Clinical observation of bronchoscopy alveolar lavage combined with thoracoscopy in the treatment of empyema in children

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Abstract
The objective of this study was to investigate the therapeutic effects of bronchoscopy alveolar lavage (BAL) combined with thoracoscopy in the treatment of empyema in children.

Retrospectively analyzed 174 cases of pediatric empyema treated with thoracoscopy combined with BAL from January 2010 to December 2016 in our hospital. All the cases, according to admission order, were randomly divided into 2 groups, the control group (group A), which contained 89 cases, was treated with thoracoscopy; and the experimental group (group B), which contained 85 cases, was treated with BAL combined with thoracoscopy. The results of BAL treatment, the inflammatory indexes including body temperature, total leukocyte count in peripheral blood and CRP, and the therapeutic effect and prognosis including the days of antibiotic use, hospital stay, the incidence of thoracotomy and lobectomy were compared between the 2 groups.

1. There was no significant difference in inflammatory indexes between the 2 groups: body temperature (°C), (39.06 ± 0.047 and 39.08 ± 0.050), P > .855; routine leukocyte count (× 10⁹/L), (25.93 ± 1.035 and 24.76 ± 1.019), P > .425); C-reactive protein (mg/L), (128.7 ± 6.633 and 138.6 ± 7.53), P > .328.

2. The results of BAL: hyperemia and edema was detected in trachea intima of all cases, including 32 cases of purulent secretion and ulcer, 21 cases of lumen deformation and 5 cases of foreign body.

3. There were statistical significances in the curative effects of the control group and the experimental group: the duration of antibiotic use (days), (21.07 ± 0.342 and 17.07 ± 0.288), P < .0001); the average hospital stay (days), (22.91 ± 0.347 and 18.79 ± 0.287), P < .0001; secondary surgery (thoracotomy), 15 cases in the control group, 5 cases in the experimental group, P < .023; lung lobectomy (disability rate), 13 cases in the control group and 3 cases in the experimental group, P < .011.

There was statistical difference in all the therapeutic indexes (P < .05).

Bronchoscopy alveolar lavage combined with thoracoscopy has a higher success rate in the treatment of pediatric empyema, and is more comprehensive, safe and effective in controlling inflammation.

Abbreviations: BAL = bronchoscopy alveolar lavage, VATS = video-assisted thoracic surgery.

Keywords: bronchoscopy alveolar lavage, pediatric empyema, thoracoscopy, treatment

1. Introduction
Empyema has been described by Hippocrates[1] in about 2000 years ago, which is a supplicative infection that accumulates purulent exudates in the pleural cavity,[2] with children as susceptible and high risk population. The incidence of empyema is increasing year by year widely,[3,4] which is often accompanied by symptoms such as high fever, cough, expectoration, chest tightness, and chest pain. The fatality rate of improper treatment can be as high as 15%.[1]

There are 3 main approaches of pediatric empyema infection: direct infection, lymphatic infection, and hematogenous dissemination. Direct infection is mainly secondary to pulmonary infection, 50% to 70% of the lung infection can cause pleural effusion, of which 28% to 53% can form empyema,[1,4,5,6]; besides, direct infection can also happen through thoracic surgery and chest trauma.

The main pathogens of pediatric empyema are Staphylococcus aureus, Pneumococcus, and Staphylococcus saprophytics. With
the extensively use of antibiotics, fungal infection has increased gradually, but there are certain differences in different regions.\cite{7-8} The occurrence and development of empyema is related to the toxicity of pathogenic bacteria,\cite{9-11} and the empyema caused by strong inflammatory response to these pathogens is not easily controlled clinically.\cite{12-13}

