The Effects of Early Chest Tube Placement on Empyema Resolution*

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Study objectives: The objective of this study was to determine the impact of the timing of chest tube insertion on outcome for the treatment of empyema, using a new animal model of empyema. Design: A prospective, controlled randomized, blinded design was used. Setting: The study was conducted in an animal research laboratory. Patients or participants: Sixty-six 2- to 3-kg rabbits were used in this study. Interventions: After induction of empyema, the rabbits were divided into four groups. Fourteen rabbits had chest tubes placed at 24 h after empyema induction. Seventeen rabbits had chest tubes placed at 48 h and 14 rabbits had chest tubes placed at 72 h after empyema induction. Twenty-one rabbits served as control rabbits and had no chest tubes placed. Measurements and results: Ten days after induction of empyema, the rabbits were killed. The pleural spaces of each rabbit were examined and a gross score, pleural peel score, and a microscopic score were calculated for each rabbit. The median gross score, mean pleural peel score, and median microscopic scores were significantly higher in the rabbits that underwent late chest tube placement (72 h) relative to those that underwent early chest tube placement (24 or 48 h). Conclusions: This study supports previous expert opinion statements and conclusions from retrospective analyses that early chest tube placement (relative to delayed chest tube placement) is beneficial for the treatment of empyema.

Key words: empyema; *Pasteurella multocida*; pleural fluid; rabbits

Thoracic empyema continues to remain a significant medical problem. A multitude of different treatment methods have now been proposed. These range from antibiotics alone1 to thoracoscopy to thoracoplasty with muscle transposition.2 The choice of therapy is usually dictated by the severity of disease on presentation. All treatment methods have as their goals the eradication of infectious agents, as well as the drainage and obliteration of the pleural space with consequent full expansion of the lung. The usual (most common) initial treatment remains parenteral antibiotics with chest tube placement.

When should chest tubes be placed after an empyema is diagnosed? Does placement of chest tubes at an earlier stage of empyema development influence outcome? Early drainage of empyema has previously been recommended based on case series investigations.3-5 Two recent retrospective studies have also been completed in which the consequences of delays in drainage of empyema have been analyzed.6,7 In the first study6 involving 39 patients, a delay in a chest drainage procedure (either chest tube placement or an open drainage procedure) after diagnosis of complicated parapneumonic effusions led to increased hospitalization times (31 vs 21 days) and increased hospitalization costs. There were no differences in mortality between the delayed and prompt drainage groups, however. In the second study,7 a delay of >3 days from the recognition of empyema to placement of a chest tube led to increased mor-

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tality in the delayed group (16% vs 3.4%), although the difference did not achieve statistical significance.

Prospective, controlled studies (in humans or animals) in which chest tubes are placed at different stages of empyema development have not been performed. Human clinical trials are extremely difficult to carry out, due to the relatively small number of patients with empyema at a single medical center during a reasonable time period, the heterogeneity of patients with empyema, and the high costs of conducting such a multicenter study. To our knowledge, there have been no prior animal studies addressing this issue. This is primarily because of the absence of an animal model in which a persistent empyema is consistently formed, permitting randomization into different treatment groups.

We hypothesized that early chest tube placement was important for the resolution of an empyema. Early chest tube placement prior to the formation of loculations should allow more adequate drainage of the infected pleural space. Using our newly developed animal model of empyema in the rabbit, we tested this hypothesis in a prospective, controlled, blinded experimental study. Chest tubes were placed at 24, 48, and 72 h after empyema induction and the following end points were compared among the different groups: mortality rate, gross appearance of the pleural space at autopsy, thickness of the pleural peel macroscopically, and thickness of the pleural peel by microscopy. An empyema was also induced in a control group that had no chest tubes placed for comparison.

**Materials and Methods**

This project was approved by the animal subjects committee at our medical center prior to the start of the study. Sixty-six 2- to 3-kg rabbits were used for this study. The rabbits were divided into four groups. Our goal was to have at least 10 rabbits in each group that survived to day 10 for autopsy analysis. The first group of 14 rabbits underwent chest tube placement at 24 h after empyema induction. The second group of 17 rabbits underwent chest tube placement at 48 h and the third group of 14 rabbits underwent chest tube placement at 72 h. Group 4 served as a control group in which 21 rabbits underwent induction of empyema without chest tube placement.

