Title	Timely thoracoscopic decortication promotes the recovery of paediatric parapneumonic empyema
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Introduction

Parapneumonic empyema is defined as the presence of pus in the pleural cavity secondary to pneumonia. According to the World Health Organisation in 2006, pneumonia remained the key leading cause of death in children less than 5 years old. The estimated prevalence of childhood pneumonia in developed world was approximately 33 per 10000 and 14.5 per 10000 in children younger than 5 and from 0 to 16 years old respectively [1]. Parapneumonic empyema had previously been a rare complication of childhood pneumonia which constituted less than 1% among those hospitalized for the disease [2]. Despite the ubiquitous uptake of pneumococcal vaccine leading to the bacteria's consequential decline in the incidence of childhood pneumonia worldwide, the prevalence of parapneumonic empyema has been escalating recently [3-8]. The prognosis of parapneumonic empyema in children is generally good with less than 5% mortality rate [9] as compared to near 20% in adults [10]. Notwithstanding, its impact on family and hospital burden is still considerable.

Being one of the most commonly encountered yet difficult to manage paediatric thoracic conditions, there are myriads of management strategies towards parapneumonic empyema advocated worldwide. These include both conservative and surgical management. Hospitalisation and high dose broad spectrum intravenous antibiotics are the first step of management employed in most centres. Therapeutic

thoracocentesis can also be used for empyema drainage. However, the British Thoracic Society guidelines recommended a chest tube for cases in which the first thoracocentesis failed to adequately drain the effusion in order to avoid multiple attempts [7]. Hence, insertion of chest tube drainage remained the traditional and mainstay of management for majority of cases. Although high dose intravenous antibiotics and chest drain insertion may be adequate in some cases, chest tube drainage is frequently impaired by the presence of fibrin strands and loculation in complicated cases. For these patients, chemical debridement with fibrinolytic agents such as urokinase, streptokinase and tissue plasminogen activator has been proposed [11], but surgical decortication of empyema remains the last resort of management in refractory cases where these measures failed [12]. There are several non-randomised studies comparing patients who underwent thoracoscopic decortication versus thoracotomy and made credits on the thoracoscopic approach for its advantage of decreased postoperative pain, faster recovery, shorter hospital stay and less long term morbidity [11]. However few studies explored the effect of timing of decortication on the peri-operative outcome. Therefore this study was carried out to investigate the potential benefit of early decortication in paediatric patient with parapneumonic empyema.

Methods

A retrospective analysis was conducted using our electronic patient database for patients with parapneumonic empyema treated at our tertiary referral centre between 1999 and 2013. An approval from the ethics committee was sought before conducting the study. All patients with confirmed diagnosis were identified and their records were reviewed. No patient was excluded from the study. All patients received chest X-ray and computed tomography of thorax to confirm the diagnosis and to evaluate disease progression. All patients received intravenous antibiotics as soon as the diagnosis of pneumonia or empyema was made and chest drainage by means of chest drain or pigtail catheter insertion was given to patients subsequently for drainage. No fibrinolytic agent was used in any of the patients because its use in pleural cavity was not licensed in our locality. Indication for thoracoscopic decortication included 1) persistent fever >38.5 degree Celsius or increasing white cell count despite appropriate intravenous antibiotics and chest drainage for more than 72 hours or 2) loculated empyema on reassessment computed tomography of thorax. This protocol has been consistent during the whole study period and emergency operations were arranged once patients met the criteria.

Selected patients were transferred to intensive care unit for post-operative monitoring following the procedure. All patients were continued with intravenous antibiotics post-operatively with regular chest physiotherapy. The demographics of patients

including gender, age at presentation, maturity at birth, weight at birth, vaccination received and past medical history were collected. Their presenting symptoms, date of fever from symptoms onset, laboratory results including white cell counts, the timing of computed tomography received, the site and size of empyema, any presence of loculation, the duration and output of chest drain insertion were analysed. Peri-operative data such as timing of operation, total operative time and intraoperative blood loss were recorded. Medical records were reviewed for days of post-operative intubation, length of post-operative intensive care unit stay, presence of post-operative fever, complications, length of post-operative hospitalization and long term complications on follow-up.

Thoracoscopic decortication was performed under general anaesthesia. Patient was placed in lateral decubitus position with the diseased side up. The ipsilateral arm was placed and fixed over patients' head. Single lung ventilation was not necessary. Pneumothorax with insufflation of carbon dioxide at low flow (1 L/min) and low pressure (2-4 mmHg) was usually adequate for good exposure. Three 5mm ports were placed, one for the camera and two additional ports as working channels. The camera port was inserted in the third intercostal space at the mid-axillary line with open method. If a chest drain was inserted before the operation then the site was used for camera port placement. A 5 mm 30° telescope was then inserted to directly visualize

the placement of the two working ports, which were inserted in the fourth intercostal space at the anterior and posterior axillary line respectively. Fibrinous and purulent material in the pleural cavity was suctioned. Loculations were broken down with forceps and pleura decorticated mechanically. Thoracic cavity was then irrigated after adequate debridement and decortication. Once expansion of lung is visualized and confirmed, a chest tube would be left in-situ post-operatively and connected to under water seal. Reassessment chest X-rays were done during the post-operative period for monitoring clinical progress.