The key to the treatment of empyema is to control infection, eliminate empyema and abscess cavity, and promote lung expansion.\cite{14-15} Empyema is classified into 3 stages by the American Association for Thoracic Surgery, namely stage I, the exudative stage; stage II, the fibrinopurulent stage; and stage III, the organizing stage.\cite{16} The traditional treatment of stage I empyema is to eliminate empyema through thoracic puncture or closed thoracic drainage; most stage I empyema patients can be cured after treatment.\cite{3} Petratski et al also reported that intrathoracic perfusion of fibrin kinase can treat empyema to some extent, which has few curative effect to the stage II and stage III empyema.\cite{17} The traditional treatment of stage II and III is the excision of the thoracic empyema and fibroboard striping, but these surgeries have features such as heavy bleeding, great trauma, large wound, large scar, high economic burden, and long hospital stay.\cite{18} In 1998, Striffeler et al\cite{19} reported for the first time the treatment of empyema by video-assisted thoracic surgery (VATS). Compared with thoracotomy, VATS has less bleeding, smaller trauma, shorter hospital stay, smaller surgical wound, and smaller scar; however, it is difficult to treat stage III empyema with VATS.\cite{20} In conclusion, although there are some differences between thoracotomy and VATS, both of them have been proved to be superior to medical treatment.\cite{21}

Inflammation of the empyema is not only pleural cavity pus, but also inflammation of the lungs, which is characterized by the inflammation of the endobronchial membrane and alveoli in children, or even atelectasis or necrosis of the lung parenchyma, purulent pneumothorax, and pleural bronchial fistula; all these symptoms endanger the life of children.\cite{22} Cleaning up pleural cavity pus is only a part of the treatment, while the effect of bronchoalveolar inflammation treatment only by drugs is slowly, and the hospital stay is long. The repatency of complicated (branch) trachea blockage only by medicine treatment is difficult, and part of the disturbed lung cannot be repaired, which can only excised by surgery. This problem has been resolved by combining bronchofibroscopic alveolar lavage, which reduced the risk of lobectomy.

Tracing back the history of bronchofibroscopy, Ikeda et al\cite{23} first applied bronchoscopy to clinical practice in 1968, and Reynolds et al\cite{24} applied bronchoscopy alveolar lavage (BAL) to the treatment of respiratory diseases in 1974. BAL has the advantages of observing bronchial structure directly, cleaning up inflammatory secretion, phlegm thrombus, purulent fur, granulation or foreign body in the airway, relieving airway obstruction, restoring airway function, promoting lung reexpansion, and eliminating pus cavity.\cite{25-26} Meanwhile, accurate administration of drugs under direct vision of the bronchial cavity can improve the drug concentration of the lesion, and control the inflammation more effectively. Bronchofibroscopic is soft and fine, with good curvature, which can reach the depth of the bronchus cavity during the examination and treatment of the alveolar lavage, and cause little pain in children, resulting in good compliance and good clinical effect.\cite{27} The effect of BAL in the treatment of bronchoalveolar inflammation is obvious, but the effect on pleural cavity accumulation of pus is poor.

For the treatment of pediatric empyema, thoracoscopy was used to treat intrapleural inflammation, and BAL to treat bronchoalveolar inflammation; the combination of the 2 methods can solve intrapleural and intraalveolar inflammation at the same time, which plays a decisive role in the treatment of pediatric empyema, and improve the clinical efficacy.

This study retrospectively analyzed the experience of surgical treatment of pediatric empyema from January 1, 2010 to December 31, 2016, and objectively evaluated the safety, feasibility, and practicability of BAL combined with thoracoscopy in the treatment of pediatric empyema.

2. Methods

To study the therapeutic effect of BAL combined with thoracoscopy in the treatment of pediatric empyema, children were randomly divided into 2 groups according to the control group (group A) and the experimental group (group B). This study summarized 177 cases of pediatric empyema treated thoracoscopy combined with BAL from January 2010 to December 2016 in our hospital, and 3 cases were transferred to other hospitals due to personal reasons, the control group (group A), which contained 89 cases with age ranged from 1 month to 14 years (mean 2.716±0.369 years), was treated with thoracoscopy; and the experimental group (group B), which contained 85 cases with age ranged from 1 month to 14 years (mean 2.967±0.395 years), was treated with BAL combined with thoracoscopy. The institutional review board approved the study, and all patients provided informed consent for study inclusion.

