



## Whole Lung Lavage in a Pulmonary Alveolar Proteinosis Patient with Severe Respiratory Failure

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Pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease that develops as a result of defects in the clearance of surfactant by alveolar macrophages. The accumulation of lipid- and protein-rich substances in the alveoli constitutes the main pathology of this disease. PAP has three types of aetiology: autoimmune (primary), congenital and secondary. The most common form in adults is autoimmune PAP. Whole lung lavage is a commonly performed method for treatment of this form of disease, especially in more severe cases. Performed under general anaesthesia, the material deposited in the alveoli is removed by washing. In this paper, we present a whole lung lavage under anaesthesia in a PAP patient who had severe respiratory failure.

**Keywords:** Whole lung lavage, anaesthesia, pulmonary alveolar proteinosis

### Introduction

Pulmonary alveolar proteinosis (PAP) is a rarely observed interstitial lung disease, and it was initially defined on the basis of a 27-case series performed by Rosen et al. (1) in 1958 with a literature review. The first PAP case reports in Turkey were published in 1964, and 24 cases have been reported between 1958 and 2010 (2). The defect in the cleaning of surfactant released by type II pneumocytes by alveolar macrophages constitutes the pathogenesis of the disease. As a result, surfactant, which is rich from lipid and protein, accumulates in the alveoli (3). In the pathological examination of the material taken from the lung under microscope, periodic acid-Schiff (PAS)-positive granular and eosinophilic lipoprotein materials that fill in the alveoli can be observed (4).

PAP is divided into 3 types according to its aetiology: autoimmune (primary), hereditary and secondary PAP. Autoimmune (primary) PAP, which accounts for 90% of cases, occurs as a result of GM-CSF autoantibodies that bind to granulocyte/macrophage colony-stimulating factor (GM-CSF) with high affinity. Secondary PAP develops because of a decreased number or functioning of alveolar macrophages, depending on underlying diseases (immunodeficiency, hematopoietic, genetic, autoimmune, infection diseases and inhalation of toxic inorganic agents) (3-5). On the other hand, hereditary PAP occurs because of mutation of the genes coding surfactant proteins and GM-CSF receptor chain; it is characterized by respiratory distress that rapidly progresses after birth.

The treatment of pulmonary alveolar proteinosis must target its etiological cause. The treatment of underlying cause or disease is at the forefront in secondary PAP, and supportive treatment or lung transplantation is the principal aim in hereditary PAP (4, 5). In severe autoimmune PAP cases, common treatment method is whole-lung lavage under general anaesthesia, and it provides a clinically and radiologically effective treatment opportunity (3-6).

In this study, it was aimed to discuss the administration method of whole-lung lavage performed under general anaesthesia along with its intraoperative and postoperative complications in a PAP patient followed up for severe respiratory failure.

## Case Presentation

A 37-year-old male patient had been admitted to the chest diseases clinic of our hospital 7 years ago with the complaint of shortness of breath. His chest radiography had revealed bilateral diffuse infiltration; subsequently, bronchoalveolar lavage analysis was performed and the results were consistent with PAP. During follow-up examinations, it was revealed that the patient had undergone whole-lung lavage 7 times (once a year) under general anaesthesia at different centres. The last lavage had been performed on both lungs 1 year ago. Because his symptoms had improved and diffuse infiltration had been detected in both lungs, right lung lavage had been performed at another centre 15 days ago. The patient was hospitalized in the clinic for left lung lavage because of his clinical condition.

In the preoperative assessment, it was found that the patient had a history of substance use and smoking at 25 pack year<sup>-1</sup>; however, he had no comorbidities. His examination revealed dyspnoea, cyanosis of the extremities and lips, and crepitant rales in both lungs, which were particularly prominent in the left lung. Chest radiography revealed an infiltrative appearance in the basal regions (Figure 1). Electrocardiography (ECG) revealed a normal sinus rhythm. Transthoracic echocardiography showed that the ejection fraction was 60% and right and left cardiac chambers were normal. In the laboratory findings, there was no abnormal result except the values of AST 50 U L<sup>-1</sup>, GGT 89 U L<sup>-1</sup> and LDH 589 U L<sup>-1</sup>. Restrictive respiratory disorder was observed in the respiratory function test performed approximately 3 months ago (FEV<sub>1</sub> 1.77 L, FVC 2.04 L and VC 2.07 L).