From our previous experience using this model of empyema, loculations began to form at approximately the 72-h time point. We chose this time point and two earlier time points (prior to loculation formation) to determine the impact of timing of chest tube placement.

**Empyema Induction**

The bacteria were prepared and injected using methods previously described from our laboratory. In brief, the rabbits were anesthetized with ketamine, 35 mg/kg IM, and xylazine, 5 mg/kg intramuscularly (IM). The right chest wall of the rabbit was shaved and 10⁶ *Pasteurella multocida* bacteria (in a 2-mL volume of 0.5% brain heart infusion agar) were injected into the right pleural space. The position of the catheter in the pleural space was verified by observing a characteristic pleural pressure tracing on an oscilloscope prior to injection of the bacteria. Penicillin, 200,000 U IM, was administered once daily, starting at 24 h after empyema induction to prevent early death of the animals from overwhelming sepsis. Buprenorphine hydrochloride, 0.05 mg/kg, subcutaneously, was also administered twice daily for analgesia.

**Diagnostic Thoracentesis**

A diagnostic thoracentesis was performed on all animals 24 h after bacterial injection to verify that an empyema was present. After injection of 1% lidocaine locally along the chest wall, a 19-gauge needle was inserted into the right fifth intercostal space and a maximum of 2 mL of pleural fluid was removed for pleural fluid analysis. Pleural fluid specimens were analyzed for pH and glucose levels.

**Chest Tube Placement**

The rabbits undergoing chest tube placement were anesthetized with ketamine, 17 mg/kg, and xylazine, 2.5 mg/kg IM, and then placed in supine position on the operating table under a warming lamp. A 0.5-cm skin incision was made over the right anterior chest. A 16F pediatric chest tube was inserted through the right fifth intercostal space and any pleural fluid was evacuated from the right pleural space. The catheter was then sutured in place using a purse string stitch. The chest tubes were attached to a Heimlich valve with a three-way stopcock in-line between the chest tube and the Heimlich valve (Fig 1). The rabbits were also placed in a rabbit vest and the chest tubes were attached to the vest (Fig 1). A chest tube protector (made of molded aluminum metal) was placed around the chest tube (between the rabbit and the Heimlich valve) to protect the chest tube from mastication. The chest tubes were allowed to drain spontaneously through the Heimlich valve. In addition, the chest tubes were aspirated twice daily using the three-way stopcock.

**Method of Euthanasia at 10 Days**

Pentobarbital sodium (Nembutal), 60 mg IV, was injected through the marginal ear vein of the rabbit. The thorax was then dissected from the carcass and the chest was bisected along a

**Figure 1.** A rabbit with chest tube, vest, and three-way stopcock in place.
coronal plane from the diaphragm to the neck for examination. A gross score, pleural peel score, and a microscopic score were then determined as below.

**Gross Score**

A scoring system of 0 to 4 was used to grade the degree of pleural peel and empyema seen grossly immediately at autopsy, where 0=normal pleural space and lung; 1=adhesions between the visceral and parietal pleura only; 2=minimal pleural peel without the presence of gross pus; 3=moderate pleural peel without gross pus; and 4=pleural peel with gross pus.

The scoring was performed in a blinded fashion as the rabbits were identified by number only. Half integer values (ie, 2.5, 3.5) were also used if the appearance was intermediate between the above integer score descriptions. The scorer did not know the treatment conditions of the rabbit.

**Pleural Peel Score**

The pleural peel score was determined in a blinded fashion by the same grader throughout the experiment. Immediately after killing the rabbits, the pleural peel score was obtained by measuring the thickness of the pleural peel (from the lung surface to the distal edge of the pleural peel) using a caliper at four different sites of the lung, ie, inferiorly, superiorly, medially, and laterally. The thickness at each of the four sites (in millimeters) was summed to give the pleural peel score. At sites in which no pleural peel was present, an arbitrary score of 0.5 was assigned if adhesions were present. A score of zero was given if the pleural surfaces appeared normal.

