Comparison of the methods of fibrinolysis by tube thoracostomy and thoracoscopic decortication in children with stage II and III empyema: a prospective randomized study

Ufuk Cobanoglu, Fuat Sayr, Salim Bilici, Mehmet Melek, Abidin Şehitoğlu, Van State Hospital Department of Thoracic Surgery, Van, Turkey

Abstract

Today, in spite of the developments in imaging methods and antibiotic therapy, childhood pleural empyema is a prominent cause of morbidity and mortality. In recent years, it has been shown that there has been an increase in the frequency of pleural empyema in children, and antibiotic resistance in microorganisms causing pleural empyema has made treatment difficult. Despite the many studies investigating thoracoscopic debridement and fibrinolytic treatment separately in the management of this disease, there is not enough studies comparing these two treatments. The aim of this study was to prospectively compare the efficacy of two different treatment methods in stage II and III empyema cases and to present a perspective for treatment options.

We excluded from the study cases with: i) thoracoscopic intervention and fibrinolytic agent were contraindicated; ii) immunosuppression or additional infection focus; iii) concomitant diseases, those with bronchopleural fistula diagnosed radiologically, and Stage I cases. This gave a total of 54 cases: 23 (42.6%) in stage II, and 31 (57.4%) in stage III. These patients were randomized into two groups of 27 cases each for debridement by VATS or fibrinolytic agent administration (Figure 1).

Introduction

Bacterial pneumonia in children is frequently complicated by pleural effusion and its incidence varies between 20 and 91%.1,2 When pleural effusion is treated with appropriate antibiotics, it generally recovers spontaneously. When treated inappropriately, as a result of fibrin deposition, the accumulation of bacterial products and leukocytes in the pleural cavity and complicated parapneumonic effusion develop.1

Causes such as socioeconomic insufficiency, insensitive antibiotic use, pneumonia findings which mask the symptoms of empyema resulting in delayed diagnosis, use of antibiotics only in the acute stages, and consequent delays in referral to a thoracic surgery unit, all play a role in the conversion of parapneumonic effusion to empyema.

According to the classification of the American Thorax Association, empyema develops in three different stages:4 stage I (exudative), fluid accumulation, pH over 7.2, lactate dehydrogenase below 1000 IU/L, glucose over 60 mg/dL, negative culture and no loculations; stage II (fibrinopurulent), pH below 7.2, lactate dehydrogenase over 1000 IU/L, glucose below 60 mg/dL, increased loculation or positive culture or presence of suppuration in the pleural cavity by fibrin deposition (empyema); stage III (organized), in addition to stage II, organized multiloculated parapneumonic effusion, trapped lung and pleural cortex formation.

Treatment options for this disease are observation, therapeutic thoracotomy, tube thoracostomy, intrapleural fibrinolytics, decortication with thoracotomy and scarring, and open drainage procedures.5,6

In the progress of a thoracic empyema or complicated (persistent or loculated) parapneumonic effusion, viscous fluid with obstructing fibrinous debris and non-communicating fluid locules may develop; a single thoracic tube for drainage remains insufficient.7,8 Insufficient treatment in the fibrinopurulent period causes pleural fluid organization and scar formation in the pleural cavity and the neighboring lung tissue.7 In order to prevent this, and to clear out the fibrinous debris, numerous studies suggest video-assisted thoracoscopic decortication (VATS) or fibrinolytic treatment in the early stages.8-11

The aim of this study was to prospectively compare thoracoscopic debridement and fibrinolytic treatment in cases with stage II and III empyema and to present a perspective for treatment options.
were performed. The number of cells and the cell characteristics were determined in the pleural fluid. Furthermore, the pH, protein, glucose, lactate dehydrogenase and density measurements in the pleural fluid and simultaneous serum protein, serum glucose and lactate dehydrogenase measurements were taken. The pleural fluid was sent for Gram staining and culture. The presence of the following characteristics in the thoracentesis fluid led to the diagnosis of empyema: pH < below 7.2, glucose below 60 mg/dL, protein over 3 g/dL, LDH over 1000 IU, leukocyte over 5x10^9/L or presence of bacteria in direct examination or culture of the pleural fluid.

In patients who were diagnosed with empyema, as suggested in the book of Pediatric Respiratory Medicine, an empiric treatment with ampicillin sulbactam plus cepotaxime was initiated. This regime was then changed when necessary according to culture results.

An 18-24 Fr chest tube was initially inserted in all cases and connected to a closed drainage system and 15-20 cm H2O negative suction was applied. Thoracic tube insertion was performed in the operating theater under intravenous sedation and monitoring.