When the patient was taken into the operating room, his blood pressure was 160/110 mm Hg, heart rate was 109 beat min<sup>-1</sup>, and peripheral oxygen saturation at room temperature (SpO<sub>2</sub>) was 62%. The patient, who was administered oxygen, was administered 150 µg fentanyl, 200 mg propofol and 50 mg rocuronium. He was intubated with

37 F left double-lumen tube and the position of the tube was confirmed through fibre-optic bronchoscope. Twenty minutes after the intubation, when FiO<sub>2</sub> was 100%, SpO<sub>2</sub> was found to be 92%. For the maintenance of anaesthesia, inhalation anaesthetics were not used. The patient was administered total intravenous anaesthesia (TIVA) with propofol 5–10 mg kg<sup>-1</sup> h<sup>-1</sup> and remifentanyl 0.5 µg kg<sup>-1</sup> min<sup>-1</sup> infusion. The left bronchus was clamped. Single-lung ventilation was performed for the right lung with volume-controlled ventilation so that the tidal volume was 6 mL kg<sup>-1</sup>, according to ideal body weight, and the positive end-expiratory pressure (PEEP) was 5 mm Hg. Hemodynamic and ventilation parameters during the procedure are shown in Table 1. Blood gas evaluation was performed with invasive artery pressure monitoring (Table 2).

An aspiration catheter was advanced from the left bronchus side of intubation tube. A total of 3000 mL 0.9% NaCl solution, which was pre-heated at 37°C, was administered through the tip of intubation tube. Bronchoalveolar lavage was initiated in the supine position. At the beginning, approximately 300–400 mL 0.9% NaCl solution was administered into the left lung through the tube at every turn. Then, it was drained into another container under the



Figure 1. Preoperative chest radiography

Table 1. Intraoperative haemodynamic and ventilation parameters

Time	Blood pressure (mm Hg)	Heart rate (min)	SpO <sub>2</sub> (%)	FiO <sub>2</sub> (%)	EtCO <sub>2</sub> (mm Hg)	Ppeak (cm H <sub>2</sub> O)
Before procedure	160/110	109	62	21	-	-
Intubation	150/101	100	92	96	36	38
Intraoperative 0 <sup>th</sup> min	160/105	101	90	95	37	41
Intraoperative 30 <sup>th</sup> min	152/100	96	92	95	37	41
Intraoperative 60 <sup>th</sup> min	135/83	90	91	95	38	41
Intraoperative 90 <sup>th</sup> min	145/97	88	89	96	38	41
Intraoperative 120 <sup>th</sup> min	144/89	86	95	96	40	40
Intraoperative 150 <sup>th</sup> min	127/86	84	87	95	35	38
End of procedure	144/98	90	90	95	35	37

influence of gravity. Washing fluid, collected in one-litre containers, was milky at the beginning, but its colour got pale during the procedure (Figure 2). Lavage was performed with 15 L of fluid in the left lung. At the end of the process, which lasted for 180 minutes, single-lung ventilation was terminated. Both lungs were ventilated for some time and remifentanyl and propofol infusions were discontinued. Intravenous sugammadex 200 mg was administered for the reversal of muscle relaxation and the patient was extubated.

Laboratory results of fluid samples taken from the first and last containers were analysed. The value of protein was 1 g dL<sup>-1</sup>, LDH was 1795 U L<sup>-1</sup>, cholesterol was 6 mg dL<sup>-1</sup> and triglyceride was 4 mg dL<sup>-1</sup> in the samples from the first container; however, in the samples from the last container, the values were 0.1 g dL<sup>-1</sup>, 75 U L<sup>-1</sup>, 0 mg dL<sup>-1</sup> and 2 mg dL<sup>-1</sup>, respectively. Hypoxemia was observed to continue in the postoperative monitoring, and the appearance of infiltration was still observed in the basal regions on chest radiography. Blood gas analysis results obtained in the postoperative period are provided in Table 2. Serum LDH values were 591 UL<sup>-1</sup> on the postoperative 10th day and 714 U L<sup>-1</sup> on the postoperative 17th day. The patient was administered antibiotic and steroid therapy and his general condition was good. Eventually, he was discharged from the hospital with oxygen concentrator on the postoperative 33<sup>rd</sup> day. In the CO diffusion test that was performed 42 days after discharge, FRC was found to be 1.77 L, VC was 1.93 L, TL<sub>CO</sub> (Hb) was 1.11 mmol kPa<sup>-1</sup> min<sup>-1</sup> and K<sub>CO</sub> (Hb) was 0.41 mmol kPa min<sup>-1</sup>.