**Microscopic Score**

A specimen from the right lower lobe of the lung of all rabbits was placed in formaldehyde solution at autopsy. An adjacent section of overlying chest wall was also placed in formaldehyde solution. The microscopic sections were sliced and stained with hematoxylin-eosin. The slide was then examined under the microscope at X40 power and visually divided into thirds. The pleural peel thickness was measured in each of the three sections and an average pleural thickness was calculated. The microscopic score was derived by summing the average thickness of the visceral pleural specimen and the parietal pleural specimen.

**Statistical Analysis**

Mortality rates were compared between groups using χ² analysis. For gross score and microscopic score comparisons, analysis of variance on ranks was used to compare the median values. (Median values were compared as the values were not normally distributed.) Pairwise comparisons of medians were carried out using Dunn’s method. The proportions of rabbits with a gross score of 4 (indicating the presence of pus at autopsy) were compared between groups using χ² analysis. For mean pleural peel score comparisons, one-way analysis of variance was used, with the Student-Newman-Keuls method used for pairwise comparisons. Computer programs (Sigmapstat and Sigmaplot; Jandel Scientific, San Rafael, Calif) were employed for this analysis. A p value of 0.05 was designated as the level of significance.

**RESULTS**

The mean pH and glucose values from the diagnostic thoracenteses performed at 24 h in each of the four groups are shown in Table 1. The mean values were not significantly different among groups. The mean pH and glucose values were <7.1 and 17 mg/dL, respectively, consistent with empyema formation.

Sixteen rabbits died prior to autopsy at day 10 (Table 1). The differences in death rates between the groups were not significant. Six of the 16 total deaths occurred during the immediate postoperative period after chest tube insertion (Table 1). If these six deaths are excluded, the new mortality rates in each group were 14% in the 24-h group, 6% in the 48-h group, 7% in the 72-h group, and 29% in the control group. These death rates were also not significantly different among groups (p=0.12). Other than during the immediate postoperative period, rabbits died primarily because of overwhelming sepsis or bowel perforations. The gross scores, pleural peel scores, and microscopic scores were determined from the rabbits surviving to 10 days after bacteria injection.

**Gross Score**

The median gross score was the lowest in the 24-h chest tube group followed by the 48-h chest tube group (Fig 2). The median gross score for the 24-h chest tube group was 2.5. The median gross score for the 48-h chest tube group was 2.75 and the median gross score for the 72-h chest tube group was 4.0. The median gross score for the control group was 3.5. The median gross scores of the 24- and 48-h chest tube groups were significantly lower than the median score of the 72-h chest tube group. There was a trend toward lower median gross scores in the

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Total Deaths, No. (%)</th>
<th>Perioperative Deaths</th>
<th>Mean pH (±SD)</th>
<th>Mean Glucose Level (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (no chest tube)</td>
<td>21</td>
<td>6 (29)</td>
<td>0</td>
<td>6.97±0.15</td>
<td>12±3</td>
</tr>
<tr>
<td>24-h chest tube</td>
<td>14</td>
<td>3 (21)</td>
<td>1</td>
<td>7.06±0.13</td>
<td>11±3</td>
</tr>
<tr>
<td>48-h chest tube</td>
<td>17</td>
<td>3 (18)</td>
<td>2</td>
<td>7.05±0.08</td>
<td>17±15</td>
</tr>
<tr>
<td>72-h chest tube</td>
<td>14</td>
<td>4 (7.1)</td>
<td>3</td>
<td>6.92±0.13</td>
<td>14±0.3</td>
</tr>
</tbody>
</table>

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24- and 48-h groups relative to the control group, but statistical significance was not reached.

The proportion of rabbits with a gross score of 4 (indicating the presence of pus at autopsy) was significantly greater in the 72-h group relative to the 24-h and 48-h groups. The number of rabbits with a gross score of 4 was 3 of 11 (27%) in the 24-h group, 3 of 14 (21%) in the 48-h group, 8 of 10 (80%) in the 72-h group, and 6 of 15 (40%) in the control group.


