Editorial

Initial treatment of septated parapneumonic empyema with drainage plus fibrinolytic agents is equally effective as video-assisted thoracoscopic surgery, and is suitable as first-line therapy

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Abstract: It is thought that 0.6-2% of cases of pneumonia in children are complicated by parapneumonic empyema. The mainstay treatment options for empyema are pleural chest drainage plus fibrinolysis or video-assisted thoracoscopic surgery (VATS). Marhuenda *et al*. reported the results of a prospective, multicenter, clinical trial in which patients with parapneumonic empyema were randomized to either drainage plus urokinase or to VATS. That showed that the median postoperative stay, median hospital stay, and number of febrile days after treatment were not significantly different between the VATS group and the urokinase group. Only three other prospective randomized trials have been conducted with the same objective. The results in these studies had partially different among four trials. But all studies described that it is apparent that VATS is not more effective than fibrinolytic treatment. Intrapleural fibrinolytic treatment, which is much less invasive and lower inexpensive than VATS, is an effective and safe alternative to surgical treatment of complicated empyema. VATS would be reserved for patients who fail to respond to chemical/enzymatic debridement. We need additional randomized controlled trials with relevant inclusion/exclusion criteria and adequate sample sizes to determine the optimal therapy for parapneumonic-complicated empyema in children.

Keywords: Empyema; pediatric; intrapleural fibrinolytic treatment; video-assisted thoracoscopic surgery (VATS)

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It is thought that 0.6-2% of cases of pneumonia in children are complicated by parapneumonic empyema (1). The mainstay treatment options for empyema are pleural chest drainage plus fibrinolysis or video-assisted thoracoscopic surgery (VATS). These two treatments aim to degrade the septation and solid debris, which are composed of fibrin deposits. These procedures ultimately improve pleural reabsorption and alleviate empyema.

Chest tube drainage plus intrapleural fibrinolytic treatment was reported to be superior to chest tube drainage alone in previous studies (2,3). In the former procedure, fibrinolytics such as urokinase, streptokinase, or tissue plasminogen activator are administered into the pleural space. In 2005, The British Thoracic Society recommended drainage plus intrapleural fibrinolytics for treating empyema in children. At the same time, many retrospective and observational studies have recommended VATS as first-line therapy for empyema because of its perceived benefit of a shorter hospital stay compared with other procedures (4-7).

Marhuenda *et al*. (8) reported the results of a prospective, multicenter, clinical trial in which patients with parapneumonic empyema were randomized to either drainage plus urokinase or to VATS. A total of 103 patients were randomized to treatment and analyzed. To our knowledge, only three other prospective randomized trials have been conducted with the same objective (*Table 1*) (9-11). The study by Marhuenda *et al*. was the largest of these randomized trials. The authors reported that the median postoperative stay (10 *vs*. 9 days, respectively), median hospital stay (14 *vs*. 13 days, respectively), and number of febrile days after

Table 1 Clinical outcomes of randomized controlled trials comparing drainage plus fibrinolytic agents with video-assisted thoracoscopic surgery for the treatment of parapneumonic empyema in children

Study	Sonnappa *et al*. 2006 (United Kngdom) (9) Treatment group [n]			St Peter *et al*. 2009 (United States) (10) Treatment group [n]			Cobanoglu *et al*. 2011 (Turkey) (11) Treatment group [n]			Marhuenda *et al*. 2014 (Spain) (8) Treatment group [n]		
	Urokinase [30]	VATS [30]	P	tPA [18]	VATS [18]	P	Streptokinase [27]	VATS [27]	P	Urokinase [50]	VATS [53]	P
Length of stay (days)	6	6	0.31	6.8	6.9	0.96	10.4	7.4	<0.01	9	10	0.45
Charges ($)	9,127±6,914	11,379±10,146	<0.01	7,600±5,400	11,700±2,900	0.02	387±72	957±137	<0.01	NA	NA	NA
Failure rate, n (%)	5 (16.7)	5 (16.7)	NA	3 (16.7)	0 (0)	NA	8 (29.6)	6 (22.2)	0.53	5 (10.0)	8 (15.1)	0.47
Chest tube kept *in situ* (days)	NA	NA	NA	NA	NA	NA	9.5	6.6	<0.01	5	4	<0.01
Number of febrile days after intervention	2.5	2.5	0.635	3.8	3.1	0.46	3.9	3.4	0.78	6	4	0.62

P values are presented as the median or mean ± standard deviation. VATS, video-assisted thoracoscopic surgery; tPA, tissue plasminogen activator; NA, not available.

treatment (4 *vs*. 6 days, respectively) were not significantly different between the VATS group and the urokinase group. Initial treatment of septated parapneumonic empyema with drainage plus fibrinolytic agents is as effective as VATS in children. In their conclusion, the results of this multicenter study suggest that intrapleural fibrinolytic treatment should be considered as initial treatment of septated parapneumonic empyema for three reasons. First, many secondary pediatric hospitals are able to place chest tubes, enabling the administration of fibrinolytics, but are often unable to perform VATS. Second, the administration of fibrinolytics is much less invasive than VATS. Third, surgical therapy is more expensive than fibrinolytic therapy.

