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Research Paper – Araştırma Makalesi

ALVEOLAR PROTEINOSIS: BRONCHOALVEOLAR LAVAGE EXPERIENCE, CURRENT LITERATURE REVIEW

ALVEOLAR PROTEİNOZİS: BRONKOALVEOLAR LAVAJ DENEYİMİ, GÜNCEL LİTERATÜR TARAMA

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Özet

Bronkoalveoler lavaj, pulmoner alveolar proteinozis için ilk basamak tedavi olarak kabul edilmektedir. Hastalık ve tedavisiyle ilgili akılda tutulması gereken noktalar güncel literatür eşliğinde gözden geçirilmiş ve lavaj prosedürünün etkinliği konusundaki klinik deneyimlerimizle birlikte sunulmuştur. Çalışmaya alveolar proteinozis tanısı alan hastalar dahil edildi. Toplamda 6 hastaya 15 lavaj uygulandı. Preoperatif ve postoperatif 3. saat arteriyel kan gazı değerleri kaydedildi. Parsiyel oksijen basıncına ek olarak, preoperatif-postoperatif değişimler de değerlendirildi ve tüm hastaların lavaj hacimleri kaydedildi. Tedavi öncesine kıyasla parsiyel oksijen basıncında belirgin bir artış gözlendi. Parsiyel oksijen basıncı değişimi ile lavaj hacmi arasındaki paralel seyir dikkate değer bir sonuç olarak yorumlandı. Lavaj sonrası parsiyel oksijen basıncındaki artış oranı ile lavaj hacmi arasında pozitif korelasyon gözlendi. Bu durum lavaj sıvısı berrak hale geldikten sonra bir süre daha işleme devam edilmesinin işlem kalitesini artırabileceği fikrinin bir öncüsü olabilir.

Anahtar Kelimeler: Kan Gazı, Bronkoalveoler Lavaj, Alveolar Proteinozis

Abstract

Bronchoalveolar lavage (BAL) is considered as the first-line therapy for pulmonary alveolar proteinosis (PAP). The points to be kept in mind about the disease and its treatment were reviewed with current research and presented together with our clinical experience on the effectiveness of the BAL procedure. Patients with diagnosis of PAP were included. Total of 15 BALs were applied to 6 patients. Preoperative and 3rd postoperative hour arterial blood gas values were recorded. In addition to the partial oxygen pressures (PaO_2), the ratio of the difference to the preoperative value was also evaluated and the lavage volumes of all patients were recorded. A general significant increase in PaO_2 was observed compared to pre-treatment. The parallel trend between the PaO_2 change and the lavage volume per side was interpreted as a remarkable result. A positive correlation between PaO_2 change and lavage volume were observed. This may be a precursor to the idea that continuing lavage for a while after the lavage fluid has cleared improves the quality of the process.

Keywords: Blood Gas, Bronchoalveolar Lavage, Alveolar Proteinosis

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1. INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a disease characterized by abnormal accumulation of surfactants and its components in the alveoli due to interstitial inflammation or fibrosis. Its clinical course ranges from spontaneous resolving pneumonia to respiratory failure and even death (Seymour et al., 2002, p. 215-35). Described for the first time in the literature by Rosen et al. in 1958, PAP is a clinical condition that has challenges in its treatment but has a limited place in the current medical notion due to its rarity (Rosen et al., 1958, p. 1123-42).

Bronchoalveolar lavage (BAL) is the first-line treatment for PAP. It hinges on rinsing the proteinaceous material in the alveoli and restoring effective ventilation and adequate oxygenation (Michaud et al., 2009, p. 1678-81). Although nowadays modified techniques have been proposed, the procedure is generally done under general anesthesia; patients are intubated with a double-lumen endotracheal tube and saline is administered through the tube, followed by alveolar irrigation and then aspiration of the fluid.

Our study was aimed at drawing attention to lavage volume as a factor affecting the quality of the BAL procedure in cases with PAP, conducting a current literature review and comparing the literature information with our study data.