Inclusion criteria:
1. met the diagnostic criteria of pediatric empyema;
2. cases of pediatric empyema treated by thoracoscopic technique;
3. cases of pediatric empyema treated with BAL combined with thoracoscopy;
4. cases under 14 years of age;
5. The parents signed the BAL informed consent and the thoracoscopic consent and agreed to return to our outpatient clinic as required.

Exclusion criteria:
1. cases with contraindication of thoracoscopy and BAL;
2. cases refused to be treated by thoracoscopy and BAL;
3. cases with low amount of pleural effusion, and could be improved or cured by conservative treatment, thoracocentesis, or closed drainage;
4. cases with hemorrhagic, tuberculous, or chylous pleural effusion.

Withdrawal criteria:
1. the subject and the corresponding guardians changed their will and refused to cooperate halfway;
2. cases with aggravated disease or died in the course of thoracoscopic or alveolar lavage.

Treatment methods: all patients were treated as follows:
1. Monitoring blood pressure, heart rate, and blood oxygen saturation with multifunctional ECG monitor, oxygen inhalation to relieve dyspnea;
2. the examination included: whole blood cell count, CRP, chest X-ray film, CT, or ultrasound\cite{28};
3. thorax puncture was performed on selected children; the puncture fluid was purulent, pale yellow, or yellow, which was difficult to draw out. Pleural ultrasound or CT indicated that
the pleural effusion was wrapped or separated, and further thoracoscopic surgery was performed.

4. Pathology examination, select sensitive antibiotics according to the etiology, if drug sensitivity is negative, choose the third generation cephalosporin, if the effect is poor, combine the antibiotic containing β-lactamase inhibitor

5. atomization inhalation, excrete sputum using vibration sputum elimination;

6. combined with lung function exercise: balloon blowing, squat up, and climbing stairs;

7. strengthen supporting nutrition.

Control group: after thoracoscopic surgery, if satisfactory results (transform into chronic empyema) were not achieved, excision of the thoracic empyema and fibreboard stripping should be performed after 4 to 6 weeks, lobectomy should be performed in patients accompanied with pulmonary abscess.

Experimental group: after thoracoscopic operation, children were treated with BAL for 1 to 3 times to control pneumonia as soon as possible and promote the recruitment maneuver. According to the age and development of the children, bronchoalveolar lavage was performed using bronchoscope with different diameters:

1. fasting water for 4 to 6 hours before operation to prevent aspiration by mistake during operation;

2. bronchial mucosal anesthesia by spraying 2% atomized lidocaine, atomized budesonide was used to promote bronchiole dilatation;

3. observation order during operation: nasopharynx, trachea, carina, and bronchus, the lateral posterior side was treated firstly, followed by focusing on the suspicious sites;

4. after taking specimens, alveolar lavage was carried out, and the total amount of lavage fluid was limited to 3 ml/kg.

If no satisfactory results were achieved, excision of the thoracic empyema and fibreboard stripping should be performed after 4 to 6 weeks, lobectomy should be performed in patients accompanied with pulmonary abscess.

2.1. Observation indicators and methods

Recording and analyzing the characteristics of the cases (transform into chronic empyema); age, gender, medical history, thoracic side, and fever degree (body temperature);

Inflammation indexes; peripheral blood leukocyte count and CRP; etiological examination.

Outcome and prognosis indicators: average hospital stay, recuperation rate, and disability rate after lobectomy.

2.2. Rehabilitation assessment indicators

Body temperature was normal in 1 to 2 days after withdrawal, as well as white blood cell count and C-reactive protein level in blood routine. Imaging data (chest radiographs or CT) confirmed that pleural effusion disappeared or largely disappeared, and pneumonia was controlled. Cases who met the above criteria were discharged.

2.3. Statistical methods

The data were analyzed by SPSS 18.0 software. The normality of data was checked first: measurement data that accord with normal distribution were expressed as mean ± standard deviation (x ± s); the grouped t test was used for data with homogeneous variance between 2 groups, otherwise, the Wilcoxon rank sum test was used, and the intra-group pairwise comparison was performed by matched paired t test. The count data were expressed as percentage (%), and the comparison between groups was performed by x² test. P < .05 was taken as statistically significant.

