

Therapeutic Bronchoalveolar Lavage with Conventional Treatment in Allergic Bronchopulmonary Aspergillosis

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ABSTRACT

Objective: To establish the role of therapeutic bronchoalveolar lavage in addition to conventional treatment among two groups, with allergic bronchopulmonary aspergillosis, in terms of regression in serum IgE levels and clinical recurrence at 3 and 6 months of follow-up.

Study Design: A quasi-experimental study.

Place and Duration of Study: Department of Pulmonology, Fauji Foundation Hospital, Rawalpindi, from July 2010 to December 2013.

Methodology: The study was carried out on 132 patients who fulfilled the Greenberger and Patterson criteria and underwent a chest X-ray, an HRCT chest and classified radiologically as with Central Bronchiectasis (CB), High Attenuation Mucus (HAM) or Other Radiological Features (ORF). Baseline serum IgE levels were noted. All patients were given treatment including prednisolone and antifungal agent itraconazole for 4 months. Patients with ORF on HRCT chest and just received the medical treatment were labeled as conventional group. Those patients who had CB or HAM radiological features also underwent bronchoscopy with therapeutic Bronchoalveolar Lavage (BAL), labeled as BAL group. Clinical recurrence and serum IgE levels were noted at 3 and 6 months. Values were compared using chi-square and Mann-Whitney tests respectively.

Results: Around 78 (59.1%) of patients underwent bronchoscopy with therapeutic bronchoalveolar lavage to remove the mucus plugs. The mean serum IgE levels at baseline were 3312.04 ± 2526.217 and 3486.15 ± 2528.324 IU/ml in the BAL and conventional groups respectively. There was a statistically significant reduction in the mean serum IgE levels at 3 ($p < 0.00$) and 6 months ($p < 0.001$) of follow-up in BAL as compared to conventional group. There was no significant difference in the clinical recurrence rate in both the groups ($p=0.078$ at 3 and 0.343 at 6 months respectively).

Conclusion: Therapeutic bronchoalveolar lavage may be a useful adjunct to treatment in patients with allergic bronchopulmonary aspergillosis, serum in terms of IgE level reduction.

Key Words: *Bronchoalveolar lavage. All bronchopulmonary aspergillosis (ABPA). Computed tomography. Itraconazole. Prednisolone. Immunoglobulin E.*

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is a hypersensitivity response to fungal antigens, complicating patients with asthma and cystic fibrosis.¹ It is classically described by Greenberger and Patterson criteria that include asthma, immediate skin reactivity to *Aspergillus fumigatus*, serum precipitins to *Aspergillus*, increased serum IgE and IgG to *Aspergillus*, total serum IgE > 1000 IU/ml, current or previous pulmonary infiltrates, central bronchiectasis and peripheral eosinophilia > 1000.²

Radiologically patients with ABPA present as fleeting pulmonary infiltrates.³ Central Bronchiectasis (CB) signifies high recurrence rate and relatively poor response to treatment.⁴ Agarwal *et al.* gave an alternate

classification for ABPA based on CT scan findings and presence of High Attenuation Mucus (HAM) as serological (ABPA-S), with central bronchiectasis (ABPA-CB) and with high attenuation mucus (ABPA-CB-HAM).⁵

Laboratory tests supporting the diagnosis of ABPA include demonstration of immunological response to *Aspergillus* such as positive skin test to *Aspergillus* antigens.² Serum IgE levels are also increased in these patients, values as high as 30,000 IU/ml have been demonstrated, their increasing values having a prognostic significance and may indicate a clinical relapse.²

Management of ABPA includes corticosteroids in a dose of 0.5 mg/kg for 4 - 8 weeks and then gradually tapered off. Patients usually respond to oral antifungal agent, itraconazole 200 - 400 mg/day in two divided doses for 16 weeks, both these agents have a collective response rate of 60%.⁶ Alternate agents with a response rate of 70 - 80% include new generation azole anti-fungals, voriconazole and posaconazole and anti-IgE, omalizumab. These agents are expensive and can have serious side effects.^{7,8}

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Received: February 28, 2014; Accepted: March 12, 2015.

Bronchoscopy with therapeutic bronchoalveolar lavage is a simple, cost effective procedure to remove mucus plugs in patients with ABPA. Numerous case reports have used this treatment in patients with high attenuation mucus.^{2,9,10}

As ABPA is associated with frequent relapses and raised serum IgE levels being a marker of “disease flare-up” therapeutic bronchoalveolar lavage, if found effective to prevent relapse or reduce serum IgE levels, may be a useful adjunct to treatment in these patients.¹¹

The aim of this study was to evaluate the usefulness of therapeutic bronchoalveolar lavage, in addition to conventional treatment for patients with Allergic Bronchopulmonary Aspergillosis (ABPA).