The results of the other three prospective, randomized trials that compared drainage plus fibrinolysis with VATS for the treatment of empyema in children are listed in *Table 1* (9-11). All three studies were conducted in single centers and had similar designs. In the study by Sonnappa (9) published in 2006, which included 60 patients, and the study by St Peter (10) published in 2009, which included 36 patients, there were no statistically significant differences between fibrinolysis and VATS regarding the length of post-treatment stay, total hospital stay, or the number of febrile days after treatment. The consistent results of these three studies highlight that chest tube drainage with fibrinolytic instillation and VATS are equally effective for the treatment of empyema in children. In contrast, Cobanoglu's study (11) published in 2011, which included 54 patients, showed that the length of post-treatment hospital stay and the time for which the chest tube was kept *in situ* were significantly shorter in the VATS group than in the fibrinolysis group. There were no significant differences with respect to failure rates or number of afebrile days after the interventions between the two groups. Marhuenda's and Cobanoglu's studies included patients with parapneumonic -complicated (fibrinopurulent or organizational) pleural effusion but not patients with exudative effusion. These two studies included patients with more severe empyema than the other studies.

All of the studies reported adequate randomization methods and complete data for each treatment. Based on these characteristics, all of the studies had a low risk of bias. The discrepancy between Cobanoglu's study and the other studies may relate to differences in the fibrinolysis agent protocols. In Cobanoglu's study, streptokinase was used as the fibrinolytic agent and the chest tube was kept *in situ* for 9.5 days, which was longer than that in the other studies. The success rate in those undergoing fibrinolytic treatment was 70.4%, which was much lower than that of the other

three studies. These findings indicate that the streptokinase regimen used in that study is unsuitable for the treatment of parapneumonic-complicated pleural effusion.

The three earlier randomized studies (9-11) reported that the overall costs and hospital charges were significantly higher in the VATS group than in the fibrinolysis group. Regarding post-treatment complications, St Peter reported that two patients in the VATS group required ventilator support after therapy, and one of them continued to have progressive sepsis resulting in transient renal failure requiring temporary dialysis. In the same study, none of the patients in the fibrinolysis group showed clinical deteriorations after starting therapy, and none of the patients in either group were readmitted after discharge for ongoing or recurrent pulmonary disease. Sonnappa reported that four patients developed lung abscess (three in the VATS group), two developed hemolytic uremic syndrome (both in the VATS group), and one developed acute glomerulonephritis (urokinase group). Marhuenda reported two major treatment-related complications: severe bronchospasm requiring tracheal intubation in the urokinase group and bronchopleural fistula in the VATS group. There were no significant differences in the incidence of post-treatment complications, but we consider that more severe complications are likely to occur in the VATS group, whose procedure mechanically damage the lung and pleura.

Marhuenda's study is particularly important, being the first randomized, multicenter clinical trial to compare drainage plus urokinase with VATS for the treatment of parapneumonic empyema in children. However, this study has some limitations that need to be discussed. First, it was conducted without initially calculating the required sample size because of the unfeasibly large number of patients that would have been needed to perform an equivalence study. Second, because the diagnostic sonographic images did not undergo centralized review, it is possible that some variability exists between the sonographic readers in the different centers.

Our conclusions are based on the results of four randomized trials, which had some methodological limitations and involved relatively small numbers of patients. It is apparent from these studies that VATS is not more effective than fibrinolytic treatment. The similar success rates of thoracoscopic drainage and enzymatic debridement, together with the lower cost and reduced invasiveness of fibrinolytic treatment, suggest that intrapleural fibrinolytic treatment is an effective and safe alternative to surgical treatment of complicated empyema. The results of the clinical trials of primary fibrinolytic therapy in children with empyema showed that most patients were successfully treated without requiring surgical treatment (7).

Surgical therapy should be reserved for patients who fail to respond to chemical/enzymatic debridement. Therefore, it is important to identify risk factors associated with patient who fail fibrinolytic therapy and who may benefit from primary mechanical debridement. Additional randomized controlled trials with relevant inclusion/exclusion criteria and adequate sample sizes are needed to determine the optimal therapy for parapneumonic-complicated empyema in children. These studies should include the extensive informations about re-intervention cases with this condition.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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