Whole lung lavage for pulmonary alveolar proteinosis:
still the most up-to-date treatment

Pulmoner alveoler proteinozis için tüm akciğer lavaji: Hala en güncel tedavi

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ÖZ
Amaç: Bu çalışmada, pulmoner alveoler proteinozlu hastalarda tüm akciğer lavajının lavaj öncesi ve sonrası kan gazı analizi değerlerindeki önemi değerlendirildi.


Sonuç: Deneyimimizde lavajın erken dönemde tamamen uyuşması ve Lavaj sonrası semptomatik düzelmeler hızlı bir şekilde oluştu. Lavaj sonrası oksijen saturasyonunun düzelmesi ve semptomatik düzelmelerin hızlı olması, lavajın efektifliği ve güvenilirlüğünü belirtir.

Anahtar sözcükler: lavaj, pulmoner alveoler proteinoz, akciğer lavajı.
Whole lung lavage is a method of choice to remove alveolar phospholipoproteins which are responsible for the gas-exchange abnormalities.[1] Idiopathic pulmonary alveolar proteinosis (PAP) is a rare lung disease of impaired alveolar macrophage function, suggesting mainly a defect in granulocyte-macrophage colony stimulating factor (GM-CSF) signaling.[2] Currently, PAP occurs in three clinically distinct forms which are acquired (or idiopathic), congenital, and secondary PAP.[3] Alveolar macrophages in acquired form of PAP show less chemotactic and phagocytic activity and reduced cellular adherence due to anti-GM-CSF antibodies.[2,5] The congenital form, characterized by an acute onset after birth, is caused by mutations of the genes encoding surfactant protein B or C or the GM-CSF receptor beta subunit, or ABCA3.[6-9] Secondary PAP develops in association with conditions involving functional impairment of alveolar macrophages which are inhalation of inorganic dust, malignancies, immunodeficiency disorders, hematologic disorders, and pharmacologic immunosuppression.[10]

In acquired PAP, dyspnea, the most common presenting symptom, and cough occur on mild to moderate exertion. Some patients may become symptomatic acutely after supervening infection. Physical examination is often normal, clubbing is present in about one third of cases. Patients with advanced disease may have central and peripheral cyanosis.[11]

The series reported in the literature suggest a male preponderance (male:female ratio 3:1). Peak onset is in the third or fourth decade of life with over 80% of reported cases occurring in this age group.[2] However, there are reports of the disease occurring in neonates, children, and the elderly.[5,12]

Because of the pathogenesis is not completely known, the current mainstay of treatment for PAP is the mechanical removal of the proteinaceous material which is responsible for the functional and gas-exchange abnormalities observed in this disorder via whole lung lavage. The main indication for whole lung lavage is a method of choice to remove alveolar phospholipoproteins which are responsible for the gas-exchange abnormalities. Currently, PAP occurs in three clinically distinct forms which are acquired (or idiopathic), congenital, and secondary PAP. Alveolar macrophages in acquired form of PAP show less chemotactic and phagocytic activity and reduced cellular adherence due to anti-GM-CSF antibodies. The congenital form, characterized by an acute onset after birth, is caused by mutations of the genes encoding surfactant protein B or C or the GM-CSF receptor beta subunit, or ABCA3. Secondary PAP develops in association with conditions involving functional impairment of alveolar macrophages which are inhalation of inorganic dust, malignancies, immunodeficiency disorders, hematologic disorders, and pharmacologic immunosuppression.

In this study, we aimed to evaluate the value of whole lung lavage on prelavage and postlavage blood gas analysis values of patients with PAP.

