define the independent factors for successful outcome of complicated parapneumonic effusion management.

Length of treatment was defined from the day of admittance to thoracic surgical department until the day of exit from hospital for the successful cases or until the day of surgery for the rest ones.

Statistical analysis was performed using Student’s t-test (otherwise the Wilcoxon rank-sum test) and chi square test (Fisher’s Exact test when needed) where appropriate. Multiple logistic regression was used for multivariate analysis.

3. Results

One hundred and thirty-five consecutive patients consisted the study group (Table 1). Seventy cases were managed by chest tube thoracostomy (group A), while in 65 patients streptokinase was instilled intrapleurally (group B). Eight cases of group B were lost during follow-up because of not completing the protocol.

The most frequent clinical symptoms were fever (88%), cough (73%), chest pain (66%), dyspnea (41%). Seven patients (5.5%) were in severe sepsis. The most common comorbid factors were diabetes mellitus (14%), chronic obstructive pulmonary disease (13%), ischemic heart disease (6%) and liver disease (0.6%). Pleural fluid cultures were positive in 96 cases (75.5%). Multimicrobial cultures were detected in 41 cases (32.2%). The most frequent isolated bacteria were...
Klebsiella pneumoniae, Pneumococcus, Hemophilus influenzae, Streptococcus, Enterobacter, Escherichia coli, Bacteroides, Fusobacterium, Pseudomonas, etc.

The age of patients in group A ranged from 22 to 73 years (mean 46) and in group B from 19 to 77 years (mean 45). The majority of cases were referred for chest tube thoracostomy±fibrinolysis management after 1 week from symptoms’ onset (91.5% of cases from group A and 93% of ones in group B).

In the majority of cases (84.2%), the aspirated fluid was thin in both groups.

Chest tube thoracostomy was successful in 47 (67.1%) cases (group A), while fibrinolysis led to a favorable outcome in 50 cases (87.7%), which was statistically significant ($P<0.05$). The characteristics of both groups are presented in Table 2. Reduction in fever, dyspnea, debilitation and discomfort was noted in all but 8 patients in group B (86%), but in only 33 (47%) in the control group ($P<0.001$).

The length of stay in thoracic surgical department was significantly longer for group A ($P<0.001$). The mean length after the beginning of therapy was 15.5±4 days (range 8–24 days) for the chest tube thoracostomy group and 7±1.7 days (range 4–14 days) for the streptokinase group. The follow-up did not reveal any recurrences for both groups.

Mortality rate in group A was significantly higher ($P<0.001$). Totally, 4 patients (3.1%) died, 3 because of overwhelming sepsis and subsequent multiple organ dysfunction and 1 due to myocardial infarction.

There were no complications of tube thoracostomy. No systematic adverse effects of streptokinase were recorded, i.e. allergic reaction, hypotension and coagulopathy. In 9 patients (15.7%), a mild discomfort with dull pain was noted.

### Table 1
Study flow diagram

- Assessed for eligibility (n= 147)
- Excluded (n= 12)
  - Not meeting inclusion criteria (n= 12)
  - Refused to participate (n= 0)
- Randomised (n= 135)
- Allocated to Group A (n= 70)
  - Received allocated intervention (n= 70)
  - Lost to follow-up (n= 0)
  - Discininated intervention (n= 0)
- Allocated to Group B (n= 65)
  - Received allocated intervention (n= 65)
  - Lost to follow-up (n= 8)
  - Discininated intervention (n= 0)
- Analysed (n= 70)
  - Analysed (n= 57)

### Table 2
Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>70</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (72.8%)</td>
<td>39 (68.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>19 (27.2%)</td>
<td>18 (31.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration from Symptoms onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>6 (8.5%)</td>
<td>4 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 1 week&lt;2 weeks</td>
<td>57 (81.5%)</td>
<td>45 (79%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 2 weeks&lt;4 weeks</td>
<td>7 (10%)</td>
<td>8 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turbid thin fluid</td>
<td>60 (85.7%)</td>
<td>47 (82.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Frank pus</td>
<td>10 (14.3%)</td>
<td>10 (17.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH &lt; 7.2</td>
<td>66 (94.2%)</td>
<td>54 (94.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>GLU &lt; 40 mg/dl</td>
<td>61 (87.1%)</td>
<td>45 (78.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>LDH &gt; 1000 IU/l</td>
<td>46 (65.7%)</td>
<td>33 (57.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>WBC &gt; 10,000</td>
<td>50 (71.4%)</td>
<td>47 (82.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Culture positive</td>
<td>53 (75.7%)</td>
<td>50 (87.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/US multiple loculations</td>
<td>4 (5.7%)</td>
<td>5 (8.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Successful outcome</td>
<td>47 (67.1%)</td>
<td>50 (87.7%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Length of treatment (days)</td>
<td>15.5±4</td>
<td>7±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (4.2%)</td>
<td>1 (1.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
after streptokinase instillation, which was easily managed with analgesic therapy.

