Role of Chymotrypsin in Management of Moderate Parapneumonic Pleural Effusion in Children

Rawan Mohamed Eldeeb1, Md Ahmed Abd El Basset Abo El Ezz1, Md Mohamed Adel Eltomey2 and Md Mohamed Basiony Hamza1

1Department of Pediatric, Faculty of Medicine, Tanta University, Egypt.
2Department of Radiology, Faculty of Medicine, Tanta University, Egypt.

Authors’ contributions

This work was carried out in collaboration among all authors. Authors MAABA and RME designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MAABA and MMBH managed the analyses of the study. Author MMAE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To show the benefit of chymotrypsin as an adjuvant therapy in cases of moderate parapneumonic pleural effusion in children.

Study Design: Randomized controlled trial.

Place and Duration of Study: Pulmonology Unit, Pediatric Department and Radiology Department, Tanta University Hospital, Egypt between February, 2019 to February, 2020.

Methodology: Subjects comprised of 60 children randomized into three groups 20 children each (41 males, 19 females; age range 1-14 years) with moderate parapneumonic pleural effusion by chest ultrasound. Clinical as well as complete blood count, C-reactive protein and chest ultrasonography at time of presentation, after one week (first end point) and after two weeks (second end point). Management with antibiotics, analgesics, antipyretics, chest tube insertion and oral chymotrypsin in group 2 and intramuscular chymotrypsin in group 3.

Results: There was statistically significant decrease in fluid thickness by chest u/s (mm) in group 2 (Mean ±SD= 6.400±3.872) and group 3 (Mean ±SD= 6.150±2.720) after one week and after two
weeks group 2 (Mean ±SD= 15.3±4.658) while group 3 (Mean ±SD= 3.3±1.559) in comparison to group 1 after one week (Mean ±SD= 16.100±10.351) and after two weeks (Mean ±SD= 11.35±7.066) (P < 0.001), duration of hospitalization (days) and chest tube (days) were statistically significant lower in group 2 (Mean±SD= 15.200±4.112), (Mean±SD= 9.100±2.808) respectively and group 3 (Mean±SD= 14.050±3.300), (Mean±SD= 7.400±1.698), in relative to group 1 (Mean±SD= 18.65±3.329), (Mean±SD= 9.85±3.265), (P <0.001, P=0.017 respectively) and percentage of decortication was statistically significant lower in group 2 and 3 in relative to group 1. (P =0.017).

**Conclusion:** Chymotrypsin has an adjuvant role in management of moderate parapneumonic pleural effusion evidenced by earlier recovery less hospital stay, decrease in chest tube insertion and need for decortication and intramuscular chymotrypsin injection has better effect than oral chymotrypsin in moderate parapneumonic pleural effusion.

**Keywords:** Parapneumonic; chymotrypsin; fibrinolytics.

1. **INTRODUCTION**

Parapneumonic fluid collection is mostly because of pneumonia while empyema is pus in the pleural cavity [1]. Most common pathogens are streptococcus pneumoniae (serotype 1,3,14,19A) responsible for 10-66% of empyema, staphylococcus aureus (4-30%) and staphylococcus pyogenes [2]. The evolution of parapneumonic fluid collection can be divided into three stages exudative, fibrinopurulent and organizational:

**Exudative stage:** in which there is rapid outpouring of fluid into the pleural space and the pleural fluid in this stage is characterized by negative bacterial studies, a glucose level above 60 mg/dl, pH > 7.20, and lactic acid dehydrogenase (LDH) level of less than three times the upper normal limit. If the patient does not see a physician or receives the wrong antibiotic, the effusion may proceed to the second stage.

**Fibrinopurulent stage:** which is characterized by positive bacterial studies, a glucose level < 60 mg/dl, pH < 7.20, and pleural fluid LDH more than three times the upper normal limit, the pleural fluid becomes infected and progressively loculated.

**Organizational stage:** in which, fibroblasts grow on both parietal and visceral pleural surfaces, forming an inelastic membrane that restricts lung's reexpansion, impairs lung function and creates a persistent pleural space with ongoing potential for infection. At this stage, thoracentesis may yield "dry tap" [3].

On chest examination, There are decrease in chest movements during respiration, tactile fremitus, dullness to percussion, decrease vocal resonance, decreased or absent breath sounds, rales or crackles and/or bronchial breathing [4].

