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TANAFFOS

Comparison between Levofloxacin and Azithromycin in Short-term Spirometry and Oxygen Saturation Indices in Patients with Exacerbated Bronchiectasis: A Randomized Double-blind Clinical Trial

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Background: Bronchiectasis is a chronic pulmonary disease characterized by abnormal and permanent dilatation of the airways in the lung. This study was conducted to compare the effect of levofloxacin with azithromycin in improving the lung function of these patients.

Materials and Methods: In this parallel double-blinded randomized clinical trial, 72 patients with exacerbated bronchiectasis were included and randomly divided into two intervention groups. One group was treated with levofloxacin (500 mg daily for two weeks at first and then 250 mg daily in the next four weeks), and the other group with azithromycin (500 mg daily in the first two weeks and then with a dose of 250 mg daily for the next four weeks) for 6 weeks. The pulmonary function tests were performed and analyzed at the beginning of the study, two, four, and six weeks after the intervention.

Results: The mean expiratory volume in the first second (FEV1) and the percentage of oxygen saturation (O_2Sat) in the levofloxacin group and the azithromycin group were not significantly different at the beginning of the study. Importantly, six weeks after the initiation, the mean FEV1 (61.02±8.54% vs. 56.88±7.13%, p=0.029) and O_2Sat (91.00±1.72% vs. 85.44±1.77%, p=0.001) in the levofloxacin group were significantly higher than those in the azithromycin group.

Conclusion: The present study showed that the favorable effect of six-week therapy with levofloxacin compared to azithromycin can significantly increase the pulmonary values of FEV1 and O_2Sat in patients with exacerbated bronchiectasis.

Keywords: Levofloxacin; Azithromycin; Bronchiectasis; Respiratory Function

INTRODUCTION

Bronchiectasis is a chronic pulmonary disease characterized by abnormal and permanent dilatation of the airways in the lung. Given the differences in diagnostic approaches, the prevalence of bronchiectasis is still not completely clear (1). It is reported that bronchiectasis is more common in women and increases with age (2, 3). Cough, shortness of breath, sputum production, and recurrent respiratory attacks are considered the main symptoms of bronchiectasis. The etiology of bronchiectasis is not exactly transparent. However, cystic fibrosis is recognized as a key cause of bronchiectasis in half of the

patients (4). Given the fact that about half of the non-cystic fibrosis bronchiectasis cases are idiopathic, recent studies stated that bacterial colonization and its effect on the incidence of bronchiectasis attacks have played a prominent role (5).

Usually, the lungs of these patients contain infectious organisms such as *Haemophilus influenzae* and *Pseudomonas aeruginosa*, and to a lesser extent, Streptococcus. Considering that bronchiectasis has several pulmonary complications, the most important one is a severe decrease in lung function. Although there is no definite cure for this disease, various treatments have been proposed for it based on the patient's condition (5-7). In addition, it is mentioned that antibiotics can reduce inflammation, improve symptoms, lower the frequency of lung attacks, maintain lung function, and enhance the quality of life (2-4, 8).

Azithromycin is one of the most commonly used antibiotics in bronchiectasis globally (9). In addition to its antibiotic features, this drug exerts immunomodulatory effects on the patient's inflammatory response without systemic suppression of the immune system, which includes modifying mucus production, inhibiting biofilm production, and suppressing inflammatory mediators (9-12). On the other hand, levofloxacin is also a fluoroquinolone antibiotic that has antimicrobial effects and can fight various types of bacterial infections in the body; however, its effect on patients with bronchiectasis is not clear yet (13).

Bearing the above nuances in mind, the present clinical trial aims to compare the effect of levofloxacin with azithromycin on lung function in hospitalized patients with exacerbated bronchiectasis.

MATERIALS AND METHODS

Study design and participants

The current study is a parallel randomized clinical trial that was conducted on eligible patients with exacerbated bronchiectasis who were admitted to Imam Hossein Hospital, Shahroud, Iran, from March 2022 to September 2022. Informed consent was obtained from all patients, and the ethical code was received from the Research Vice-Chancellor of Shahroud University of Medical Sciences, and the protocol was registered and reviewed in the Iranian Registry of Clinical Trials (IRCT20100102002954N28).