Pleural Peel Scores

The mean pleural peel scores were highest in the control and 72-h chest tube groups (Fig 3). The mean (±SEM) pleural peel score from the 24-h chest tube group was 7.8 (±1.4). The mean pleural peel score from the 48-h chest tube group was 8.2 (±1.4), while the mean pleural peel scores from the 72-h chest tube group and the control group were 16.3 (±1.0) and 12.8 (±1.5), respectively. The mean scores of the control and 72-h groups were significantly greater than the values from the 24- or 48-h chest tube groups. Comparisons of the mean scores between the control group and the 72-h chest tube group or the 24-h group and the 48-h group did not show significant differences.

Microscopic Scores

Microscopic scoring revealed a significantly greater score in the 72-h group relative to all other groups (Fig 4). Considerable variability of the microscopic score was present within individual groups.

Discussion

To our knowledge, this is the first study performed in a prospective, controlled fashion that confirms the results from previous case series reports,3-5 retrospective analyses,6,7 and the expert opinion statements8,9 that early chest tube placement leads to more effective empyema resolution. Using this model of empyema in the rabbit, our data demonstrate that early chest tube placement (at 24 or 48 h) leads to a significant reduction in the amount of pleural peel present at autopsy after 10 days, relative
to late chest tube placement (72 h) or to control animals that had no chest tubes placed. The number of rabbits with gross pus at autopsy (gross score of 4) was also less in the rabbits that had chest tubes placed at 24 or 48 h. Under the conditions of this model, there appears to be a critical window period for placement of chest tubes of <48 h. When chest tubes are placed outside of this time period, the pleural changes seen at autopsy are not improved relative to control rabbits that had no chest tubes placed.

Although rabbits are different from humans, the rabbit empyema that results using this model is remarkably similar to human empyema. This model begins from the time point in the course of a human empyema in which the patient demonstrates infected pleural fluid as evidenced by pleural fluid with a low pH, a low glucose level, an elevated lactate dehydrogenase value, and positive cultures. Using this model, an empyema is consistently formed that evolves from thin pleural fluid to thick pus with pleural peel formation. In addition, an antibiotic (penicillin) must be administered to the animals to prevent overwhelming sepsis from the empyema.

Although the differences in mortality rates between the groups were not significantly different, there was a trend toward lower mortality rates in the rabbits that received chest tubes relative to those that did not. The mortality rates among the three groups receiving chest tubes were also not significantly different.

The two primary end points used to assess the effectiveness of therapy in this empyema model were the pleural peel score and the number of rabbits with gross pus at autopsy (ie, gross score of 4). The pleural peel score consists of the sum of pleural peel thicknesses at four different sites, which should provide a better overall measure of the pleural surfaces even when considerable variability of the pleural peel thickness occurs. In some cases, the pleural peel may be thick in one area (medially for example), but relatively normal in other areas. Our microscopic score obviously suffers from the problem that it was obtained from a single site (right lower lobe). When variability of the pleural thickness is present, it would not be captured by the microscopic analysis at a single site. This may explain the unexpectedly low microscopic score obtained from the control group (Fig 4).

The presence of gross pus at autopsy clearly indicates treatment failure. The percentage of rabbits with gross pus at autopsy was the highest in the control and 72-h groups. It was somewhat surprising that there was a trend toward a greater percentage of rabbits with pus in the 72-h chest tube group relative to the control group (although not statistically significant). A possible explanation for this trend is that the chest tube itself may have added an additional degree of inflammation. However, in uninfected animals, chest tube placement alone led to only minimal adhesions in the pleural space.

Using this animal model of empyema in which the bacterium P. multocida is injected into the pleural space of the rabbit with nutrient agar, early chest tube placement led to a significantly lower pleural peel score at autopsy after 10 days. The presence of frank pus at autopsy was decreased in the early chest tube groups and there was a trend toward less mortality in the rabbits that received chest tubes. This study confirms the results of previous case series reports3-5 two recent retrospective analyses relating to chest tube placement,6,7 and the prior expert opinion statement11 that chest tubes should be placed early after the diagnosis of an empyema.

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