2. METHODS

Six cases with a histopathological diagnosis of PAP referred to our clinic for bronchoalveolar lavage between February 2012 and November 2020 were included in the study. There were no exclusion criteria in our study. All the cases were evaluated preoperatively with complete blood count, hepatic and renal function markers, coagulation tests and arterial blood gas (ABG). Patients deemed fit for operation had the procedure done under general anesthesia. Patients were intubated with a double lumen intubation tube positioned supinely on the operating table. In cases where unilateral procedure was planned, the lung to be lavaged was positioned down and supported with rubber cushions, with the patient angled at 45 degrees. Bilateral sessions were planned in patients deemed likely to tolerate the procedure. In cases where bilateral lavage would be done, the procedure was performed reversing the position after the other side's procedure was terminated. Fiberoptic bronchoscopy was used to confirm intubation tube placement. Using the bronchoscope's working channel, 500cc of saline was infused into the planned bronchial tree one time. Manual percussion was done to the lavaged hemithorax just before the fluid was aspirated, and continuous vibration was applied during the procedure with the help of a vibration device. All the fluid was then aspirated again with the help of a bronchoscope. This process was continued until clear fluid was aspirated (Figure 1). After the procedure, the patients were followed up in the intensive care unit (ICU). The cases whose respiratory parameters were unsatisfactory were kept intubated. The patients were evaluated with ABG and chest X-ray at the time of admission into the ICU, and another ABG during the third postoperative hour. Patients with satisfactory third hour ABG values were followed up in the ward and discharged subsequently after the appropriate inward follow-up period.

Figure 1: Aspiration materials of a patient's first, middle and last lavage in the same session are displayed.

Patients' age, gender, comorbidity, smoking history, diagnosis method, age at diagnosis, number of BALs done throughout lifetime, the side of each lavage done, preoperative, postoperative ICU admission and third hour partial oxygen (PaO_2) and partial carbon dioxide ($PaCO_2$) pressure values, time between two procedures and survival time, were recorded. The findings were evaluated together with literature data. Web of Science database was used for literature review. Articles containing the keywords "volume" or "blood gas" in the text and the keywords "bronchoalveolar lavage" or "alveolar proteinosis" in the title were included. The articles, which include all of the parameters such as volume and blood gas values used in our study were included in the study. Statistical analysis could not be performed due to the small number of cases. Descriptive data was presented as mean, standard deviation, median, minimum, and maximum in accordance with its type. Categorical data was given as frequency and percentage values. SPSS packet data program was used.

The study was conducted in accordance with the Declaration of Helsinki, with the approval of the Ege University School of Medicine Non-Pharmaceutical Scientific Research Ethics Committee (Approval No: 23-3.1T/34). Informed consent was obtained from all participants.

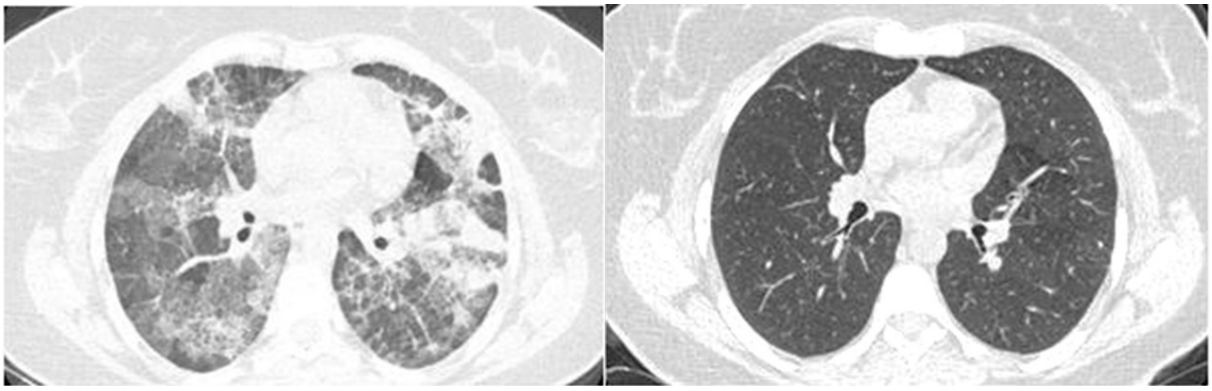
3. RESULTS

All the cases had prior examination history for nonspecific respiratory symptoms such as dyspnea and cough before being admitted to our clinic and were diagnosed with PAP histopathologically after suspicious tomography findings. Three (50%) of the six patients were women. The mean age at diagnosis was 37.67±7.68 (27-47). Bronchoscopic biopsy was performed in three patients while videothoracoscopic wedge resection was the diagnostic procedure in the other three patients. Although five cases (83.3%) had a history of smoking, only one (16.7%) was an active smoker. The median amount of use of smokers was found to be 30 (8-90) pack-year (the number of packs used per day multiplied by the total number of smoking years). Hypertension was the only comorbidity, present in one patient only (case 3). In our study, each patient's lavage was recorded. The mean lavage volume was 5944 ± 2357 (3000-12000) cc for each hemithorax.