METHODOLOGY

This was a quasi-experimental study, carried out in the Department of Pulmonology, Fauji Foundation Hospital, Rawalpindi, from July 2010 to December 2013, on 132 patients who fulfilled the Greenberger and Patterson criteria of allergic bronchopulmonary aspergillosis. By using the sensitivity calculator and an absolute precision of 0.08, the sample size was 132.

Therapeutic Bronchoalveolar Lavage (BAL) was defined, aliquots of normal saline were used during bronchoscopy to remove and clear the mucus plugs in patients with ABPA.² Clinical recurrence was defined as symptoms of cough with sputum, shortness of breath or fever that required treatment with systemic steroids.

Following written consent for treatment including bronchoscopy, demographic and clinical data were collected. Symptoms, pre-morbid conditions and previous treatment with tuberculosis was noted. All patients underwent a chest X-ray, followed by an HRCT chest and classified radiologically with Central Bronchiectasis (CB), High Attenuation Mucus (HAM) or Other Radiological Features (ORF).^{4,5} Baseline serum IgE levels were noted.

All patients who fulfilled the Greenberger and Patterson criteria for ABPA were given treatment including prednisolone 0.5 mg/kg/d for 6 weeks and they were tapered off in the next 6 weeks. Antifungal agent itraconazole was given in a dose of 200 mg twice a day for 4 months.⁵ Patients with ORF on HRCT chest and just received the medical treatment were labeled as conventional group.

Those patients who had CB or HAM radiological features received the medical treatment and also underwent bronchoscopy with therapeutic bronchoalveolar lavage. They were labeled as BAL group. CXR was done immediately after the procedure to look for radiological signs of improvement.

Patients were followed for a mean duration of 6 months, clinical recurrence and serum IgE levels were noted at 3 and 6 months.

SPSS version 16 and 21 was used for analysis. Demographic, radiological features, serum IgE levels and clinical recurrence was noted in the BAL and conventional arm. Clinical recurrence at 3 and 6 months were compared in both groups using a chi-square test. Mean serum IgE levels were compared at baseline, 3 and 6 months in BAL and conventional group using Mann-Whitney test. A p-value less than or equal to 0.05 was noted as statistically significant.

RESULTS

The mean age of patients was 30.61 years. About 67 (50.8%) of patients were male and the rest were female. Presenting complaints included cough with sputum in 71 (53.8%), shortness of breath in 51 (38.6%) and fever in 10 (7.6%) of patients.

One hundred and one (76.5%) of patients had asthma, 23 (17.4%) had cystic fibrosis or congenital bronchiectasis and 8 (6.1%) had other pre-morbid conditions. Fifty two (39.4%) of patients were previously treated for tuberculosis.

Radiologically 23 (17.4%) of patients had CB, 57 (43.2%) had HAM and 52 (39.4%) had ORF on HRCT chest.

These demographic and clinical characteristics of patients is given in Table I.

Table I: Demographic and clinical features of patients.

Characteristics	Number (percentage)
Age	Mean 30.61 ± 11.787 years
Gender	
Male	67 (50.8%)
Female	65 (49.2%)
Presenting complaints	
Cough with sputum	71 (53.8%)
Shortness of breath (SOB)	51 (38.6%)
Fever	10 (7.6%)
Premorbid conditions	
Asthma	101 (76.5%)
Cystic fibrosis/congenital bronchiectasis	23 (17.4%)
Others	8 (6.1%)
Previous treatment for tuberculosis	
Yes	52 (39.4%)
No	80 (60.6%)
Radiological features on HRCT chest	
CB	23 (17.4%)
HAM	57 (43.2%)
ORF	52 (39.4%)

Table II: Clinical recurrence in BAL and conventional group at 3 and 6 months.

Clinical recurrence	BAL Group n=78 (59.1%)	Conventional Group n= 54 (40.9%)	Chi-square test (p-value)
Clinical recurrence at 3 months	24 (30.76%)	24 (44.44%)	0.108
Clinical recurrence at 6 months	26 (33.3%)	24 (44.4%)	0.196

p-value < 0.05 statistically significant.

Table III: Mean serum IgE levels in BAL and conventional groups.

	Two Groups	N	Mean Rank	Sum of Ranks	p-value
Baseline IgE levels	BAL group	78	65.12	5079.00	0.617
	Conventional group	54	68.50	3699.00	
	Total	132			
IgE levels at 3 m	BAL group	78	53.88	4203.00	0.000*
	Conventional group	54	84.72	4575.00	
	Total	132			
IgE levels at 6 m	BAL group	78	55.87	4357.50	0.000*
	Conventional group	54	81.86	4420.50	
	Total	132			

* p-value \leq 0.05 statistically significant.