In this study, 72 patients with exacerbated bronchiectasis were eligible and included based on our inclusion criteria, and were then randomly divided into two groups of 36 people. The selection process was performed using blocked randomization, and the eligible patients were divided into the levofloxacin and the azithromycin groups. Each selection was provided to the researcher in a closed envelope, and after choosing the patient and obtaining informed consent, the envelope was opened based on the predetermined sequence. The patient was assigned to the levofloxacin and the azithromycin groups based on the envelope. In this study, both the researcher who divided the patients and the analyst were blinded about the levofloxacin and the azithromycin groups. No dropouts among the included patients were reported throughout the study, and all selected patients completed the study period.

Inclusion and exclusion criteria

Our inclusion criteria include patients with a definite diagnosis of aggravated non-fibrocystic bronchiectasis, not having moderate to severe heart failure (EF>50), in an age range of 18-65 years, stable vital signs, and having a controlled and stable medication regimen during the study. Our exclusion criteria include the presence of digestive symptoms such as severe nausea and vomiting, various cancers of the respiratory system, simultaneous chronic kidney and liver failure, history of any surgery on the respiratory system in the past year, history of receiving any antibiotics in the past month, history of receiving any medication containing corticosteroids in the past month, pregnancy and breastfeeding, a history of tendon disorders, QT prolongation, a history of epilepsy, and withdrawal from participating in the study at any stage of the research.

Before starting the trial, the hemoglobin serum level was adjusted between the two groups to a level of 11 to 12 grams per deciliter, and therefore, the patients were also controlled in terms of anemia.

Study flow

After randomly dividing the eligible patients with exacerbated bronchiectasis into two groups, levofloxacin and azithromycin, the interventions were administered for six weeks. In the intervention group, routine treatments included the use of oxygen, bronchodilators, and expectorant drugs. Alongside these treatments, patients were prescribed levofloxacin tablets, starting with an initial dose of 500 mg daily for the first two weeks. This was followed by a reduced dose of 250 mg daily for the next four weeks. In the azithromycin group, oxygen, bronchodilators, and expectorants, along with azithromycin tablets with an initial dose of 500 mg daily in the first two weeks and then with a dose of 250 mg daily, were prescribed in the next four weeks. The dosing regimen for levofloxacin and azithromycin was chosen on the basis of balancing efficacy with limited side effects, as the planned course of treatment was six weeks. The higher initial doses were used to manage the acute exacerbation effectively, and the lower doses were used to maintain a therapeutic level of levofloxacin and azithromycin with a limited risk for side effects. During the trial, all patients and the researcher investigating the respiratory function status were not aware of the type of prescribed medications.

Outcome variables and statistical analysis

The variables to be measured and investigated include gender, age, hemoglobin serum levels, and pulmonary function variables. The pulmonary function results and oxygen saturation were recorded every two weeks and compared. To determine pulmonary function, the following criteria were used: measurement of pulmonary volumes and capacities and oxygen saturation (O_2 sat) in a standard method using a standard pulse oximetry device, and every two weeks from the initiation of treatments until six weeks. Moreover, the possible side effects of the medications were regularly monitored. The sample size was calculated based on expected differences in FEV1 between the two treatment groups, with an alpha level of 0.05 and a power of 80%.

The outcome variables were obtained as mean ± standard deviation (Mean ± SD) as well as frequency and percentage. Quantitative variables were measured and used using independent t-test, Fisher's, and ANOVA tests. In all cases, $p<0.05$ was considered statistically significant in all analytical models. SPSS version 16 was used in all analyses.

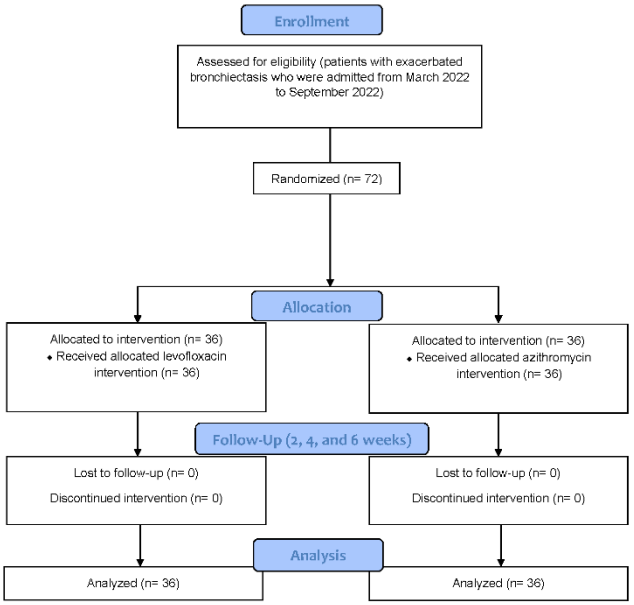

Figure 1. The CONSORT diagram of the clinical trial

Ethical Approval and Informed Consent

This study was performed in accordance with the ethical principles originating from the Declaration of Helsinki, and the institutional review board at each participating site approved the protocol and other relevant documents. This study was approved by ethical committee of Shahroud University of Medical Sciences (IR.SHMU.REC.1401.126).

