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Original Article

Effect of Long-term Azithromycin in Reducing Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: To determine the effect of long-term Azithromycin administration in reducing acute exacerbation of Chronic Obstructive Pulmonary Diseases.

Study Design: Quasi-experimental study.

Place and Duration of Study: Medicine and Pulmonology Departments of Combined Military Hospital, Peshawar Pakistan, from Jun 2019 to May 2020.

Methodology: Patients of Chronic Obstructive Pulmonary Diseases who had more than three hospital admissions in the last one year or required parenteral steroids for management were included in the study. They were randomly divided into two groups where Group-I was administered Azithromycin 500mg, thrice weekly, in addition to routine Chronic Obstructive Pulmonary Diseases medications, and Group-2 received only routine Chronic Obstructive Pulmonary Diseases medications. Both groups were compared for hospital admission due to Chronic Obstructive Pulmonary Diseases, hospital admission due to other causes, parenteral steroid use and Emergency Department visits after six months.

Results: Out of 150 patients of Chronic Obstructive Pulmonary Diseases, 78(52%) received Azithromycin for six months while 72(48%) received only usual treatment of Chronic Obstructive Pulmonary Diseases, while 13(16.6%) patients from Azithromycin-Group had more than three Chronic Obstructive Pulmonary Disease related hospital admissions in six months. However, 34(47.2%) patients in non-Azithromycin-Group had more than three such admissions. More than three Chronic Obstructive Pulmonary Disease related hospital admissions and use of parenteral steroids were found significantly more in non-Azithromycin-Group (p-value <0.001).

Conclusion: Long-term Azithromycin use was found beneficial for patients suffering from Chronic Obstructive Pulmonary Diseases. Use of parenteral steroids and Chronic Obstructive Pulmonary Disease related hospital admissions were significantly reduced in patients taking long term Azithromycin.

Keywords: Azithromycin, Acute exacerbation, Chronic Obstructive Pulmonary Disease.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the common obstructive airway diseases managed by clinicians in wards.[1] Etiology of this disorder is usually multifactorial but changes in environment and lifestyle of people have made this chronic debilitating condition more common all over the world.[2] Oxygen supply to tissues is critically important for their survival and lack of oxygenation especially in chronic conditions may lead to poor functioning and ultimately, death.[3] Literature has shown compromised quality of life in all the chronic diseases including the chronic obstructive pulmonary disease.[4] Acute exacerbations of COPD are sometime major predictor of poor quality of life among patients.[5] Clinicians and researchers across the globe have proposed strategies to reduce the frequency and severity of these exacerbations in order to improve overall quality of life of the patients suffering from COPD.[6] Shteinberg *et al*. found that Azithromycin seemed to be safest of all the macrolides with minimum drug interactions.[7] Naderi *et al*. concluded that patients who were prescribed long-term Azithromycin were at clear advantage as compared to those who were not, in terms of reducing acute exacerbations of disease and avoiding hospital admissions.[8] Herath *et al*. revealed that a clinically significant benefit in reducing exacerbations in COPD patient could be observed in patients put on long-term antibiotics but these findings could not be generalized to all the patients and clinicians should consider the adverse effects of long-term use as well.[9] Burden of COPD is increasing in our part of the world and clinicians have

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to manage these cases in various clinical settings from outpatient departments to critical care units.[10] We planned this study with the rationale to determine the effect of long-term Azithromycin administration in reducing acute exacerbation of chronic obstructive pulmonary disease.

METHODOLOGY

The quasi-experimental study was conducted at Medicine and Pulmonology Departments of Combined Military Hospital, Peshawar Pakistan, from June 2019 to May 2020. Non-probability consecutive sampling was done on patients reporting in the Medical and Pulmonology Outpatient Department and having more than three admissions in preceding one year or requirement of parenteral steroid therapy. Sample size was calculated by using the WHO sample size calculator by using population prevalence proportion of 23% risk reduction of AECOPD with Azithromycin.[11]

Inclusion Criteria: Patients of either gender, aged 25 to 65 years who had been suffering from acute exacerbation of COPD having more than three admissions in last one year or requirement of parenteral steroid therapy, were included.

Exclusion Criteria: Patients with allergies secondary to identifiable causes and having known allergy to Azithromycin or who refused to take Azithromycin, or with any contraindication to Azithromycin other than allergies, were excluded.

Acute exacerbation of COPD was diagnosed by consultant pulmonologist on the basis of clinical criteria supported by relevant investigations.[12] After getting ethical approval from the hospital Ethics Review Board (via letter number 24/21), written informed consent was taken from all the participants of this study and patients were randomly divided into two groups via lottery method. Group-I received Azithromycin 500mg thrice weekly[13] for six months in addition to routine medications for COPD while Group-II only received the routine COPD medications (Figure). All the patients were assessed by an independent assessor for hospital admission due to COPD or other causes, Emergency Department visits and use of parenteral steroid therapy after six months of start of study.