The data that was inaccessible due to patients' procedures done in other centers was indicated as missing data. The patients had at least 2 and at most 4 sessions of lavage done throughout their lives.

When the characteristics of the cases were examined in detail, cases 1,2,4,5 and 6 had a smoking history of 8, 40, 18, 90 and 30 pack-years, respectively. The third case indicated never having a smoking history throughout their life and the fifth case expressed being an active smoker. All patients who registered no complications were discharged on the second postoperative day. In the third lavage of the third case, the need for re-intubation arose in the postoperative ICU and stayed intubated for four days in the ICU during the last procedure. The data of all BAL procedures done throughout the lifetime of the cases were summarized in Table-1. In addition, the thorax computed tomography image taken before and after the lavage of the third case is shown in Figure-2.

Figure 2: Thoracic computed tomography image of a case before and after lavage



A chart containing preoperative and postoperative 3rd hour ABG values was prepared with the thought that blood gas taken as soon as the patients were admitted to the ICU in the early postoperative period would not show the effectiveness of the procedure due to bronchospasm or effects of anesthesia. In addition to the preoperative and postoperative partial oxygen pressures, the ratio of the difference to the preoperative value was also evaluated in the graph.

The lavage volumes of all cases were included in the graph. In cases where bilateral procedures were performed, in regard to surgical notes, equal distribution of volume to the right and left lungs was detected. We subtracted the lavage volume per side in the graph. The lavage volume per side was included in the graph. Although statistical significance couldn't be reported, the fact that the rate of change and the lavage volume per side were parallel in the majority of the graph was considered substantial data (Figure 3).

Figure 3: Preoperative (pre-op), postoperative (post-op) partial oxygen pressures, rate of change in post-operative oxygen pressure (%) and flushing volume per hemithorax in the related lavage procedure on the basis of case and lavage. P: Patient, L: Lavage