Patients were divided into 2 groups according to the duration from symptom onset to operation. The arbitrary cut-off point of 14 days to define early surgery was used because we postulated that patient can benefit more if surgery was performed during the initial exudative or fibrinopurulent phase of empyema.

All data were statistically compared. Statistical analysis of data was performed using SPSS (version 17; SPSS, Chicago, IL). Continuous variables were analyzed using Student's t test, ordinal variables were analyzed using Mann-Whitney U test and categorical variables were analyzed using chi-square test respectively. Data were presented as mean ± standard deviation and range. $p < 0.05$ was considered statistically significant.

Results

A total of 37 patients were admitted for the diagnosis of empyema during the study period, with 9 patients being treated medically and 28 eventually required operative treatment. All the 9 patients treated successfully with conservative treatment responded well to antibiotics within 14 days. 12 males and 16 females received thoracoscopic decortication. The mean age of patients was 4.5 years old (range 12 months to 14 years). The mean body weight at the time of operation was 20.0 kg (range 9.9 - 47.5kg). Right-sided empyema was involved in 15 patients. 6 patients had received pneumococcal vaccination prior to the onset of chest symptoms. All patients received thoracic computed tomography before operation to confirm the diagnosis. Intravenous antibiotics and chest drainage procedure were given to all patients once the diagnosis was made.

Subgroup analysis for the 2 groups of patients was shown in Table 1. Patients who had operation within 2 weeks from symptom onset were assigned to group 1 (16 patients) and those more than or equal to 2 weeks were assigned to group 2 (12 patients). Both groups had similar demographics in terms of age, sex, body weight and laterality of lesion. 6 (37.5%) patients in group 1 had chest drain inserted before operation and 7 (58.3%) in group 2. The rest of the patients who did not receive chest drain insertion underwent pigtail catheter insertion for drainage. None of the patients

in group 1 received chest drainage revision after its insertion but it was necessary in 5 of the patients in group 2.

Group 1 patients received thoracoscopic decortication at 9.5 days on average (range 5-13 days) while those in group 2 had operation at 18.4 days (range 14-25 days). The mean operative time in group 1 was comparable to that of group 2 (80.3 vs 95.3 minutes, p=0.3). Mean operative blood loss in group 1 and 2 were 46.9 and 106.3 ml respectively (p=0.06). One patient in group 1 required conversion to open thoracotomy due to severe adhesion, while 2 patients in group 2 were converted due to same reason. Another patient in group 2 was converted due to severe bleeding and unstable hemodynamics.

3 patients in each group were kept intubated post-operatively but all of them were extubated the next day. The average intensive care unit stay for group 1 and 2 were 3.6 (range 0-10 days) and 7.8 days (range 0-23 days) respectively (p=0.1). The mean time for patient to become afebrile in group 1 was 2.5 days (range 1-10 days) while that for group 2 was 7 days (range 2-20 days, p=0.04). Chest drains were removed 5.0 days (range 3-9 days) and 8.9 days (range 2-31 days) after the operation for group 1 and 2 respectively (p=0.11). The duration of intravenous antibiotics required after operation was 9.6 days (range 2-17 days) in group 1 and 15.8 days (range 4-28 days) in group 2. Patients in group 1 showed significant shorter post-operative hospital stay

(mean 9.5 days, range 5-19 days) than group 2 (mean 20.4 days, range 5-42 days, p=0.003). The mean total hospitalization duration in group 1 was also significantly shorter than that of group 2 (mean 19.3 vs 38.8 days, p<0.001). Correlation study demonstrated a positive relationship between delay in operation and prolonged hospitalization (r=0.63, p=0.001). No major post-operative complication was encountered except for one patient requiring a second decortication for residual empyema. Summary of operative outcomes are shown in table 2.

Discussion

The best treatment approach for parapneumonic empyema has long been debated. Choices for treatment include conservative ways such as high dose intravenous antibiotics and chest tube drainage. In complicated cases which involve loculations, surgical intervention such as thoracoscopic or open decortication is beneficial and essential for drainage of empyema. The top priorities of treatment are to achieve clearance of infectious material in the pleural cavity and to attain re-expansion of the lungs. While empyema could lead to increased morbidity and mortality with its rapidly progressive course, it has been a question for surgeons on the optimal timing of decortication or surgical drainage.

The development of parapneumonic empyema is generally divided into three stages.

They are comprised of: Stage 1, which is an exudative phase characterized by a clear, thin, and sterile pleural effusion; Stage 2, which is a transitional or fibrinopurulent phase where the fluid becomes thick, infected, and purulent; and lastly Stage 3, which is an organizing or consolidative phase in which granulation tissue is formed and encases the lung [13]. Clinical and pathological stages of parapneumonic empyema pose great influence on choices as well as effect of different management strategies. For instance, during early stage where the effusion is of lower cellular content and better fluidity, thoracocentesis or chest tube insertion alone may be sufficient for achieving the treatment goals as mentioned above. However as the exudative phase is generally brief and often missed, most cases are admitted to the hospital during their fibrinopurulent phase in which fluid became denser and simple drainage may not be adequate for clearance of empyema [14].