PATIENTS AND METHODS
We retrospectively reviewed medical records of nine patients (1 male, 8 females; mean age 38.2 years; range 29 to 60 years) undergoing pulmonary alveolar lavage with the diagnosis of PAP between January 1998 and May 2010 at Marmara University Hospital Department of Thoracic Surgery. We performed a total of 19 lavages. Procedure was performed unilaterally, five times in one patient, once in two patients, and bilateral sequential lavage was done to the remaining. We followed-up the patients at the intensive care unit (ICU) after the procedure. The study protocol was approved by the Medical Faculty of Marmara University Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Prelavage evaluation included chest X-rays and high resolution computed tomographic (CT) scans of thorax, complete blood counts, arterial blood gas measurements, and pulmonary function testing. Pulmonary function tests of the whole group showed a restrictive ventilatory pattern with an impaired gas exchange. Bronchoscopy in eight patients and pathological examination of biopsied lingula in one patient confirmed the diagnosis of PAP.

For lung lavage, we chose the side to be washed depending on the distribution and severity of alveolar involvement as evidenced on radiologic images. Patients underwent double lumen intubation under general anesthesia. Both lungs were ventilated with 100% oxygen to eliminate nitrogen from the alveolar gas. We then isolated the lung to be treated at the end of the expiration. We instilled warm (36-37 °C) neutral sterile saline (0.9% saline with 0.6 mmol/L sodium bicarbonate per liter saline) into the lung through a closed system at the same rate as oxygen was adsorbed until the estimated functional residual capacity value has been reached. At this point, the lung was completely de-gassed and filled full of saline. We let tidal volume increments (500-1200 mL) of the saline into the lung under gravitational force at each cycle. We controlled the temperature, volume of saline instilled, and fluid balance carefully. After passive recovery of the opaque fluid over a closed silicon tube system, we began the next washing cycle. We performed vigorous chest percussion during all cycles of instillation and recovery. Every six-cycle, we changed the position from supine to left lateral or right lateral oblique.
position. The initial returns were typically very milky or turbid and we repeated the process of filling and draining the lungs with saline until the fluid recovered was clear (Figure 1). We performed whole lung lavage procedures in an identical way, each lung being lavaged with volumes of 15-30 L of saline solution. At the end of the procedure, the residual saline from the lung and resumed ventilation with 100% oxygen was drained and aspirated. We replaced the double lumen tube with a single lumen tube and examined the endobronchial system by a fiberoptic bronchoscope to check for the patency and to aspirate the remaining lavage fluid. Vital parameters such as arterial saturation of oxygen, central venous pressure, end-tidal carbon dioxide blood pressure, airway pressure, ventilation per minute, body temperature, and heart rate were recorded to control hemodynamic stability during the procedure. The patients were transferred to the ICU intubated and continued mechanical ventilation with positive end expiratory pressure (PEEP) of 7.5 cm H₂O. Criteria for extubation were partial pressure of carbon dioxide <40 mmHg, partial pressure of oxygen (pO₂) >65 mmHg, vital capacity >10 mL/kg, fraction of inspired oxygen <0.5, tidal volume >5 mL/kg, PEEP <5 cmH₂O, and spontaneous respiration of 20-30/minute with no excessive or thick secretions. Chest radiographs were taken and arterial blood gases, electrolytes, and complete blood counts were measured routinely during the postlavage period. For staged lavages, we preferred an interval of at least one week.

Statistical analysis

Prelavage and postlavage blood gas values were analyzed by Wilcoxon signed ranks test. We considered a p value of 0.05 or less to indicate a statistically significant outcome. Statistical analysis was performed with IBM SPSS version 19.0 software (IBM Corporation, Armonk, NY, USA).

RESULTS

All patients with idiopathic PAP underwent whole lung lavage. The major symptom was dyspnea in all patients. Cough was the coexisting symptom in two patients. Chest radiographs demonstrated bilateral infiltration with reticular pattern and CT of thorax showed the appearance of wide spread air space consolidation, with bilaterally thickened interlobular septa (Figure 2). Prelavage arterial blood gases were

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**Figure 1.** Appearance of viscous, milky lipoprotein material removed by lavage. Bottle on left was obtained from the very first cycle, precipitation of lipoprotein material at the bottom was noted. Bottle on right is from the last cycle of same patient.