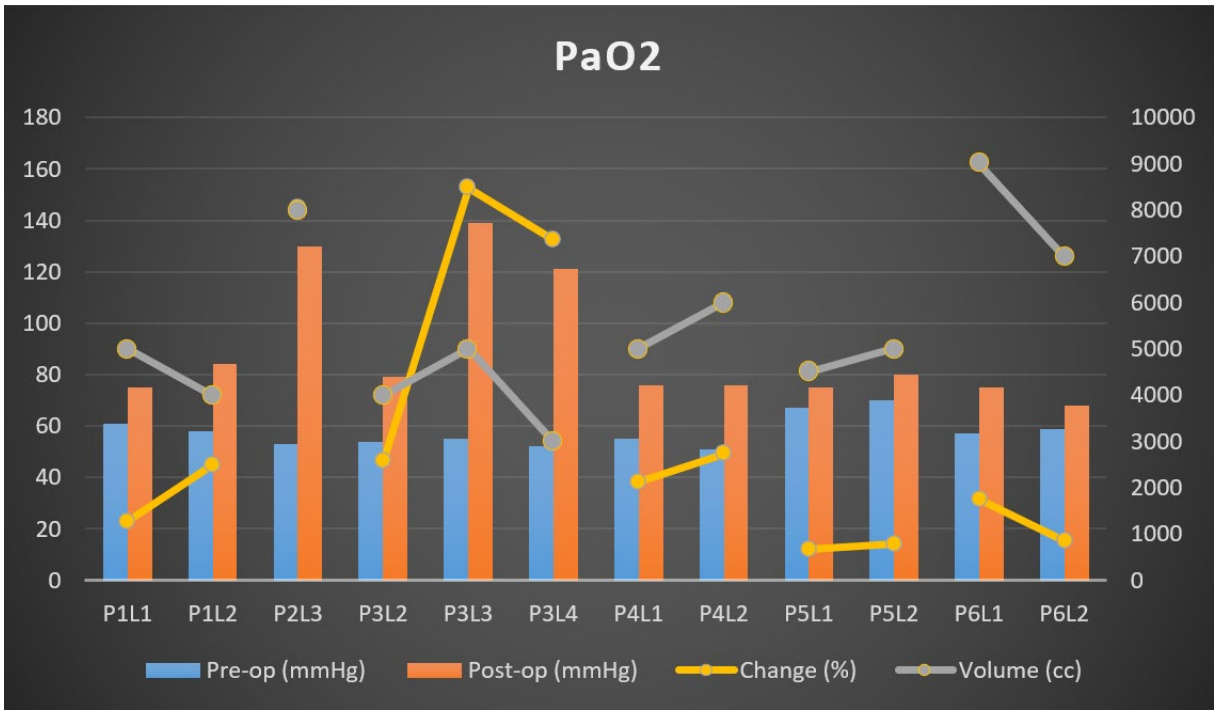


Table 1: Patient and procedure characteristics

Case Number	Lavage count	Gender	Diagnosis age	Interval (month)	Side	Volume (cc)	Preop. PaO2	0. h PaO2	3. h PaO2	Preop PaCO2	0. h PaCO2	3. h PaCO2	Complication	Status	Survival (Month)
1	**1th**	F	37	2	L*	5000	61	60	75	19	25	25	-	ALIVE	61
	2nd			1	R*	4000	58	59	84	22	29	29	-		
2	**1th**	F	46	1	L	12000	M*	M	M	M	M	M	-	ALIVE	55
	2nd			1	R	10000	M	M	M	M	M	M	-		

	3rd			1	R	8000	53	73	130	38	49	42	-		
3	**1th**	F	27	36	BL*	10000	M	M	M	M	M	M	-	EXITUS	214
	2nd			156	R	4000	54	66	79	30	44	47	-		
	3rd			1	L	5000	55	63	139	33	46	43	+		
	4th			5	R	3000	52	42	121	60	48	30	+		
4	**1th**	M	33	3	L	5000	52	55	76	38	36	31	-	ALIVE	64
	2nd			1	R	6000	51	55	76	36	35	35	-		
5	**1th**	M	47	1	BL	9000	67	72	75	29	30	32	-	ALIVE	130
	2nd			1	BL	10000	70	72	80	30	34	36	-		
6	**1th**	M	36	1	R	9000	57	60	75	30	32	30	-	ALIVE	164
	2nd			1	L	7000	59	64	68	28	32	35	-		

* L: Left hemithorax, R: Right hemithorax, BL: Bilateral lavage, M: Missing value

4. DISCUSSION

Pulmonary alveolar proteinosis (PAP), which is basically defined as excessive surfactant accumulation in the alveoli, may be idiopathic or develop secondary to another underlying disease (usually hematological diseases). Its prevalence is approximately 4 cases per 1 million and risk groups include males, smokers, and those working in high-risk industries (quarrying, coal mining) (Michaud et al., 2009, p. 1678-81). Although detailed history, physical examination and radiological evaluations are important for diagnosis, bronchoalveolar lavage (BAL) cytology and/or lung biopsy, that is, histopathological evaluation, are essential for the definitive diagnosis of the disease (Misra et al., 2020, p. 250-7). Our case group consisted of idiopathic PAP patients and had a histopathologic definitive diagnosis, as recommended in the literature.

The clinical course of the disease may vary from remission to severe respiratory failure. Age at diagnosis and smoking status are important points in its clinical course and BAL is still the best treatment option. In addition, especially in cases of PAP secondary to hematological diseases, improvements have been reported with stem cell transplantation. Experimental therapy of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) has shown promising results for PAP, with bilateral lung transplantation as a last-ditch option. Likewise, anti-B cell therapy with rituximab or plasmapheresis has been reported as experimental treatment for cases of autoimmune PAP in the literature (Suzuki et al., 2016, p. 431-40).

BAL is an effective procedure in the treatment of PAP. Unilateral or bilateral BAL can be performed in patients intubated with double lumen endotracheal tube. The main bronchus of the side planned for BAL is unventilated and warm saline is given. Afterwards, pulmonary physiotherapy is done (manually or with a physiotherapy device). The given saline is then

aspirated. This process is repeated until the color and consistency of the aspirated fluid approaches the given saline, and the process is complete (Figure 1). This process aims at cleaning the alveolar bed thus preventing disorderly gas exchange. Vo et al. also stated that BAL, despite complications such as hypoxemia, fever, pneumonia, pleural effusion, and fluid infusion into the ventilated lung, is an invasive but safe procedure (Vo et al., 2020, p. 877-8).