Clinical Trial Registration: Iranian Registry of Clinical Trials (IRCT20100102002954N28)

RESULTS

Demographic and clinical information

In this study, out of all included patients, 40 (63.9%) were female, and no significant difference was detected in terms of gender between the two groups. Considering the mean age, we showed that there is no significant difference between the two groups. The detailed analytical results of demographic information and clinical history between the levofloxacin and the azithromycin groups are presented in Table 1.

Respiratory function tests

As shown in Table 2, on initial phase and two weeks after initial phase, no statistical differences in the mean forced expiratory volume in 1 second (FEV1), percentage of oxygen saturation (O_2Sat), and the ratio of the forced expiratory volume in the first one second to the forced vital capacity (FEV1/FVC) was seen between levofloxacin and the azithromycin groups.

Importantly, six weeks after the initiation, the mean FEV1 (61.02±8.54% vs. 56.88±7.13%, p=0.029) and O_2Sat (91.00±1.72% vs. 85.44±1.77%, p=0.001) in the intervention group with levofloxacin were significantly higher than those in the group with azithromycin. The detailed respiratory information of both intervention groups at different time intervals is presented in Table 2.

Table 1. Demographic and clinical information of patients with exacerbated bronchiectasis in the initial phase of the study

Demographic and clinical information		Levofloxacin group (%)	Azithromycin group (%)	p-value
Age (mean + SD)		54.44±17.03	53.72±16.33	0.855
Female		17 (47.2)	23 (63.9)	0.155
Male		19 (52.8)	13 (36.1)	0.155
Past Medical History	No record	13 (36.1)	20 (55.6)	0.252
	DM	11 (30.6)	8 (22.2)	0.252
	HTN	8 (22.2)	4 (11.1)	0.252
	Hyperlipidemia	2 (5.6)	0 (0.0)	0.252
	Cardiac	2 (5.6)	3 (8.3)	0.252
	Renal	0 (0.0)	1 (2.8)	0.252
	Total	36 (100)	36 (100)	0.252
Alcohol Consumption	No	35 (97.2)	36 (100)	0.999
	Yes	1 (2.8)	0 (0.0)	0.999
	Total	36 (100)	36 (100)	0.999
Addiction	No	29 (80.6)	30 (91.7)	0.173
	Yes	7 (19.4)	3 (8.3)	0.173
	Total	36 (100)	36 (100)	0.173
Smoking	No	30 (83.3)	30 (91.7)	0.478
	Yes	6 (16.7)	3 (8.3)	0.478
	Total	36 (100)	36 (100)	0.478

Table 2. Mean spirometry variables between the intervention and control group in different time intervals

Mean spirometry variables	On initiation of the study			Two weeks after initiation			Four weeks after initiation			Six weeks after initiation		
	Levofloxacin group	Azithromycin group	p-value	Levofloxacin group	Azithromycin group	p-value	Levofloxacin group	Azithromycin group	p-value	Levofloxacin group	Azithromycin group	p-value
FEV1	56.25±5.69	55.19±7.19	0.493	58.11±6.53	55.83±7.29	0.167	58.83±8.19	56.44±7.04	0.189	61.02±8.54	56.88±7.13	**0.029**
O_2Sat	88.22±1.55	87.80±1.30	0.222	89.00±1.62	88.47±1.40	0.144	89.91±1.66	89.00±1.72	0.025	91.00±1.72	89.44±1.77	**0.001**
FEV1/FVC	54.97±5.93	54.44±7.57	0.743	57.19±6.56	55.13±7.35	0.215	58.13±8.00	55.55±6.83	0.145	60.36±8.66	56.66±7.63	0.059