Thoracoscopic decortication has been advocated to treat parapneumonic empyema for its benefits of less pain, more rapid recovery, lower postoperative morbidities, complications and mortalities. There are myriads of studies carried out to evaluate the role of thoracoscopic decortication in parapneumonic empyema. Shivachev et al recruited 87 children from 2004 to 2006 and proved that thoracoscopic decortication was effective in managing children with complicated parapneumonic effusion in the second (fibrino-purulent) stage, as well as by in the third (organizing) stage for some

[15]. Shahin et al found that 62% of the patients with stage 3 empyema in their study underwent VATS decortication with a successful outcome. The postoperative length of hospital stay was shorter and the postoperative complications were less when compared with the open approach [13]. In a large retrospective study by Bishay et al in 2008 with 114 children with empyema, 91% had full resolution of their symptoms with thoracoscopic approach and demonstrated that if performed with expertise excellent results can be achieved in children with empyema [16]. In another major study by Luh et al with 234 patients, 86.3% of them achieved satisfactory results with thoracoscopic treatment [17]. Yamaguchi et al assessed complications and failures in 151 children with empyema treated with thoracoscopic means and the quoted success rate was 82.6% [18]. The role of thoracoscopic decortication in the management of parapneumonic empyema has been compared with chest tube drainage alone or with the aid of fibrinolytics. Biligin et al concluded that thoracoscopic surgery is cost-effective and could shorten the hospitalization time with early discharge of patients from the hospital when compared to pure chest tube drainage [14]. They recommended that thoracoscopic surgery would be beneficial in well-equipped major centres and should be done early in the fibropurulent phase to allow early recovery and prevent further complications. In a study by Klena et al with 21 patients identified between 1994 and 1997, thoracoscopic decortication was found to be most likely

successful within 1 week after the diagnosis of empyema [19]. The use of fibrinolytic agents had raised much attention in recent years [20]. There had been results from randomized trials suggesting a statistical significant shorter hospital stay by 2 days [21]. However its use has not gained universal acceptance due to contradicting results from large multi-centre retrospective studies which showed similar hospital stays and significant increase in failure rate [22, 23]. Reports of severe life threatening complication such as haemothorax and allergy also limited its popularity [24, 25].

Thus far only few studies in the literature have investigated the effect of timing of thoracoscopic decortication in childhood empyema. In a recent study reported by Chung et al [26] focusing on this issue in adult population, comparisons were made between patients operated within 2 weeks, 2 to 4 weeks and beyond 4 weeks from symptom onset. The operative time was significantly shorter in those operated early (100.93 vs 125 minutes) owing to the less severe adhesions and debris organization. It was in contrast to our results here, which showed the mean operative time was comparable between the two groups (80.3 vs 95.3 minutes, p=0.31). Nonetheless, we did notice a marked decrease in operative blood loss in group 1 (46.9ml) with a mean difference of 60ml from group 2 (106.3ml). It was probably due to the same reason of less severe adhesion in the early-operated group, though statistical significance was not reached (p=0.06) owing to the small sample size. In Chung's study the duration of

chest tube drainage, post-operative hospitalization and intensive care unit stay were all shorter in those operated less than 2 weeks, with all of them showing statistical significance except the last one. The results were similar in our study where chest tubes were removed 5 days after operation in group 1 compared to 8.9 days in group 2 (p=0.11). In addition, the post-operative hospital stay (mean 9.5 vs 20.4 days, p=0.003) and total hospitalization duration (mean 19.3 vs 38.8 days, p<0.001) were significantly shorter in group 1.

The reason behind the earlier recovery and discharge was partly due to the shorter febrile duration, which was 4.5 days shorter in group 1 (p=0.04). The better clearance of dense fibrinopurulent material in parapneumonic empyema by thoracoscopic means as compared to pure chest tube drainage is furthered affirmed with this finding. Earlier chest drain removal and shorter febrile period all added up to the faster cessation of intravenous antibiotics therapy, and subsequently translated into the speedy discharge and recovery. There was no major post-operative complication identified in our study except in one patient with recurrence and required second thoracoscopic decortication, who had a very delayed presentation.

With the aforementioned results, timely thoracoscopic decortication of parapneumonic empyema was justified to promote earlier recovery of paediatric patients in concordance with previous studies. This could be explained by the fact that

most cases are presented at stage 2 (fibrinopurulent) where chest tube drainage would not be sufficient in enhancing the clearance of empyema. Thus, the shorter the time it takes to performing thoracoscopic decortication, from symptom onset, the better the benefit of rapid recovery could be attained. We acknowledge that this study had limitations with its small sample, and as a result, some of the peri-operative outcomes did not reach statistical significance. Furthermore, the retrospective nature of the study might have limited its validity.

In conclusion, we would recommend early thoracoscopic decortication in managing children with parapneumonic empyema. Large scale randomized study is essential for more robust data.

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