There are very few published articles with patient series on the diagnosis-treatment and management of PAP in the literature. Our clinical knowledge is mostly supplied by case reports. In line with the limited literature information, it can be easily said the patients who had the BAL procedure had positive changes in blood gas, pulmonary function test (PFT) parameters and of course, radiological improvement. It has also been reported to have a positive effect on the survival rate. In the review of Seymour and Presneill's case reports in 2002, they found a 5-year survival rate of 94±2% in patients who had BAL procedure done at any time during their illness, compared to 85±5% in patients with no BAL history (Seymour et al., 2002, p. 215-35).

In a study by Smith et al. in which they examined 79 patients; It was found that there was a decrease in supplemental oxygen use following the procedure (55% of the patients had preoperative supplemental oxygen requirement, while the rate of patients requiring supplemental oxygen at discharge was 46%), and improvements in PFT parameters (Smith et al., 2019, p. 2453-61). In the study, lavage volumes were also recorded; an average of 8416 cc saline for the right lung, 7694 cc for the left lung, and a total average of 15262 cc saline was reportedly applied. It was also stated that there were improvements in PaO_2 in the ABG evaluations before and after the procedure, though they were not recorded. It was emphasized that procedure-specific complications were observed in 7 patients (9%) and that this procedure can be successful when performed by an experienced multidisciplinary team using a consistent approach.

An article, possibly considered as one of the most valuable studies on BAL treatment in patients with PAP, is a multicenter study presented by GELF (Groupe d'Endoscopie Thoracique de Langue Française-French Thoracic Endoscopy Group) (Gay et al., 2017, p. 526-31). In the study by Gay et al., a total of 33 patients from 12 centers were included. In the study consisting of 23 men and 10 women, with a mean age of 44 (13–77), lavage volumes were reported to be very variable (5-40L per lung, mean 12L saline). In the post-procedure ABG evaluation, a significant improvement of 6.375 mmHg ($p=0.02$) in partial oxygen pressure was reported. All patients were followed up, except for one, and recurrence was observed in 19 (57.6%) patients, and BAL was re-administered to 9 (27.3%) patients after recurrence. Procedural complications occurred in 11 (33.3%) patients, with desaturation reported as the most common complication seen in 5 (12.1%) patients.

In another study, which also compared BAL volume and pre- and post-procedural ABG assessment with PaO_2, as in our study, Beccaria et al. examined 21 PAP cases who underwent BAL (Beccaria et al., 2004, p. 526-31). BAL was done with a total of 25-40L of saline per lung for approximately 3 hours, and lavage and percussion were continued until the resulting fluid was completely clear. In their study, they reported that the need for repetition of the procedure was below 30% in the 7-year follow-up, and also PaO_2 improved significantly shortly after the procedure and tended to increase up to 1 year. The results were statistically significant ($p<0.001$).

In a study by Mo et al. in which they examined 11 PAP patients, a total of 8 patients had BAL procedure done. Their results showed that patients with a large alveolar lavage volume and/or bilateral lavage had a greater improvement in PaO_2 than those who had less volume

and/or unilateral lavage, subsequently leading to the conclusion that high-volume lavage is more effective in the treatment of PAP (Mo et al., 2016; p. 1-5).

In another study comparing PaO_2 before and after the procedure, Zhou et al. examined a total of 11 patients diagnosed with primary PAP. In the study, the majority of the patients described shortness of breath (90%), cough (27.3%) and sputum (27.3%) at the time of diagnosis and saline warmed to body temperature was used as lavage fluid (Zhou et al., 2014, p. 763-8). The patients' lavage was performed with approximately 6-26 L of warm saline, until fluid, which initially was opaque and milky in consistency became clear. The mean PaO_2 was 54.8±7.4 mmHg before the procedure and 68.0±8.5 mmHg after the procedure (p=0.01).

Silva et al. in their study published in 2014; BAL was done to 3 PAP patients (2 men and 1 woman), each time bilaterally for a total of six times (Silva et al., 2014, p. 254-9). All the six procedures were done according to the protocol with no significant complications noted. A minimum of 20 L and a maximum of 30.6 L were used for lavage in total and improvements in PaO_2 values were shown after each lavage, although statistical significance was not stated.