A delayed or improper treatment result in deposition of fibrinous material, formation of loculations and entrapment of the lung. The contemporary methods for treating complicated parapneumonic pleural effusion and empyema remain debatable. The dispute over the optimal therapeutic approach has accentuated since the introduction of early thoracotomy and decortication, video-assisted thoracic surgery (VATS) and the use of instillation of fibrinolytic agents as an adjunctive or alone [5].

Chymotrypsin is a widely used oral proteolytic enzyme combination to hasten repair of traumatic, surgical, and orthopedic injuries. It shows high bioavailability without losing its biological activities as an anti-inflammatory, anti-edematous, fibrinolytic, antioxidant, and anti-infective agent. It also demonstrates analgesic effects and reduces the pain associated with healing [6].

Following an acute injury, there is a sharp rise in the levels of protease inhibitors a1-antitrypsin and a2-macroglobulin. These acute phase reactants inhibit several proteolytic enzymes which if uncontrolled can lead to unregulated inflammation and impair healing. The order of affinity of that a1-antitrypsin with the other proteolytic enzymes elastase > chymotrypsin > cathepsin G > trypsin > plasmin. At this point, it must be reiterated that plasmin causes fibrinolysis and its inhibition prevents fibrinolysis. Therefore, a steep rise in a1-antitrypsin and a2-macroglobulin following acute injury leads to a period of fibrinolytic shutdown, with consequent...
maintenance of inflammatory response and edema and delay in repair. Oral chymotrypsin targets this early stage of inflammation. Since α1-antitrypsin shows greater affinity for trypsin and chymotrypsin compared to plasmin, oral supplementation ensures that plasmin remains available for fibrinolysis and the period of fibrinolytic shutdown is shortened. As a result, local microcirculation is restored, inflammatory edema is cleared, and tissue repair is facilitated [7].

2. MATERIALS AND METHODS

**Study place**: Pediatric Pulmonology Unit, Pediatric Department, Tanta University Hospital, Egypt.

**Study duration**: one year.

**Study type**: Randomized controlled trial, written informed permission obtained from all parents or guardians of the children

**Data collection**: this study included sixty children with moderate parapneumonic pleural effusion who were recruited, then screened clinically, radiologically (chest USG) and laboratory (complete blood count and C-reactive protein).

Then sixty children were randomized into three groups. Group 1, twenty children received medical treatment plus chest tube insertion with no chymotrypsin in their management, Group 2, twenty children received medical treatment plus chest tube insertion and oral chymotrypsin from one to three tablets per day for two weeks and Group 3, twenty children received medical treatment, chest tube insertion and IM chymotrypsin from 2.5 to 5 mg (ampoule 5 mg ) for two weeks after sensitivity test.

**Inclusion criteria**: were age more than one year and less than fourteen years, having moderate parapneumonic effusion confirmed by clinical examination, chest XRay and chest USG (>10 mm thickness and less than hemithorax ) [8].

**Exclusion criteria**: were transudate, hemothorax, chylothorax: identified by physical, chemical and cytological analysis of pleural fluid sample, mild amount of effusion<10 mm thickness by chest USG and large amount more than hemothorax and systemic diseases or malignancy with pleural fluid collection.

All included children were subjected to the following:

1-**Clinical**: detailed history taking with special emphasis on respiratory symptoms: cough, chest pain, dyspnea, fever, thorough clinical examination with special emphasis on (signs of respiratory distress). Chest examination with special emphasis on:
- Inspection: decrease of chest movements on affected side, dullness on percussion and absent air entry on auscultation or bronchial breathing .

2-**Radiologically**: with Chest Xray and Chest USG.

3-**Laboratory**: (C-reactive protein and total leukocytic count).

There were two end points first after one week and second after two weeks , follow up clinically, radiologically with chest USG and laboratory investigations (like CRP and TLC) and then if cases did respond then decision for decortications.

2.1 Statistical Analysis

Data were fed to the computer and analyzed using SPSS software version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using frequency and percentages. Quantitative data were described using mean and standard deviation (M±SD). The Kolmogorov Smirnov test was used to verify the normality of distribution. Chi square test was used to compare qualitative data between the two groups, While Student’s t test was used to compare quantitative data between the two groups.

3. RESULTS

The demographic data of the three studied groups are summarized in Table 1. The mean age of group 1 was 5.642±3.909 years and 55% were males, while the mean age of group 2 was 5.550±3.703 and 85 % were males and in group 3 mean age was 6.700±2.105 and 65% were males. There was no significant difference between the three groups as regards to age sex, residence and socioeconomic state.