DISCUSSION

In the present study, we investigated the effects of two common medications, levofloxacin and azithromycin, on 72 eligible patients with exacerbated bronchiectasis. Although the effect of levofloxacin and azithromycin in improving the respiration quality of patients was not statistically different at the beginning of the study, levofloxacin demonstrated a significantly higher impact on improving FEV1 and O_2Sat compared to azithromycin after six weeks of treatment. In line with our results, Chalmers and colleagues suggested that broad-spectrum antibiotics such as ciprofloxacin can be effective in reducing the severity of bronchiectasis, and they even showed higher favorable outcomes than azithromycin in the long term (more than 8 weeks), especially in increasing the O_2Sat of arterial blood (14). In this manner, it is reported that azithromycin and ceftriaxone are among the best antibiotics for managing exacerbated bronchiectasis in children (15).

Some shred of evidence has shown that patients with bronchiectasis receiving oral levofloxacin compared to those receiving oral ceftazidime have a significant improvement in the 24-hour sputum volume, sputum purulence score, cough score, and shortness of breath score. In line with our findings, it is reported that the oral administration of levofloxacin could be as effective as the infusion of ceftazidime in the treatment of exacerbated bronchiectasis (7).

Accordingly, it is suggested that the use of different antibiotics can reduce the severity of bronchiectasis, but the correct category of antibiotics with the exact dose and duration is still controversial (14, 16-18). In addition, Serisier and Martin have found that six weeks of erythromycin, like azithromycin, can be as effective as a 7-day course of other broad-spectrum antibiotics such as levofloxacin in the treatment of chronic and exacerbated bronchitis. However, it should be used in patients with strict dose control (19). On the other side, Martinez et al. have reported no significant differences in the outcomes of spirometry findings between levofloxacin and azithromycin in patients with chronic lung diseases (20).

Furthermore, in a study to control the severity of bronchiectasis, patients were prescribed azithromycin 500 mg or a placebo three times a week for 6 months, and thus, the number of respiratory attacks in the levofloxacin group was much less than in the azithromycin group. However, no significant difference was observed in the O_2Sat and FEV1 scales of the two groups (21). In this line, Cymbala et al. reported that the changes in FEV1 over time were notably improved in patients with bronchiectasis receiving azithromycin compared to placebo, which signifies that the effect of macrolides is to control the severity of bronchiectasis (22). It is worth mentioning that some of these studies are limited and have been designed and implemented in different races (European, American, African, Asian, and Australian) and with different samples (bronchiectasis patients with and without fibrocystic disease). Also, some have been conducted based on emergency patients referred to emergency units, while others are population-based (23-25).

CONCLUSION

In conclusion, the present study showed that the use of levofloxacin and azithromycin can similarly improve the respiratory function of patients with exacerbated bronchiectasis. The effect of both medications was the same at the beginning of the treatment. But as the trial continued up to six weeks, the favorable effect of levofloxacin increased significantly compared to azithromycin. Our findings suggest that levofloxacin can be used as an alternative treatment to control exacerbated bronchiectasis, while keeping an eye on the appropriate duration of treatment. Nevertheless, given the potential safety concerns and the relatively limited duration of this study, further research is necessary to evaluate the long-term safety and comparative effectiveness of levofloxacin versus azithromycin in this patient population.

Limitations

In this study, some restrictions should be noted. The sample size of 72 patients is suitable for a pilot study, but is not large enough to fully represent the entire

bronchiectasis population. A larger study is needed to confirm the results and provide stronger evidence. The study was only over six weeks with no long-term follow-up. This means we are unable to confirm whether there were any late or rare side effects from the use of azithromycin and levofloxacin; fluoroquinolones have been associated with long-term side effects.

In addition, the study does not explore the impact of multiple courses of antibiotics over time, a common scenario in chronic conditions like bronchiectasis, where patients can experience multiple exacerbations in a year. This study does not compare the safety or efficacy of different antibiotic regimens over a longer period. Although we did look for side effects, the six-week period may not capture all potential safety issues that might arise from longer-term antibiotic use. Moreover, as the main outcomes of this study, we were particularly interested in determining the improvements in FEV1 and O2Sat as these are important measures of lung function and oxygenation status among individuals with bronchiectasis; however, we were unable to assess sputum culture eradication in this study.

Also, the study only took place at a single site, so we may have introduced local biases. In the future, we hope to do a multicenter study and include more patients with bronchiectasis and have a longer follow-up.

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Declaration of Interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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