In 27 cases undergoing video-assisted thoracoscopic surgery, routine pulse oximetry, ECG, non-invasive blood pressure monitoring and end-tidal CO2 measurements were routinely performed during the anesthesia. During the procedure, the patients were placed in the lateral decubitis position. Video equipment was placed on both sides of the head. In all cases, a 5 mm 30° scope (Karl Storz, Tuttlingen, Germany) was used. The fifth or sixth intercostal space in the mid-axillary line was selected as the primary port (5 mm) site. The apical port (10 mm) was inserted through the third intercostal space in order to better visualize the costophrenic sinus, diaphragm and the inferior region. The third port (10 mm) was inserted at the auscultation triangle in order to explore the anterior thoracic wall and mediastinal structures. During the thoracoscopy, the mediastinum, the pericardium, the chest wall, the lung and the diaphragm were carefully investigated. Large cup forceps were used to clear the debris. Fluid and debris particles were sent for culture. When the procedure was brought to an end, the ports were removed under direct vision and insertion of the 18-24 Fr thoracic tube into the intrapleural space followed. Following this, for the other 27 cases in which a remarkable amount of fluid persisted despite drainage of less than 50 mL determined by ultrasonography and direct chest X-ray, enzymatic debridement was performed using streptokinase (STK) (Streptase; Hoechst, Istanbul). Before and after the fibrinolytic treatment, the prothrombin time, activated partial thromboplastin time (aPTT) and fibrinogen were measured and a complete blood count was performed. Following steroid and antihistaminic treatment as pre-medications, the patients were laid on one side where the lesion was in the upper position. Normal saline with 250,000 U/100 mL STK was administered into the pleural cavity through the thoracic tube in 70-120 mL volume once a day and the tube was held by a clamp for 4-6 h. The period of fibrinolytic treatment was determined as 4.45 days (3-5 days). The first drainage fluid was sent for culture and the thoracic tubes were connected to a -15-20 cm H2O negative suction after the clamp was opened.

The pleural fluid drainage, after the video-assisted thoracoscopic surgery and STK application, were recorded for 24 h.

In the VATS cases, conversions to minithoracotomy, and in the fibrinolysis cases, conversions to VATS were considered failures. Radiological recovery was assessed by the criteria of Sanchez et al.

These were: i) maximum (normal or near-normal pulmonary X-ray); ii) medium (pleural effusion cleared in 50-80%); iii) minimal (pleural effusion cleared in less than 50%); iv) none (no changes).

In these cases, thoracic tube drainage was terminated when the daily amount of drainage decreased to less than 50 cc, pleural fluid culture became negative, and radiological healing and full expansion were detected.

All cases were assessed for a variety of parameters, such as the success of the two treatment modalities, duration of thoracic tube drainage, length of hospital stay (LHS), morbidity, mortality and cost.

Figure 1. Treatment algorithm applied in children with empyema.
Statistical analysis

The descriptive statistics for the considered characteristics for the groups were expressed as median, mean, standard deviation, minimum and maximum values. The Kruskal-Wallis test was used to compare for these characteristics. The Z test was used to compare rates. The statistical significance level of the calculations was accepted as 5% and these calculations were performed using the SPSS (ver. 13) statistical pocket program.

Results

Twenty-two (40.74%) of the cases were female and 32 (59.26%) were male. Patients’ characteristics at the time of diagnosis are presented in Table 1.

Pleural effusion was observed on the right in 31% of cases and on the left in 23% of cases. No bilateral effusion was observed. The most frequent symptoms were respiratory distress, cough, tachycardia and fever (Table 2).

Pleural infections were found to be consequent to primary empyema in 17% and to pneumonia in 37% of cases. Pathologies frequently accompanying thoracic empyema were additional pulmonary diseases, such as bronchiectasis, perforated pyodatic cyst, and congenital pulmonary disease (20.37%) (Table 2). The results of patients’ blood, serum and pleural fluid samples, and microbiological analyses are presented in Table 3. Accordingly, bacterial growth in the blood culture was observed in 20 (37.03%) cases, and in the pleural fluid culture in 38 (70.37%) cases. The most frequently isolated (27.7%) microorganism was the Streptococcus milleri group.

The postoperative results of the cases are shown in Table 4. Accordingly, with respect to the duration of symptoms following the operation, duration of thoracic tube drainage, and the length of stay in hospital, the VATS group demonstrated shorter times than the STK with a statistically significant difference between groups (P=0.001).

The lungs were found to be fully expanded after the procedure in 19 (70.37%) of the 27 cases receiving fibrinolytic treatment and in 21 (77.77%) of the 27 cases undergoing the VATS procedure, and this was considered successful (Figure 1). The difference in success rates between the two groups was not significant (P=0.533). Following the fibrinolytic treatment, 8 (29.63%) cases in whom the lungs had not fully expanded, underwent debridement by VATS. In one case, since lung expansion was not achieved, decortication was completed by thoracotomy. Six (22.23%) cases who had undergone debridement by VATS were further converted to thoracotomy as full expansion was not achieved (Figure 1).