Table 2 showed that fluid thickness in mm by chest U/S was significantly lower in Group 2 and 3 after one week and two weeks in comparison to Group 1. (P < 0.001).
Table 3 showed that duration of hospitalization and chest tube were significantly lower in Group 2 and 3 in relative to Group 1. (P < 0.001, P =0.017 respectively).

Table 4 showed that percentage of decortication was significantly lower in Group 2 and 3 in relative to Group 1. (P=0.017).

4. DISCUSSION

Parapneumonic effusion develops in 2 to 12 percent of children with pneumonia and in up to 28 percent of children requiring hospitalization [9]. Chest tube placement with instillation of fibrinolytic medication allows efficient drain output and decreases hospital stay as in James et al.,2016 in their study to evaluate experience with lower fibrinolytic dose for parapneumonic effusions and to assess potential dose stratification based on a simple ultrasound grading system. Pleural drainage with fibrinolytic therapy was successful in 97%; only one child required surgical drainage [10].

In the present study, as regarding to demographic data, there was no significant difference between three studied groups as regarding to age (P value =0.485) with median age about 5 years in all studied groups and sex (P value =0.116) with male predominance in diseased cases in the studied groups with moderate parapneumonic effusion. That comes in agreement with Hernandez-Bou et al.,2009 in their study of pediatric parapneumonic pleural effusion: epidemiology, clinical and microbiological diagnosis they found 190 children were diagnosed with parapneumonic effusion (PPE) (52.6% male) and the average age was 4.8 years (SD 3.5 years) [11]. Also, comes in agreement with Segerer et al.,2017 that in their review to 645 children with parapneumonic effusion to evaluate the initial management of pediatric parapneumonic effusion or pleural empyema with regard to length of hospital stay by collecting parapneumonic effusion /pleural empyema (PPE/PE) cases using a nationwide surveillance system Erhebungsstelle für selten pädiatrische Erkrankungen in Deutschland (ESPED) from 10/2010 to 06/2013, in all German pediatric hospitals including PPE/PE patients <18 years of age requiring drainage or with a PPE/PE persistence >7 days. median age was 5 years[12].

Table 1. Demographic data of children with moderate parapneumonic pleural effusion

<table>
<thead>
<tr>
<th></th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group (3)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>5.64±3.909</td>
<td>5.55±3.703</td>
<td>6.70±2.105</td>
<td>0.485</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>11–9</td>
<td>17 – 3</td>
<td>13–7</td>
<td>0.116</td>
</tr>
<tr>
<td></td>
<td>55.00</td>
<td>85.00</td>
<td>65.00</td>
<td></td>
</tr>
<tr>
<td>Residence (urban:rural)</td>
<td>18-2</td>
<td>16-4</td>
<td>18-2</td>
<td>1.154</td>
</tr>
<tr>
<td></td>
<td>90.00</td>
<td>80.00</td>
<td>90.00</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic state (middle:lower)</td>
<td>10-10</td>
<td>7-13</td>
<td>9-11</td>
<td>0.622</td>
</tr>
<tr>
<td></td>
<td>50.00</td>
<td>35.00</td>
<td>45.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Thickness on chest USG at time of presentation, after one week and after two weeks

<table>
<thead>
<tr>
<th></th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group (3)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of presentation</td>
<td>32.8±6.066</td>
<td>30.1±7.333</td>
<td>31.85±7.513</td>
<td>0.470</td>
</tr>
<tr>
<td>After one week</td>
<td>16.1±10.351</td>
<td>6.4±3.872</td>
<td>6.15±2.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After two week</td>
<td>11.35±7.066</td>
<td>5.3±4.658</td>
<td>3.3±1.559</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AT-A1W</td>
<td>16.7±11.662</td>
<td>23.7±8.957</td>
<td>25.7±7.848</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1-A2W</td>
<td>4.750±9.624</td>
<td>1.1±3.538</td>
<td>2.85±2.084</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Duration of hospitalization and duration of chest tube in the groups