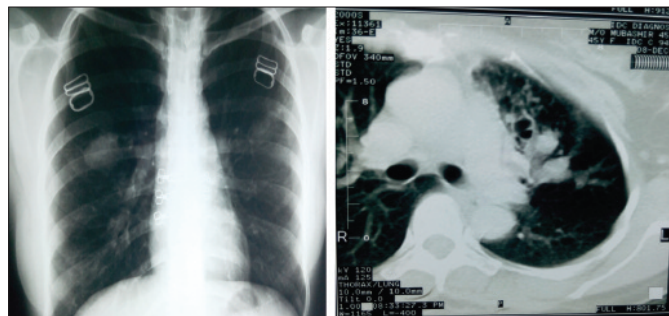


Figure 1: Radiological appearance of high attenuation mucous on CXR and HRCT chest.

Figure 1 shows the radiological appearance of ABPA with High Attenuation Mucus (HAM).

Around 78 (59.1%) of patients underwent bronchoscopy with therapeutic bronchoalveolar lavage (the BAL group), to remove the mucus plugs. Patients were followed for 6 months after the procedure. The clinical recurrence at 3 and 6 months in BAL and conventional group is presented and compared by Chi-square test as given in Table II.

As shown in the Table II, there was insignificant difference in the clinical recurrence at 3 months ($p=0.108$) and 6 months ($p=0.196$) in both the groups. Table III shows the mean IgE levels at baseline, 3 and 6 months of follow-up. There was a statistically significant reduction in the mean serum IgE levels at 3 and 6 months of follow-up, in BAL as compared to conventional group.

DISCUSSION

In this study, the author evaluated the usefulness of therapeutic bronchoalveolar lavage, in addition to conventional treatment in patients with allergic bronchopulmonary aspergillosis, based on the assumption that presence of HAM is the most important factor for adverse prognosis in this disease.⁴ High attenuation mucus is collection of desiccated mucus with calcium salts, iron and manganese. It is associated with a more severe form of disease because of inspissated mucus and more severe inflammation.^{4,16}

The results of this study suggest that those patients who underwent bronchoscopy with therapeutic BAL,

had statistically significant reduction in the mean serum IgE levels at follow-up, IgE levels being a marker of "disease flare-up".^{11,17} Hence, we can hypothesize that these patients are more likely to have a better outcome.¹¹ Further studies are required in this aspect.

In this study, there was reduction in the clinical recurrence in the BAL than conventional group but it was not statistically significant. Multi-centre and better designed trials are required.

Few studies have assessed the significance of presence of HAM in terms of relapse,^{4,18} but use of BAL to treat HAM is limited to case reports only. This is the first study, that evaluates the usefulness of bronchoscopy with therapeutic BAL, to remove mucus plugs, prevent clinical relapse and reduce the serum IgE levels. There are many clinical implications of this study on management of ABPA, that include clinical strength to the classification of ABPA as given by Agarwal *et al.*,^{4,5,19} radiological regression of disease after BAL, and reduction in serum IgE levels and hence relatively better outcome of disease at follow-up.

This study has further financial implications as well. Bronchoscopy with therapeutic BAL has minimal complications. When we combine it with the traditional medical treatment (corticosteroids and itraconazole) and compare the benefits with fancy medications for ABPA that include new generation azole anti-fungals (voriconazole and posaconazole) and anti-IgE therapy, it seems cost effective.^{13,14} So therapeutic bronchoalveolar lavage can be combined with the conventional treatment in ABPA without posing patient to any serious risks and with minimum financial burden to him.

There are few limitations of this study. First, patients were selected by non-probability consecutive sampling and those with evidence of HAM or CB on HRCT chest were placed in the BAL group on the assumption of previous case reports removing mucus plugs by bronchoscopy, hence there was a selection bias.^{2,9,10,20} Randomized controlled trials are required.

As the study was carried out in adult Pakistani population, cystic fibrosis being the underlying diagnosis in only 23 (17.4%) of patients. If a similar study is designed in the other population or age groups, the frequency of cystic

fibrosis may be higher. Bronchoscopy is an invasive procedure with few well recognized complications.¹⁵ It requires availability as well as expertise. Hence, as the procedure is not accessible to remote areas and is associated with a small but recognized risk of mortality or serious complications, so this is another source of bias in this study. Longer follow-up is required in future studies.

CONCLUSION

Therapeutic Bronchoalveolar Lavage (BAL) may be a useful adjunct to treatment in patients of allergic bronchopulmonary aspergillosis with HRCT features of Central Bronchiectasis (CB) and High Attenuation Mucus (HAM).

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