3. Result

A total of 174 patients in both groups completed the clinical study without shedding. There was no significant difference in baseline data between the 2 groups (all with P > .05), including gender, age and onset location (left or right thoracic cavity). The data of the 2 groups were balanced and comparable. (As shown in Table 1).

Pathogenic results: blood culture positive, 24 cases (27.0%) in the control group, and 22 cases (25.9%) in the experimental group; pleural fluid culture positive, 28 cases (31.5%) in the control group, and 25 cases (29.4%) in the experimental group; alveolar lavage fluid culture positive, 13 cases (15.3%) in the experimental group. Streptococcus pneumoniae infection was most frequently identified, followed by Staphylococcus aureus. The P value of the positive rate difference between blood and pleural effusion was 0.51 in the control group, and the P value of the positive rate between blood, pleural fluid and alveolar lavage fluid was .078 in the experimental group, both of these 2 were not significantly different (Table 2).

Comparison of the inflammatory indexes between control group and experimental group: body temperature (°C) (39.06 ± 0.047, 39.08 ± 0.050, P = .855); blood white blood cell (×10⁹/L), (25.93 ± 1.035 and 24.76 ± 1.019), P > .425; C-reactive protein (mg/L), (128.7 ± 6.653 and 138.6 ± 7.53), P = .328; there was no statistical difference. Cases with high fever, white blood cell count and CRP were significantly increased in both groups, with strong inflammatory reaction; there was no statistical difference and was comparability between the 2 groups. (Table 3)

Findings during bronchofibroscopic alveolar lavage in the experimental group: there were hyperemia and edema in all cases, accumulation of purulent secretion and ulcer in 32 cases, deformation of bronchial cavity in 21 cases, and foreign body in 5 cases. In the course of bronchoalveolar lavage, the blood oxygen saturation decreased to 60% to 70% in 3 cases, which returned to

| Table 1: Clinical data. |
|------------------------|
| Case number | Gender | Age (years, x ± s) | Onset location (left or right thoracic cavity) |
| Control group | 89 | Male 45 Female 44 | 2.716 ± 0.369 | Left 44 Right 43 Bilateral 2 |
| Experimental group | 85 | Male 43 Female 42 | 2.907 ± 0.395 | Left 41 Right 42 Bilateral 2 |
| χ² value | 0.000 | 0.716 | 0.026 |
| P value | .997 | .643 | .987 |
normal level after ceasing operation; and laryngeal edema after alveolar lavage was found in 2 cases, which were relieved after treatment with atomized budesonide.

After BAL treatment in the experimental group, the children in the group presented short-term cough, local inflammatory reaction, alveolar infiltration, and occasional fever, bronchospasm, laryngeal edema, arrhythmia, or bleeding (Table 4).

| Complication cases | Cases (%) | Duration |
|--------------------|-----------|----------|
| Cough              | 85 (100%) | Lasts for 1 day |
| Local inflammatory response | 25 (29.4%) | Lasts for 2–3 days |
| Alveolar infiltration | 76 (89.4%) | Lasts for 2 day |
| Fever              | 12 (14.1%) | Lasts for several hours |
| Bronchospasm       | 1 (1.1%)  | Lasts for 5–7 days |
| Laryngeal edema    | 3 (2.3%)  | Lasts for 4 hours to 2 days |
| Arrhythmias        | 1 (1.1%)  | Lasts for several hours |
| Bleeding           | 1 (1.1%)  | Duration variable |

All cases in this study met the rehabilitation evaluation criteria before discharge.

Comparison of therapeutic effects between control group and experimental group: antibiotic application time (days), (21.07 ± 0.342 and 17.07 ± 0.288), P < .0001; and average hospital stay (days), (22.91 ± 0.347 and 18.79 ± 0.287), P < .0001. After thoracoscopic or BAL treatment, for cases with residual cavity or pus cavity in the pleural cavity, unable of lung recruitment maneuver, thick fiberoard, and pulmonary abscess, second operation (thoracotomy) was performed (15 cases in the control group and 5 cases in the experimental group, P < .023). There were 13 cases of lung lobectomy (disability rate) in the control group and 3 cases in the experimental group (P < .011). The rate of secondary operation and disability in the experimental group was significantly lower than that in the control group (P < .05) (Table 5).