**Figure 2.** Radiographic appearance of pulmonary alveolar proteinosis. (a) A posteroanterior chest radiograph showing bilateral infiltrates. (b) High resolution computed tomography scan of the chest showing patchy areas of ground-glass opacification, appearance of wide spread air space consolidation, with bilaterally thickened interlobular septa.
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hypoxic in four patients (partial $pO_2 \leq 60$ mmHg) although two of them were under oxygen supply of 2 L/minute (Table 1). Partial $pO_2$ of seventh patient was at the hypoxia limit while receiving oxygen supply of 2 L/minute. We performed a total of 19 lavage procedures to nine patients. No major complication occurred perioperatively. Mean duration of lavage was 233 minutes (range, 135 to 420 minutes). Total amount of the lavage fluid volume ranged between 15 to 30 L of saline solution. An average of 1.47 L (range, 0 to 4.2 L) of saline solution remained in the lung after the procedure. The patients remained intubated for 2.6 days (range, 1 to 16 days) after the procedure. Mean stay at ICU was 3.5 days (range, 1-16 days). One patient died on 16\textsuperscript{th} postoperative day of her fifth lavage because of respiratory arrest during the attempt for percutaneous tracheostomy. Overall hospital stay was 5.4 days (range, 3 to 16 days).

Oxygen saturations and partial pressures of oxygen improved considerably after whole lung lavage and both oxygen saturations and partial pressures of oxygen were statistically significant ($p<0.05$). Median prelavage and postlavage measurements of oxygen saturation and $pO_2$ were 92% (range, 84% to 97%) and 95.5% (range, 87 to 97%), 60.8 mmHg (range, 47.7 to 86) and 73.5 mmHg (range, 64 to 88), respectively (Table 2).

### DISCUSSION

Pulmonary alveolar proteinosis, first described by Rosen et al.\cite{14} in 1958, is a rare disease of impaired alveolar macrophage function caused by neutralizing anti-GM-CSF autoantibodies and represents a syndrome with a number of possible etiologies.\cite{2-9,15} Accumulation of phospholipoproteinaceous material in the alveoli results in a non-specific radiographic pattern of air space consolidation. The consolidation is usually bilateral and patchy and in some patients is very extensive, despite relatively mild respiratory symptoms. High resolution CT of thorax demonstrates the expected appearance of wide spread air space consolidation, but also thickened interlobular septa, clearly visible within the affected lung and producing the so-called crazy paving pattern.\cite{5,16}

Although the appearance on high resolution CT scan of the thorax often indicates the diagnosis, it should be confirmed by analysis of bronchoalveolar lavage fluid. Milky fluid is usually obtained from bronchoalveolar lavage of an affected segment (Figure 1).\cite{5} Increased levels of lactate dehydrogenase,\cite{17} tumor markers,\cite{18} mucin-like glycoprotein,\cite{19} the surfactant proteins A,\cite{20} and D\cite{21} were also been recorded in PAP.

Because the pathogenesis is not completely known, the current mainstay of treatment for PAP is the mechanical removal of the proteinaceous material which is responsible for the functional and gas-exchange abnormalities observed in this disorder via whole lung lavage.\cite{11,22,23} However, the severe hypoxemia in PAP patients and the difficulty of the technique have limited its application to medical centers and to more advanced cases.\cite{24} The clinical