All statistical analysis was performed using Statistics Package for Social Sciences (SPSS) version 24.0. Descriptive statistics were used to describe the characteristics of participants and the distribution of study participants. Chi-square test was used and differences between groups were considered significant if *p*-value was ≤0.05.

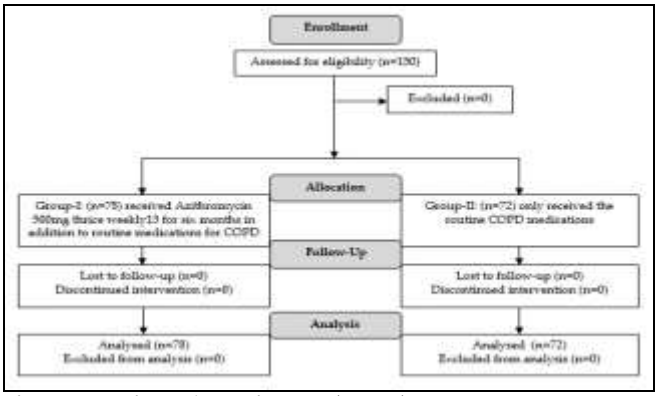

Figure-1: Patient Flow Diagram (n=150)

RESULTS

Out of 150 patients included in the study, 90(60%) were male while 60(40%) were female. 78(52%) patients received Azithromycin for six months while 72(48%) received only usual treatment of COPD. Mean age of the study participants was 51.21±6.561 years. In Azithromycin-Group, 13(16.6%) patients had more than three COPD related hospital admissions in six months while 34(47.2%) patients in non-Azithromycin-Group had more than three such admissions (Table-I).

Table-I: Characteristics of Chronic Obstructive Pulmonary Disease Patients (n=150)

Parameters	n (%)
Mean Age of Patients (years)	
Mean±SD	51.21±6.561 years
Gender	
Male	90(60%)
Female	60(40%)
Treatment administered	
Treatment as usual	72(48%)
Six months Azithromycin	78(52%)
More than three COPD related Admission	
No	103(68.7%)
Yes	47(31.3%)
Requirement of Parenteral Steroid Therapy	
No	90(60%)
Yes	60(40%)

Table-II shows that after application of chi-square test, more than three COPD related hospital admissions and use of parenteral steroids were found significantly more in non-Azithromycin-Group (*p*-value <0.001) while admissions not related to

COPD and emergency department visits were not significantly different between both groups.

Table-II: Difference in Factors Related to Clinical Outcome in Study Groups (n=150)

Factors	Group-I	Group-II	*p*-value
More than three COPD related Admissions			
No	65(83.3%)	38(52.8%)	<0.001
Yes	13(16.7%)	34(47.2%)	
More than three non-COPD Related Admissions			
No	58(74.3%)	45(62.5%)	0.117
Yes	20(25.7%)	27(37.5%)	
More than three Emergency Department visits			
No	49(62.8%)	53(73.6%)	0.156
Yes	29(37.2%)	19(26.4%)	
Parenteral Steroid Therapy			
No	61(78.2%)	29(37.2%)	<0.001
Yes	17(21.8%)	43(62.8%)	

DISCUSSION

Chronic illnesses like Diabetes Mellitus, COPD and hypertension have a drastic effect on the overall wellbeing of patients. All treatment modalities focus on minimizing the health-related damage caused by these ailments. COPD is no different in this regard and all the treatment strategies are applied to provide symptomatic relief and prevent acute exacerbations.[14] Use of long-term antibiotics has always been controversial among clinicians due to which we planned and conducted this study to determine the effect of long-term Azithromycin administration in reducing acute exacerbation of COPD among patients having frequent exacerbations in preceding one year or requiring parenteral steroid therapy. Threapleton *et al*.[15] conducted a systematic review to compare the safety and efficacy of different classes of antibiotics (continuous, intermittent or pulsed) for prophylaxis of exacerbations in patients with COPD in which they concluded that there was no difference in impact of use of any class of antibiotic on health-related outcome of COPD patients and reduction in acute exacerbations. Our findings were different from the findings generated in their review as there was clear difference in clinical outcome variables in our study among patients who took long-term Azithromycin as compared to those who did not take Azithromycin. Pomares *et al*.[16] published data of 109 patients of COPD treated with long term Azithromycin use and reported that long-term continuous cyclic use of Azithromycin caused significant reduction in acute exacerbations of COPD and also number of hospitalizations in these patients. Our results supported the findings of Pomares *et al*. as in our study patients taking Azithromycin had statistically significant chances of hospital admissions and parenteral steroid use. Choi *et al*.[17] studied same impact of Azithromycin on two different groups of COPD patients, with and without bronchiectasis, and revealed that bronchiectasis patients with chronic obstructive airway disease could benefit more from long-term Azithromycin treatment than COPD patients without bronchiectasis. We did not segregate patients on basis of presence of bronchiectasis, but our findings were similar. A randomized controlled trial was published by Albert *et al*.[18] comparing Azithromycin and placebo for prevention of exacerbations of COPD, concluded that Azithromycin taken daily for one year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of subjects. We neither studied quality of life nor the adverse effects caused by Azithromycin, but frequency of exacerbations was clearly reduced in our study participants who took Azithromycin for 6 months in addition to routine COPD treatment.