A total of 152 cases were followed up, include 70 cases in group A, in which recurrent empyema was found and cured after readmission in 2 cases, and 65 cases in group B, in which recurrent empyema was found and cured after readmission in 1 case.
4. Discussion

We believe that the treatment of empyema should include the control of inflammation in the pleural cavity and bronchoalveolar cavity, which can be achieved by thoracoscopy combined with BAL.

The first hazard of pediatric empyema is the extensive pleural inflammation in the visceral pleura during pediatric empyema. It resulted in serous exudation and pleural effusion, accumulation of cellulose and inflammatory cells, and proliferation of a large number of bacteria, forming pleural pus (Fig. 1, Fig. 2). In this group of patients, the phenomenon of massive pleural empyema can be seen in VATS surgery (Fig. 3, Fig. 4). At the same time, we conducted pleural hydrothorax bacterial culture, the positive rate of pleural fluid culture in the experimental group and the control group was 29.4% and 31.5%, respectively, which was similar to that of the children with empyema reported by Grisaru-Soen et al (19%–36%).[26] The difference might be related with the non-standard use or overuse of antibiotics, characteristics of the infected pathogenic bacteria, and the specimen collection process. In order to avoid this situation, we standardized the specimen collection process, strictly followed the principles of antibiotic use for treatment, and conducted routine blood bacterial culture and drug sensitivity test to guide drug use; the positive rate of blood culture in the experimental group and the control group was 24.7% and 26.9% respectively, which was similar to that of the children with empyema reported by Grisaru-Soen et al (26%).[31] For those with negative drug sensitivity or no results, the third generation of ceftriaxone, such as ceftriaxone, was used to control the infection and treat severe infection.[30] After this process of treatment, children with shortness of breath, fever would be very easy to control.

The second hazard of pediatric empyema is hypersensitivity, causing by bacteria, serous, and cellulose exudation of alveolar wall, which makes bacteria proliferate and proliferate in trachea and alveoli, inflammation cells, and secretions blocking fine (branch) tracheal alveolar structure, colonization and hyperplasia, destruction of surrounding structure, and formation of lung

Figure 1. Chest CT (lung window) showed left purulent pneumothorax and left atelectasis.

Figure 2. Chest CT (mediastinal window) showed exudative change, compression, and atelectasis in the left lung and accumulation of empyema in the left pleural cavity.

Figure 3. Examination during the thoracoscopic operation revealed yellow and white cheese-like pus accumulation that did not flow well, local band separation, local chest wall was seen, but no compressed lung tissue was seen.

Figure 4. Examination during the thoracoscopic operation revealed yellow pus in the chest covering the surface of the lung tissue; the gelatinized local chest wall was visible.
abscess, or pulmonary abscess (Fig. 5). It can cause coughing and shortness of breath in children. For this process, we have BAL treatment, you can see the endometrial congestion and edema, part of the bronchial lumen deformation, purulent secretion accumulation, endometrial ulcers, etc. The positive rate of alveolar lavage fluid culture was 15.3%, among which Streptococcus pneumoniae and Staphylococcus aureus were the majority, which was similar to the results of blood and pleural fluid culture, which played an effective guiding role for clinical medication.