### Table 1. Patient characteristics and preoperative blood gas analysis

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age/Gender</th>
<th>$pH$</th>
<th>$pO_2$</th>
<th>$pCO_2$</th>
<th>HCO\textsubscript{3}\textsuperscript{−}</th>
<th>$SO_2$ (%)</th>
<th>Habit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31/F</td>
<td>7.42</td>
<td>55.0</td>
<td>33.4</td>
<td>22.0</td>
<td>89.0</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>2*</td>
<td>40/F</td>
<td>7.45</td>
<td>86.0</td>
<td>29.0</td>
<td>20.2</td>
<td>96.9</td>
<td>Smoker</td>
</tr>
<tr>
<td>3</td>
<td>37/F</td>
<td>7.43</td>
<td>70.0</td>
<td>37.7</td>
<td>23.0</td>
<td>94.0</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>4*</td>
<td>41/M</td>
<td>7.41</td>
<td>50.7</td>
<td>34.9</td>
<td>21.9</td>
<td>86.0</td>
<td>Smoker</td>
</tr>
<tr>
<td>5</td>
<td>29/F</td>
<td>7.44</td>
<td>72.0</td>
<td>38.0</td>
<td>25.4</td>
<td>95.0</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>6*</td>
<td>30/F</td>
<td>7.43</td>
<td>47.7</td>
<td>41.8</td>
<td>26.8</td>
<td>84.5</td>
<td>Smoker</td>
</tr>
<tr>
<td>7*</td>
<td>46/F</td>
<td>7.42</td>
<td>61.7</td>
<td>34.3</td>
<td>22.2</td>
<td>92.0</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>8</td>
<td>60/F</td>
<td>7.47</td>
<td>60.0</td>
<td>33.1</td>
<td>23.7</td>
<td>92.6</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>9</td>
<td>32/F</td>
<td>7.42</td>
<td>75.0</td>
<td>37.0</td>
<td>24.0</td>
<td>93.0</td>
<td>Smoker</td>
</tr>
</tbody>
</table>

$pH$: Power of hydrogen; $pO_2$: Partial pressure of oxygen; $pCO_2$: Partial pressure of carbon dioxide; HCO\textsubscript{3}\textsuperscript{−}: Bicarbonate; $SO_2$: Saturation of oxygen; * Blood gas analysis under oxygen supply of 2 L/minute.

### Table 2. Table comparing median values of prelavage and postlavage oxygen saturation, partial pressure of oxygen, and carbon dioxide

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$SO_2$ %</td>
<td>92</td>
<td>95.5</td>
<td>0.017</td>
</tr>
<tr>
<td>$pO_2$ mmHg</td>
<td>60.8</td>
<td>73.5</td>
<td>0.012</td>
</tr>
<tr>
<td>$pCO_2$ mmHg</td>
<td>34.6</td>
<td>35</td>
<td>0.327</td>
</tr>
</tbody>
</table>

$SO_2$: Saturation of oxygen; $pO_2$: Partial pressure of oxygen; $pCO_2$: Partial pressure of carbon dioxide; Wilcoxon signed ranks test was used to analyze the values. Prelavage and postlavage values of oxygen saturation and partial pressures were statistically significant ($p<0.05$).
course and prognosis with or without bronchoalveolar lavage are variable. Some patients require lavage every few months while others remain in remission for several years.

Historically, corticosteroids, potassium iodide, and streptokinase were administered with variable success. Diaz et al. showed improvement in one patient with surfactant activator, ambroxol, although this would be expected to exacerbate the intraalveolar accumulation of surfactant. Some patients treated with aerosolized trypsin to hydrolize the protein material developed allergic reaction. Treatment with GM-CSF is a possibility, although its long-term safety has not been determined. An alternative procedure is selected segmental or lobar lavage by fiberoptic bronchoscopy (FOB). Lobar lavage by FOB is a simple and safe procedure that may be useful in patients with PAP in whom whole lung lavage via general anesthesia may be hazardous, and in patients with less advanced disease from whom proteinaceous substances can be removed with a small volume of lavage fluid.

Whole lung lavage is well tolerated by most patients despite concerns regarding the effect of a large-volume isotonic saline solution lavage on the lung. Safety measures include the correct placement of the double lumen endobronchial tube, checking for the leaks prior to lavage and close monitoring of the patient during the procedure. The short-term outcome and success of the procedure seem to depend on the capacity of the lung to rapidly remove the residual alveolar fluid that remains in the lung after lavage.