Multiple regression analysis disclosed as sole independent favorable factor for pleural drainage, the use of fibrinolysis during the course of chest tube drainage \((P=0.006, \text{ odds ratio 4.29, 95\% CI 1.51–12.14})\).

Multiple localizations at chest CT scan were the only unfavorable factor for effective pleural evacuation \((P=0.005, \text{ odds ratio 0.12, 95\% CI 0.02–0.54})\).

Although early management of complicated parapneumonic pleural effusion, 30 patients (23.6\%) were managed with surgical intervention (VATS or open thoracotomy decortication). In this group of patients chest tube thoracostomy was performed later than 2 weeks from symptoms’ onset in 60\% of cases and frank pus was aspirated at thoracentesis before chest tube thoracostomy in 73\% of cases. Multiple localizations of the complicated parapneumonic effusion at the initial chest CT scanning (despite the free-yielding aspiration at thoracentesis, which was the major indication for chest tube thoracostomy), were documented in 63\% of patients. Twenty-three (32.9\%) were from group A, while 7 (12.3\%) from group B \((P<0.05)\).

4. Comments

The treatment for pleural sepsis involves empirical antibiotics for the most prevalent bacteria plus expedient and safe drainage of the infected pleural cavity. There are various methods of draining the pleural cavity. These include needle aspiration, chest tube drainage, thoroscopic drainage and open thoracotomy. Recent advances in this area include the administration of adjunctive intrapleural fibrinolytic agents to facilitate fluid drainage [4-10].

The authors agree that complicated parapneumonic effusion management should be tailored to disease stage [3,11-13]. In order to define the role of chest tube thoracostomy-fibrinolysis at an early stage of thoracic empyema as the initial treatment modality, the authors conducted this prospective randomized study, towards evidence-based practice. The clinical efficacy of adjunctive fibrinolysis using streptokinase had been evaluated in four controlled trials [3-7]. Previous prospective randomized studies were characterized by the small population, the large proportion of patients with comorbidities and by the inclusion of patients at all stages. In our study, the population used was a fairly homogeneous group in which the majority of patients (90.5\%) were managed in less than 2 weeks from symptoms’ onset and in most of the cases (84.2\%) the aspirated fluid was thin, while frank pus at thoracentesis or multiple localizations at chest imaging were recorded in less than 17.5 and 8.8\% of cases, respectively. Our study included only primary thoracic empyema without concomitant end-stage disease compared to other series [14,15]. Both groups were well balanced for age, gender, time interval from symptoms’ onset to invasive thoracic empyema management, pleural fluid characteristics and findings at chest imaging (Table 2). A fairly large number of patients was included in the study groups.

Multiple regression analysis results disclosed that for established complicated parapneumonic effusion use of fibrinolysis during the course of chest tube drainage was the only favorable independent factor. No other study has used multivariate analysis in order to evaluate the role of fibrinolytics during the course of chest drainage.

Chest tube thoracostomy failure rate proved to be 32.9\%, being similar to other studies [14,15]. On the contrary, the failure rate after use of fibrinolitics was only 12.3\% which was statistically significantly lower than that of chest tube thoracostomy. Moreover, streptokinase morbidity was not substantial in order to be a contra-indication for routine use. Mortality reached 4.2\% for group A and 1.7\% for group B. This is in accordance to that demonstrated in previous reports [14]. It is widely accepted that if underlying diseases co-exist the death rate significantly increases up to 44-75\% [14-16].

In a recent well-organized study by Maskell et al. [7], the intrapleural instillation of streptokinase did not improve mortality, the rate of surgical interventions or the length of hospitalization. The fact that our results are completely different should be attributed to the entirely diverse characteristics of the two studied populations.

In conclusion, fibrinolytic agents are a useful adjunct in the management of complicated parapneumonic. Intrapleural fibrinolytics, if used early in the fibrinopurulent stage of a parapneumonic effusion, before extensive collagen is deposited in the pleural space, decrease the rate of surgical interventions (VATS or open decortication) and the length of hospital stay with minor associated morbidity. The authors suggest that the combination of chest tube drainage and fibrinolysis should be used in a routine fashion for every thoracic empyema that is less than 2 weeks old from symptoms’ onset.

References