The third hazard of pediatric empyema is compression effect. A large amount of empyema accumulates in the pleural cavity, the lung collapses, and cannot open, the lumen of bronchus is deformed, resulting in the displacement of mediastinum and heart, and the damage of cardiopulmonary function. Urek et al believe that empyema can be purged under thoracoscope, and space occupying effect can be eliminated; stripping the fiberboard and cleaning up fibrous deposit on lung surface can free the visceral pleura, release the restraint of lung surface, restore normal intercostal space and restore respiratory muscle function. Evangelos et al believe that bronchoalveolar lavage can enhance the cough reflex function, increase the intensity and frequency of cough, promote the excretion of empyema in trachea and lung, and facilitate inflammation absorption and pulmonary lobule reexpansion. This study showed that even if the pulmonary surface (pleural cavity) inflammatory environment clearance was not ideal, more effective lung expansion can be achieved once the pulmonary inflammatory environment clearance was ideal. Therefore, this method can be used in pediatric empyema. In the experimental group, only 5 cases of abscess were dissatisfied after the above treatment, 3 of them were complicated with pulmonary abscess, and secondary operation was performed in 2 cases.

Thoracoscopy combined with BAL has many advantages in the treatment of pediatric empyema, and the 2 treatments can complement each other: 1. Clean the proliferative bacteria, bacteria and the exudate or pus of their growth, and to clear the pleural cavity and the endobronchial environment of the trachea.

2. Bronchoalveolar lavage can eliminate bronchoalveolar inflammatory substances through washing and sucking, which reduce the concentration of endotracheal inflammatory substances, and therefore reduce inflammation.

3. Bronchofiberoscopic alveolar lavage can be combined with local drug administration at the same time, which can effectively improve the concentration of drugs, reduce airway exudation, and edema, enhance bacterial effect, and improve the efficacy, reduce the pulmonary lobectomy, and decrease the disability rate.

Obtain important inflammatory specimens: thoracoscopic and bronchoscopy directly act on the pleural cavity and trachea, which allows the operator obtain the specimen of the lesion area, and can effectively improve the positive rate of culture and the reliability of drug sensitivity, with less pollution, less influence factors, and more directly reflect the pathogenic bacteria. Antibiotics can be selected clinically according to the results of drug sensitivity, reducing the use of antibiotics and the emergence of drug-resistant strains.

For some empyema complicated with airway foreign body, empyema that was further induced by airway foreign body, or atypical foreign bodies in the airway, such as hair, fruit shell skin and jelly, chest CT cannot develop the relative images; after bronchoscopy examination, early detection and elimination can be achieved, avoiding the occurrence and development of missed diagnosis and misdiagnosis. In this study, 5 cases of empyema in the experimental group had severe respiratory and asthmatic symptoms, and the total number of white blood cells in routine blood test was 20 to 50 × 10⁹/L, and the C-reactive protein level was about 100 to 200 mg/L. There was no obvious interruption of trachea shadow in thoracic high-resolution CT tracheal imaging. After thoracoscopic empyema was cleared and fiberboard stripped, further bronchofiberoscopic alveolar lavage was performed. Foreign body of trachea was found (Fig. 6). After foreign body was removed, empyema was quickly controlled, and no complication was found. In this group, bronchoscopy played a complementary role in airway exploration.

Thoracoscopy combined with BAL in the treatment of pediatric empyema is safe and has few complications. There

Figure 5. Bronchoscopy showed endobronchial redness, a mucus coating on the surface and lumen of the endobronchial membrane, local ulcer formation on the endobronchial surface, and an abscess coating on the ulcer surface.

Figure 6. Bronchoscopy showed endobronchial redness, a foreign body embedded at the opening, and edema and stenosis of the opening of the bronchus.
are no cases of disability or death caused by diagnosis and treatment in this group of patients; however, there are certain limitations, this study mainly focuses on young children, whose expression ability is insufficient, and they are unable to timely and accurately judge some clinical manifestations, and there is the possibility of evaluation bias between doctors and parents.

In conclusion, compared with thoracoscopic treatment, the combination of BAL is more effective in the treatment of pediatric empyema, it can control bronchoalveolar and pleural inflammation simultaneously, and help to open the airway, promote the expansion of the lung, eliminate the residual cavity of the pleura, and improve respiratory function. Compared with thoracoscopic, BAL plays a complementary role and can identify abnormal in the airway in time. Finally, it can shorten the use time of antibiotics, hospital stay, and reduce the rate of secondary surgery and disability, which is safe, effective and feasible in the surgical treatment of pediatric empyema.

Author contributions

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