In the study of Chesnutt et al. a FOB inserted through the endobronchial tube was used to carry out sequential segmental lung lavage with serial 50 mL saline solution instillation to a total of 1.7 to 4.2 L. The authors demonstrated the rate and mechanism for removal of residual alveolar fluid after lung lavage. Alveolar epithelial clearance was rapid (53±14%/hour) and appeared to be independent of catecholamine

![Image](image-url)
mechanism. This rapid rate of alveolar epithelial fluid transport explains why patients with PAP tolerate large volumes.[27] This study also provides the first data demonstrating a rapid rate of alveolar fluid clearance from the in vivo human lung in the absence of preexistent pulmonary edema.[28]

The major adverse effect of whole lung lavage is hypoxemia, particularly during the emptying phase, which decreases airway pressure and increases the perfusion of the lavaged lung.\(^5,29\) Arterial oxygenation improves during the filling phase due to the increase in airway pressure and shunting of blood to the contralateral ventilated lung. Emptying of the lung causes a decrease in airway pressure and perfusion of the surfactant-filled alveoli creates a shunt in the lung undergoing treatment and hence a fall in partial \(pO_2\).[5]

Hemodynamic instability may occur with single lung ventilation, which may necessitate invasive monitoring and further complicate the course of treatment.\(^{29,30}\) Whole lung lavage requires general anesthesia and an experienced anesthesiologist. Leakage of the lavage fluid into the contralateral ventilated lung must be avoided.\(^{24}\) Major risks of whole lung lavage concern the correct placement of the double lumen endobronchial tube. If placed wrongly, lavage fluid may spill into the ventilated lung. Barotrauma might occur with rapid instillation of large volumes of fluid. The repeated replacement of a double-lumen endotracheal tube may lead to endotracheal granuloma and stenosis. Other reported complications include pleural collections, hydropneumothoraces, and surgical emphysema.\(^{11}\) The risk of hypothermia is minimized by careful monitoring of patient’s core temperature. A postoperative care facility is also needed.\(^{4,5}\)

During the follow-up, the major complication is infection with unusual organisms such as Mycobacterium, Aspergillus, Pneumocystis carinii, and various fungi and viruses.\(^5\) One patient in our study received intravenous antibiotics covering Gram positive and negative organisms because of high fever (>38.5 °C) and recovered in five days. In our study, all patients received prophylactic broad spectrum antibiotics for 14 days postoperatively. Corticosteroids are not advised to be used as empirical treatment due to its potential to exacerbate opportunistic infections.\(^5\)

Our study group showed significant improvement in management of the symptoms and oxygenation. Prelavage and postlavage values of oxygen saturation and partial pressures were statistically significant (Table 2). Postlavage X-rays showed clearance of the infiltrates (Figure 3). All patients are under annual follow-up. All are symptomless except for a 33-year-old patient who is still smoking one pack/day, using home oxygen.

Our study was limited by its retrospective nature. The rarity of the disease limits the number of available patients for whole lung lavage. The number of patients evaluated in this study is low due to the single center nature.

In conclusion, whole lung lavage appears to be the most effective treatment of pulmonary alveolar proteinosis. Although this is a procedure that requires general anesthesia and has the risks of hemodynamic instability, leakage of lavage fluid into the contralateral lung, pleural collection, hydropneumothorax, emphysema, and endotracheal granuloma or stenosis because of repeated procedures, whole lung lavage is a reliable technique in experienced hands. A collaborative team of anesthesiologists and chest physicians should be involved in the management of the patient from the day of admission. The patient should be informed of the need for endotracheal tube and artificial ventilation in the immediate postoperative period. Whole lung lavage is a promising intervention in optimal treatment of pulmonary alveolar proteinosis providing significant improvements in oxygenation and symptoms.

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