## Discussion

Autoimmune PAP is the most common type in adults, and its treatment includes whole-lung lavage, subcutaneous or inhalation GM-CSF application, plasmapheresis and rituximab administration (3-5). Whole-lung lavage, which was firstly defined in 1960s, has been used for more than 50 years; it is still considered a golden technique in PAP treatment (5). The evaluation of 24 cases reported in Turkey demonstrated that whole-lung lavage was performed in 25% cases and segmental bronchial lavage in 17% (2).

In whole-lung lavage, a single lung is administered heated

(temperature 37°C) sterile 0.9% NaCl solution at a volume of 15–20 L. The intervention is performed using a double-lumen tube, under general anaesthesia with muscle relaxant administration. Although ventilating the lung that will not undergo bronchoalveolar lavage (single-lung ventilation), 500 mL L<sup>-1</sup> fluid is administered at each time to the lung that will be implemented lavage. Then, the fluid is drained from the lungs into another container with manual chest percussion under the influence of gravity. This process is repeated until a total of 15–20 L 0.9% NaCl solution is used. When the lavage fluid collected in the containers is examined macroscopically, it can be observed that the colour of fluid is opaque and milky at the beginning but gets paler gradually (3-6). Similar to the findings in the literature, we used a total of 15 L 0.9% NaCl solution and a total of 15 L fluid was



Figure 2. View of bronchoalveolar lavage fluid in the first and ninth L

Table 2. Preoperative, intraoperative and postoperative blood gas values

	Preop	25. min	60. min	120. min	180. min	Postop 0	6. day	14. day	20. day	31. day
pH	7.38	7.26	7.24	7.21	7.21	7.37	7.37	7.39	7.42	7.41
PCO <sub>2</sub> (mm Hg)	37.3	52.7	55.1	57.5	55.7	34.6	39.1	40.3	39.4	39.3
PaO <sub>2</sub> (mm Hg)	52.3	97.4	85.9	78.9	84.9	52.1	50.2	49.7	50	48.7
HCO <sub>3</sub> (mmol L <sup>-1</sup> )	22.1	20.6	20.1	17.1	18.5	20.7	21.9	23.8	24.9	24.3
BE (mmol L <sup>-1</sup> )	-2.4	-3	-3.5	-5	-5.2	-4.5	-2.4	-0.1	1.1	0.4
SaO <sub>2</sub>	85.8	95.6	95.7	93.8	93.6	83.4	79.1	80.4	80.7	78.1

drained. The colour of the washing fluid got paler from the initial opaque milky appearance.

When a patient with pulmonary alveolar proteinosis presents with hypoxemia or dyspnoea which causes a clinically restricted activity, whole-lung lavage can be performed for treatment. Other indications of whole-lung lavage include  $\text{PaO}_2 < 65$  mm Hg,  $\text{P (A-a)O}_2 \geq 40$  mm Hg or shunt fraction  $> 10\text{--}12\%$  (4, 6). The presence of a cardiopulmonary instability creates relative contraindication (4). Removing materials accumulated in alveoli and locally accumulated GM-CSF antibodies through washing will improve oxygenation and decrease tachycardia and hypotension attacks. In our case, the indication for whole-lung lavage was decided by considering existent respiratory failure and low  $\text{PaO}_2$  value in the blood gas examination.