CONCLUSION

Long-term Azithromycin use was found beneficial for patients suffering from COPD where use of parenteral steroids and COPD related hospital admissions were significantly reduced.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HS & MA: Data acquisition, critical review, approval of the final version to be published.

SAAG & MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Z & HS: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin–oxygen dissociation curve. Breathe 2015; 11(3): 194-201. https://doi.org/10.1183/20734735.001415
2. Sutradhar I, Das Gupta R, Hasan M, Wazib A, Sarker M. Prevalence and risk factors of chronic obstructive pulmonary disease in Bangladesh: a systematic review. Cureus 2019; 11(1): e3970. https://doi.org/10.7759/cureus.3970
3. Oussedik F, Khelafi R, Skander F. The impact of acute exacerbations of COPD on mortality. Rev Mal Respir 2019; 36(1): 7-14. https://doi.org/10.1016/j.rmr.2017.12.005

4. Cappa V, Marcon A, Di Gennaro G, Chamitava L. Health-related quality of life varies in different respiratory disorders: a multi-case control population-based study. BMC Pulm Med 2019; 19(1): 32. https://doi.org/10.1186/s12890-019-0796-8
5. Lief L, McSparron J. Acute exacerbation of COPD. Evidence-Based Critical Care 2019; 169-173. https://doi.org/10.1007/978-3-030-26710-0_22
6. Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: a review focusing on exacerbations. Am J Health Syst Pharm 2020; 77(4): 259-268. https://doi.org/10.1093/ajhp/zxz306
7. Shteinberg M, Schneer S, Lavon O, Adir Y. Long-term treatment with macrolides in chronic lung diseases. Harefuah 2016; 155(9): 567-571.
8. Naderi N, Assayag D, Mostafavi-Pour-Manshadi SM, Kaddaha Z, Joubert A, Ouellet I, et al. Long-term Azithromycin therapy to reduce acute exacerbations in patients with severe chronic obstructive pulmonary disease. Respir Med 2018; 138(3): 129-136. https://doi.org/10.1016/j.rmed.2018.03.035
9. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 2018; 10(10): CD009764. https://doi.org/10.1002/14651858.CD009764.pub3
10. Sultana T, Afzal A, Sultana S, AlGhanim K, Shahid T, Jabeen Z, et al. Epidemiological estimates of respiratory diseases in the hospital population, Faisalabad, Pakistan. Braz Arch Biol Technol 2017; 60(1): e17160358.
11. Cao Y, Xuan S, Wu Y, Yao X. Effects of long-term macrolide therapy at low doses in stable COPD. Int J Chron Obstruct Pulmon Dis 2019; 14(3): 1289-1298. https://doi.org/10.2147/COPD.S205075
12. Pinto LM, Gupta N, Tan W, Li PZ, Benedetti A. Derivation of normative data for the COPD assessment test (CAT). Respir Res 2014; 15(1): 68. https://doi.org/10.1186/1465-9921-15-68
13. Taylor SP, Sellers E, Taylor BT. Azithromycin for the prevention of COPD exacerbations: the good, bad, and ugly. Am J Med 2015; 128(12): 1362.e1-6. https://doi.org/10.1016/j.amjmed.2015.07.032
14. Yawn BP, Mintz ML, Doherty DE. GOLD in practice: chronic obstructive pulmonary disease treatment and management in the primary care setting. Int J Chron Obstruct Pulmon Dis 2021; 16(3): 289-299. https://doi.org/10.2147/COPD.S222664
15. Threapleton CJ, Janjua S, Fortescue R, Baker EH. Head-to-head oral prophylactic antibiotic therapy for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2019; 5(5): CD013024. https://doi.org/10.1002/14651858.CD013024.pub2
16. Pomares X, Montón C, Bullich M, Cuevas O, Oliva JC, Gallego M, et al. Clinical and safety outcomes of long-term Azithromycin therapy in severe COPD beyond the first year of treatment. Chest 2018; 153(5): 1125-1133. https://doi.org/10.1016/j.chest.2018.01.044
17. Choi Y, Shin SH, Lee H, Cho HK, Im Y, Kang N, et al. Favorable response to long-term Azithromycin therapy in bronchiectasis patients with chronic airflow obstruction compared to chronic obstructive pulmonary disease patients without bronchiectasis. Int J Chron Obstruct Pulmon Dis 2021; 16(3): 855-863. https://doi.org/10.2147/COPD.S292297
18. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011; 365(8): 689-698. https://doi.org/10.1056/NEJMoa1104623

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