Complication rate was 12.96% of cases with no statistical difference between the two groups (P=0.589). In 4 (12.81%) cases receiving fibrinolytic treatment, hypertension, hemorrhage, sudden chest pain and sudden aphonia developed. VATS was performed in 3 (11.11%) cases; 2 cases had prolonged air leaks, and one had a wound infection. No mortality was observed.

The cases were followed-up monthly for the first three months and then on a yearly basis. There were no remission and all patients enjoy good health.

Discussion

Investigators who recommended VATS reported that fibrinolytic treatment is uncomfortable and that its resolution takes a long time. They also reported that it is not very successful in clearing out the loculation. Those who defended the fibrinolytic treatment emphasized that this method could be easily applied, decreases the rising cost of material use and preserves patients from the risk of morbidity posed by thoracic operations.

Cooté and Kay in 2005 investigated the clinical results of operative and non-operative treatment in children and adults with empyema in the Cochrane Collaboration and reported that fibrinolytic treatment resulted in lower hospital costs in the early stages. In another study, it was reported that VATS required a shorter hospital stay and gave better results. However, these studies on only a few subjects showed that larger series are needed. W hile in their retrospective analysis Doski et al. showed that VATS led to a shorter hospital stay, the difference in success rates between the two groups was not significant (P=0.589). In 4 (12.81%) cases receiving fibrinolytic treatment, hypertension, hemorrhage, sudden chest pain and sudden aphonia developed. VATS was performed in 3 (11.11%) cases; 2 cases had prolonged air leaks, and one had a wound infection. No mortality was observed.

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**Table 1. Patients’ characteristics at diagnosis.**

| Characteristic                  | STK (n. 27) | VATS (n. 27) | P   |
|--------------------------------|------------|-------------|-----|
| Age (years)                    | 7.30±2.76  | 8.74±2.60   | 0.050 |
| Sex (M/F)                      | 17/10      | 9/18        | 0.023 |
| Weight (kg)                    | 25.30±6.31 | 26.96±8.35  | 0.412 |
| Height (cm)                    | 121±16     | 122±13      | 0.445 |
| Oxygen support (L/min)         | 0.72±0.74  | 0.69±0.56   | 0.871 |
| Duration of symptoms in days   | 8.0±1.7    | 9.6±4.3     | 0.413 |
| Lateral effusion thickness (mm)| 75±39      | 79±21       | 0.844 |
| Area of shadowing (%)          | 51±21      | 54±22       | 0.816 |

**Table 2. Symptoms of the cases and accompanying diseases in the cases.**

| Symptom                                  | N. cases (%) |
|------------------------------------------|--------------|
| Fever (>38°C)                            | 35 (64.81)   |
| Cough                                    | 45 (83.33)   |
| Respiratory distress                     | 47 (87.03)   |
| Pyrulent mucus                           | 16 (32.62)   |
| Cyanosis                                 | 5 (9.25)     |
| Tachycardia                              | 37 (80.31)   |
| Pleuritic type chest pain                 | 15 (27.77)   |
| Abdominal pain                           | 4 (7.40)     |
| Severe anemia                            | 9 (16.66)    |

**Table 3. Coexisting illnesses**

| Coexisting Illness          | N. cases (%) |
|----------------------------|--------------|
| Cardiac disease            | 3 (5.55)     |
| Additional respiratory disease | 1 (20.37) |
| Diabetes mellitus          | 2 (3.70)     |
| Joint disease              | 3 (5.55)     |
| Gastro esophageal disease  | 6 (11.11)    |
| Neurological disease       | 2 (3.70)     |
| Kidney disease             | 2 (3.70)     |
| Liver disease              | 2 (3.70)     |
| Hematologic disease        | 1 (1.85)     |
between the two groups.

In the present study, VATS had advantages with respect to the duration of thoracic tube drainage, duration of symptoms after the procedure, and the length of hospital stay \((P=0.001)\). Fibrinolytic treatment had cost advantages \((P=0.0001)\) (Table 4). The success rate in those undergoing fibrinolytic treatment was 70.37\% and the failure rate was 29.62\%; these were 77.77\% and 22.22\% for VATS, respectively. There was no significant difference between the two groups in success and failure rates \((P=0.533)\).

The failure rates for both groups in this study were higher than that of other series (fibrinolitics 5-16\%, VATS 0-20\%).\(^{9,19,20}\) This result may be due to the fact that 76.3\% of patients did not receive any treatment, and in contrast to other studies\(^{9,15,19,20}\) most of the cases (57.4\%) were in stage III.