Bansal et al. reported a case diagnosed with PAP at the age of 54 which had opacities showing widespread cobblestone pattern, especially in the left lung, consistent with accompanying parenchymal disease (Bansal et al., 2013, p. 314-7). The patient, who despite high oxygen support had a PaO_2 value of 42 mmHg in ABG had BAL procedure done. It was reported that the oxygen requirement of the patient, who was lavaged with a total of 15.5 L of saline unilaterally (left), decreased gradually in the postoperative period, and the PaO_2 value in the ABG evaluation performed in room air at the time of discharge was 68mmHg.

Powers et al. reported another case of a 29-year-old male patient in which they stated that the radiological findings of the disease could be confused with the current Covid-19 pneumonia. The patient who despite being diagnosed with PAP 4 years ago didn't receive any treatment and was followed up in ICU due to Covid-19 pneumonia, had BAL done as the cause of patient's clinical deterioration was attributed to PAP exacerbation. They stated that lavage was done to both the left and right lung respectively in the same manner a few days apart with 18L of saline. It was reported that the patient who was extubated the day after the procedure was discharged 3 days later with nasal cannula O2 of 3L/min at rest and 4L/min with effort (Powers et al., 2022, p. 1-4).

In their study, Alasiri et al. reported a case of a 15-year-old male with widespread involvement detected in both lungs. There was a dramatic improvement was observed in dyspnea symptoms and oxygen demand, after lavage with 10 L of saline for both the left and right lung respectively, in 2 sessions performed 72 hours apart, lasting approximately 4 hours. After a 6-month follow-up, it was reported that the patient's room air oxygen saturation was 93% and his symptoms had completely resolved (Alasiri et al., 2021p. 340). The studies shared in the literature review and their characteristics are summarized in Table-2.

Table 2: Data of the studies in the literature

Author	n	Gender	Symptom	Side	Lavage Volume (L-Mean)	Preop PaO_2 (mmHg) (Mean)	Postop PaO_2 (mmHg) (Mean)	PaO_2 change (mmHg) (Mean)	Complication
Smith et al. (7)	79	M: 57 F: 22	dyspnea cyanosis fever	BL*	R*: 8.416 L*: 7.694 T*: 15.262	M*	M	⬆M	7 patients (%9)
Gay et al. (GELF) (8)	33	M: 23 F: 10	dyspnea respiratory failure	R: 14 L: 15 BL: 4	T: 12	59.1	65.2	⬆ 6.375	11 patients (%33)
Beccaria et al. (9)	21	M: 17 F: 4	respiratory failure	BL	T: 25-40	55	78	⬆23	None
Mo et al. (10)	11	M: 7 F: 4	dyspnea fever cough chest pain	R: 2 BL: 6	R: 9.47 L: 11.72 T: 10.59	M	77	⬆M	M
Zhou et al. (11)	11	M: 3 F: 3	dyspnea cough sputum	BL	T: 6-26	54.8	68.0	⬆13.2	None
Silva et al. (12)	3	M: 2 F: 1	cough dyspnea respiratory failure	BL	T: 25.35	51.28	70.03	⬆18.75	None
Bansal et al. (13)	1 (CR*)	M	fever cough dyspnea	L	L: 15.5	53	62	⬆9	None
Powers et al. (14)	1 (CR*)	M	cyanosis dyspnea secretion	L	L: 18	M	M	⬆M	None
Alasiri et al. (15)	1 (CR*)	M	cyanosis exertional dyspnea	BL	R: 10 L L: 10 L T: 20 L	M	M	⬆M	None

* L: Left hemithorax, R: Right hemithorax, BL: Bilateral lavage
T: Total volume, M: Missing value, CR: Case report

Although the main limitation of our study is the number of cases, we assert that case series, albeit small, are important due to the rarity of the disease. Statistical analysis was deemed inappropriate owing to the limited number of cases. However, we are of the opinion that we can draw attention to the lavage volume with graphics and tables and that we can contribute a healthy data set for future meta-analyses on this subject.

5. CONCLUSION

BAL procedure is still known as the best treatment method for PAP. Both our clinical experience and the literature review shows that the lavage volume is directly proportional to the improvement in the patient's clinical and ABG values. This should be kept in mind in patients who are scheduled for the procedure. Studies or meta-analyses that share lavage volumes and respiratory parameters in patients undergoing BAL will clarify the usefulness of the procedure and its bullet points.

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