<table>
<thead>
<tr>
<th></th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group (3)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Hospital Stay (days)</td>
<td>18.65±3.329</td>
<td>15.2±4.112</td>
<td>14.05±3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of Chest Tube (days)</td>
<td>9.85±3.265</td>
<td>9.1±2.808</td>
<td>7.4±1.698</td>
<td>0.017</td>
</tr>
<tr>
<td>TUKEY’s Test Group 1&amp;2</td>
<td>Group 1&amp;2</td>
<td>Group 1&amp;3</td>
<td>Group 2&amp;3</td>
<td></td>
</tr>
<tr>
<td>Duration of Hospital Stay</td>
<td>0.010*</td>
<td>&lt;0.001</td>
<td>0.574</td>
<td></td>
</tr>
<tr>
<td>Duration of the chest tube</td>
<td>0.650</td>
<td>0.014</td>
<td>0.119</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. The percentage of decortication

<table>
<thead>
<tr>
<th>Decortication (No:yes)</th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group(3)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:15</td>
<td>25.00</td>
<td>9:12</td>
<td>45.00</td>
<td>13:5</td>
</tr>
</tbody>
</table>

In the present study, as regarding to chest U/S at time of presentation no significant difference between all groups with P- value=0.470 but with significant difference at follow up with improvement in amount of fluid and pleural thickness in groups took chymotrypsin with mean 6.1 at intramuscular group and mean 6.4 in oral group and that comes in agreement with Yu-feng & Jian- zhong,2012 but they used chymotrypsin intrapleural to observe the local curative effect of α-chymotrypsin on the residual pleural thickening caused by pleural cavity infection on forty cases were randomly divided into treatment group and control group. (20 cases in each group). Micrtotube drainage in the pleural cavity was performed in two groups. The patient in the treatment group were given 4 000 U α-chymotrypsin dissolved in 20mL sodium chloride and the patients in the control group were only treated with the micrtotube drainage. The thickness of pleura, the size of residual cavity and the time with the tube were measured and recorded before and after the treatment and so the results were that the pleural thickness of the patients in the treatment group after the injection of α-chymotrypsin was significantly reduced compared with that in the control group; the size of residual cavity in the treatment group after the treatment was significantly different from that in the control group. The mean time with the catheterization in the treatment group was 7.25±2.53 days and that in the control group was 5.90±2.07 days which showed that the difference in the mean time between two groups was significantly different and the study concluded the curative effect of α-chymotrypsin on the pleural thickening caused by pleural cavity infection is significant, the method is simple, safe and efficient with low-cost [13].

In the present study, regarding to duration of hospitalization there was significant decrease in groups received chymotrypsin than group 1(P value < 0.05) with mean 18 ±3 days in group 1, mean 15±4 days in group 2 and 14±3 days in group 3.

In the present study, it was observed that 75% of cases who didn’t receive chymotrypsin experienced decortication while in group 2 who took oral chymotrypsin 55% experienced decortication and in group who took intramuscular chymotrypsin only 30% was experienced decortication. That partially comes in agreement with studies that recommend fibrinolytics in pediatric parapneumonic effusion and as in James et al.,2016 it was found that a lower 1-mg dosing regimen of tissue plasminogen activator was effective in all children with less complex (grade 1 ultrasound imaging) parapneumonic effusions. Grade 2 ultrasound images correlated with younger and smaller children, presence of a pleural organism, and longer or more complicated chest tube duration.

Also to some extent in agreement with Long et al.,2016 a study of 239 children were treated [age range 4 months–19 years; median 4 years]. A decreasing number of patients presenting year-on-year since 2006 with complicated pleural infections was observed. The majority of children were successfully managed without surgery using antibiotics alone (27%) or a fine-bore chest-drain and urokinase (71%). Only 2% of cases required primary thoracotomy. 14.7% cases failed fibrinolysis and required a second intervention. The only factor predictive of failure and need for surgery was suspicion of necrotizing disease on initial imaging [14].

This is explained by that one of the long term sequelae of parapneumonic effusion is persistent pleural thickening which is seen in approximately 13% of patients and the commonest comorbidity with PPE and so decortication could be performed in patients with the pleural thickening whom lung mechanics deteriorated. In this way trapped and restricted lung will be and mechanics of respiration will be provided. Patients with diffuse pleural thickening should be followed for progression to restrictive disease.

5. CONCLUSION

It was concluded that chymotrypsin has adjuvant role in management of moderate parapneumonic pleural effusion evidenced by earlier recovery,
less hospital stay, need for chest tube and less need for decortications and intramuscular chymotrypsin injection has better effect than oral chymotrypsin in moderate parapneumonic pleural effusion.

6. LIMITATIONS OF THE STUDY

Cases need longer follow up and more sample size.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained from all parents or guardians of the children. The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University. Permission number is 32950/2/19.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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