In conclusion, pleural fluid should be drained early and effectively before it becomes organized and before it changes into a hard pleural layer that is hard to manage. Drainage should be rendered faster by thoroscopic or enzymatic debridement if needed. The similar success rates of thoracoscopic drainage and enzymatic debridement, and the lower cost of enzymatic drainage, means that intrapleural streptokinase treatment is an effective and safe method for reducing the need for surgery in complicated empyema.

### Table 3. Patients’ blood or serum, pleural fluid, and microbiological characteristics.

| Analyzed material/parameters | STK (n. 27) | VATS (n. 27) | P     |
|------------------------------|------------|-------------|-------|
| **Blood or serum**           |            |             |       |
| White blood cell \((\mu L)\)  | 15,516±6,018 | 18,665±6,551 | 0.586 |
| Hb \((g/L)\)                 | 10.0±2.3   | 9.6±1.3     | 0.484 |
| PLT \((/mm^3)\)              | 395,386±236,914 | 454,134±236,566 | 0.390 |
| ESR \((mm/h)\)               | 71.9±31.3  | 94.8±36.6   | 0.038 |
| C-reactive protein > 100 mg/mL, n (%) | 11 (40.74) | 15 (55.55) | 0.062 |
| **Pleural fluid**            |            |             |       |
| Turbid or purulent, n (%)    | 18(66.6)   | 14(51.85)   | 0.262 |
| pH, mean ±SD                | 7.25±0.49  | 7.08±0.42   | 0.451 |
| Glucose, mg/dL              | 30 (0-241) | 5 (1-111)   | 0.173 |
| Lactate dehydrogenase, IU/L | 2.559 (309-40,990) | 1.340 (679-23,600) | 0.361 |
| **Microbiological characteristics** |           |             |       |
| Positive blood culture n. (%) | 21 (77.77) | 17 (62.96) | 0.227 |
| Streptococcus milleri group (S. intermedius, S. constellatus, S. mitis) | 10 (37.03) | 5 (18.5) | 0.121 |
| S. pneumoniae                | 5 (18.5)   | 7 (25.92)   | 0.511 |
| Other streptococci           | 2 (7.4)    | 3 (11.11)   | 0.638 |
| Enterobacteriaceae           | 3 (11.1)   | 4 (14.81)   | 0.885 |
| Aerobic bacteria             | 4 (14.81)  | 3 (11.11)   | 0.885 |
| Staphylococcus aureus        |            |             |       |
| Antibiotic-sensitive         | 2 (7.40)   | 3 (11.11)   | 0.638 |
| Meticillin-resistant         | 3 (11.1)   | 2 (7.40)    | 0.999 |
| Enterococci                  | 2 (7.40)   | 2 (7.40)    | 0.999 |
| Other                        | 2 (7.40)   | 1 (3.70)    | 0.551 |

### Table 4. Postoperative results of the cases.

|                | STK         | VATS        | P    |
|----------------|-------------|-------------|------|
| **Post-therapy days of O2 support** | 2.3±1.4     | 2.1±2.0     | 0.911 |
| **Afebrile days after intervention** | 3.9±2.1     | 3.4±2.4     | 0.782 |
| **Analgesia doses**               | 22.1±18.9   | 25.4±13.1   | 0.561 |
| **Chest tube removal time**       | 9.48±2.50   | 6.56±1.55   | 0.0001 |
| **Duration of hospital stay**     | 10.37±2.29  | 7.41±1.45   | 0.0001 |
| **Duration of symptoms after intervention** | 6.78±1.69   | 3.78±1.25   | 0.0001 |
| **Fluid drainage**                |            |             |      |
| Initial drainage amount           | 394.93±220.65 | 379.19±230.14 | 0.786 |
| Postoperative drainage amount     | 850.59±301.91 | 865.78±444.41 | 0.884 |
| Total drainage amount             | 1245.52±361.43 | 1243.96±552.81 | 0.990 |
| **Postoperative respiratory function test** |           |             |      |
| PV (%)                         | 62±7.021   | 55±10.13    | 0.467 |
| FEVI (%)                       | 72±6.141   | 77±6.231    | 0.618 |
| FEVI/FVC (%)                   | 112±4.268  | 119±3.233   | 0.578 |
| PEF (%)                        | 64±5.012   | 59±8.141    | 0.312 |
| MEF 25-75 (%)                  | 84±3.792   | 72±5.897    | 0.297 |
| N. cases with successful intervention | 19 (70.37) | 21 (77.77) | 0.533 |
| **Total cost**                 | 612.06±114.06 TRY* | 1,515.00±217.14 TRY* | 0.0001 |

* Turkish Lira; **, United States Dollars.

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