Because whole-lung lavage is performed under general anaesthesia, findings related to oxygenation disorder is the most common issue encountered in terms of anaesthesia. Low oxygen saturation is generally observed in monitoring. Therefore, oxygen administration before anaesthesia induction will decrease complications associated with hypoxemia to the minimum level. Although patients are generally hypoxemic, they tolerate the procedure well (5, 6). In our case, although our patient had severe hypoxemia findings, no problem related to oxygenation was observed during the procedure. Removing materials in the alveoli through washing causes increases in the values of  $\text{SpO}_2$  and arterial blood  $\text{PaO}_2$  (7). However, increased blood flow and perfusion and decreased airway pressure in the lung during drainage phase of lavage can cause a temporary decrease in  $\text{SpO}_2$  (5, 7). Similarly, the values of  $\text{SpO}_2$  and  $\text{PaO}_2$ , which were low before surgery, increased with the beginning of lavage process in our case; this was consistent with the findings reported in literature. However, short decreases were sometimes observed in  $\text{SpO}_2$  values during the drainage of fluid into containers (Table 1).

Another problem that can be encountered during anaesthesia and administration is hypothermia. Hypothermia results from an excessive amount of fluid used during the process and the duration of procedure (approximately 3–4 hours). For this complication to be prevented, the fluid that will be used must be heated to  $37^\circ\text{C}$  before the process, and the patient must be kept warm with a heated blanket during the process (5-7).

After the end of the procedure, attention must be paid to the discontinuation of anaesthesia and extubation of patient. At the end of anaesthesia, single-lung ventilation is stopped and ventilation of both lungs is provided for some time. Patient is extubated when haemodynamic, oxygenation and respiration functions are adequate. Extubation of patient in the operating room immediately after the completion of the procedure is ideal (6). However, in some conditions, considering the general health state of patient, extubation can be performed after monitoring in the intensive care units

(3, 6). For the complete reversal of respiratory functions after general anaesthesia, the termination of the action times of muscle relaxants is another issue that must be paid attention to. For this purpose, the preference of steroid non-depolarising muscle relaxants will allow the complete reversal of their effects by forming complexes with sugammadex at the ratio of 1:1 (8). Therefore, in our case, the use of steroidal rocuronium was preferred as a muscle relaxant.

Other complications that can develop during the procedure are pleural effusion, pneumothorax, hydrothorax, pneumonia, sepsis, and acute respiratory distress syndrome (ARDS) (3-6). Therefore, it is essential to perform laboratory and imaging examinations for these complications during the flow-up after the procedure. In our case, no complication was observed during the follow-up examinations.

Lavage procedure can be performed in the same session for both lungs or it can be done at 24–48-hour intervals (3, 5-7). After the procedure, patients generally have recovery in terms of symptoms, radiological findings and functions (3, 5). However, in our case, whole-lung lavage was performed in the contralateral lung after 15 days; this caused hypoxemia (Table 2) and infiltration appearance in chest radiography to continue and LDH values to increase again. Hence, it is suggested that this situation limits the observation of well-being condition stated in literature.

Recently, multicentre phase II studies have been conducted on the use of GM-CSF therapy with inhalation in the treatment of PAP disease. With this treatment, a decrease has been detected in anti-GM-CSF antibody titre in the bronchoalveolar lavage fluid (9, 10). However, the relationship between PAP disease and pulmonary fibrosis shows that fibrotic changes in the lung tissue can be maintained even after whole-lung lavage or GM-CSF treatment (9). This drug, with the active ingredient of sargramostim, is not yet licensed in Turkey. Hence, it can be imported only after various procedures. Therefore, no additional treatment method was used after whole-lung lavage in our case. Further detailed studies must be conducted in the future to obtain more data on the effects of treatment methods such as whole-lavage lavage and GM-CSF combination with inhalation.

## Conclusion

Whole-lung lavage positively contributes to the treatment of the disease by removing local GM-CSF antibodies and lipoprotein materials accumulated in the alveoli. Although the process seems easy, it can be complicated because of the severity of respiratory failure, prolonged duration of anaesthesia, and possible complications. Lavage procedure that will be performed in both lungs can be performed in the same session or in different sessions. However, in cases where intermittent lavages must be administered, the time between two lavage procedures is important. As evidenced in this case report, long intervals between lavage procedures performed

in both lungs do not contribute to clinical recovery to a great extent. We think that the positive effect decreases if lavage procedures are performed at more than 24–48-hour intervals. It is recommended that this condition should be taken into consideration for symptomatic and functional recovery in patients.

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