Open Access

Original

Comparison of Efficacy of Nebulized Salbutamol with Salbutamol / Ipratropium Combination in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Muhammad Nadeem Ashraf, Muhammad Arif Khan*, Muhammad Imran, Imran Fazal, Zubia Hassan, Laima Alam

Department of Medicine, Pak Emirate Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Medicine, Combine Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objectives: To compare the nebulized salbutamol alone with combination of nebulized salbutamol and ipratropium for acute exacerbation of chronic obstructive pulmonary disease in terms of mean length of stay.

Study Design: Quasi-experimental study

Place and Duration of Study: Department of Medicine, Military Hospital, Rawalpindi Pakistan. Study was carried out over a period of six months from May to Nov 2017.

Methodology: A total of 300 patients of chronic obstructive pulmonary disease (150 in each group) were recruited in the study. Group A received nebulized salbutamol (5mg) alone and Group B received a combination of nebulized salbutamol (5mg) and ipratropium bromide (0.5mg).

Results: Mean age of the patients was 66.4±6.4 years and 65.7±6.8 years in Group-A and B, respectively. In Group-A, there were 136(90.7%) and in Group-B 134(89.3%) were males while 14(9.3%) and 16(10.7%) were females in Group-A and B, respectively. Mean duration of disease in Group-A was 5.2±2.4 years and in group-B 6.0±1.6 years. Comparison of mean length of stay (days) revealed in hospital between nebulized Salbutamol alone 5.0±0.5 days with combination of nebulized Salbutamol and Ipratropium 4.3±0.6 days with *p*-value <0.001.

Conclusion: In conclusion, the routine addition of nebulized ipratropium bromide to salbutamol appears to be of benefit in the treatment of acute exacerbations of chronic obstructive pulmonary disease and in terms of mean length of hospital stay.

Keyword: Acute exacerbation of chronic obstructive pulmonary disease, Ipratropium, Salbutamol.

How to Cite This Article: *Ashraf MN, Khan MA, Imran M, Fazal I, Hassan Z, Alam L. Comparison of Efficacy of Nebulized Salbutamol with Salbutamol / Ipratropium Combination in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Pak Armed Forces Med J 2023; 73(Suppl-1): S36-39. DOI: https://doi.org/10.51253/pafmj.v73iSUPPL-1.2430*

INTRODUCTION

Chronic obstructive pulmonary disease is a progressive inflammatory lung disease characterized by persistent airflow obstruction to the lungs that is not reversible.[1-3] Almost 24 million American adults are living with COPD.[4] Airway obstruction results from bronchospasm, edema of mucous membrane, inflammatory reaction, hyper secretion of mucous and development of mucous plug. Some structural changes such as hypertrophy and hyperplasia of airway smooth muscles are also contributing factors.[5] Progressive dyspnea, sputum production, chronic cough that worsens with exertion. COPD is likely sec to irritants, tobacco smoking, occupational and family history. CORD can be diagnosed by history examination and Spirometry FEV1/FVC<70%. COPD is classified into 4 types by GOLD classification (global strategy for diagnosis management and prevention of COPD) i.e., GOLD1 mild FVC<80%, GOLD 2 FVC 50 79%, GOLD3 FVC 30-49%, GOLD4 FVC<30%.[5]

Correspondence: Dr Muhammad Nadeem Ashraf, Department of Medicine, Pak Emirate Military Hospital Rawalpindi Pakistan

Received: 06 Feb 2019; revision received: 07 Oct 2020; accepted: 14 Oct 2020

Acute exacerbation and subsequent hospitalizations are responsible for most of the health care expenditure.[2] According to local study in Peshawar majority of exacerbation is due to lack of vaccination and poor compliance to medicine.[3] Treatment of acute exacerbation involves bronchodilators, oxygen, steroids and antibiotics,[1] Ipratropium and salbutamol provide better bronchodilator effect than each of them alone.[1] A study done regarding comparison of salbutamol vs salbutamol and ipratropium, showed length of stay of salbutamol alone was 10.5±4.7 and salbutamol ipratropium combination was 11.8±4.4.[6] Days of nebulization for salbutamol vs salbutamol ipratropium combination were 8.5±4 vs 8.2±3.6. Number of days for improvement for salbutamol were 4.5±1.8 and for combination were 4.8±2.4 days.[6] The rationale of this study was regarding bronchodilators efficacy alone or in combination in acute exacerbation of CORD. This project was designed to evaluate the superior efficacy of nebulized salbutamol and ipratropium combination as compared to nebulized salbutamol alone. This will help in providing evidence based treatment to patients with acute exacerbations of CORD. In turn, this measure will help achieve shorter stay in hospital and

quicker patient disposal. The burden on hospital would thus be reduced significantly.

METHODOLOGY

The quasi-experimental study was carried out in Pak emirates military hospital department of medicine, military hospital, Rawalpindi. Study was carried out over a period of six months from May 2017 to November 2017 which enrolled 300 cases divided into two groups (g1 and g2) 150 cases in each group using non-probability, consecutive sampling technique with level of significance assigned 5% and power of test 80% with population mean g1 being 10.5±4.7 6and population mean of g2 being 11.8±4.4.6 Group 1 was administered salbutamol alone and Group 2 was administered salbutamol/ipratropium combination.[2]

Inclusion Criteria: All patients with acute exacerbation of COPD of both genders with age 50-80 years of age and patients on no COPD medications or poor compliance of medication were included.

Exclusion Criteria: Patients with isolated asthma or patients with rhinitis or patients with h/o pulmonary tuberculosis or pa-tients with any trauma to respiratory air way or patients with pneumothorax or who did not com-prehend the technique of using peak flow meter, were excluded.

This study was started after obtaining permission from Ethics Review Committee of the hospital. and approval of synopsis by RTMC. Patients with acute exacerbation of COPD presenting to ER was assessed for inclusion in this study based on the selection criteria mentioned above. Clinical assessment and treatment was started at the same time.[2] A quick history was taken, focusing on the new symptoms, their intensity and duration. Physical examination was focused on recording vital signs, including pulse, respiratory rate, cough, and sputum production and using cardiac monitor and naked eye examination. Initial treatment included nebulized bronchodilators, supplemental low flow oxygen (via nasal cannulae), hydrocortisone 200mg IV stat and ceftriaxone 1gm IV stat after test dose).[2] For the use of nebulized bronchodilators, patients were allocated to two treatment arms using Random Allocation Soft-ware Version 2.0. Group A received nebulized salbutamol (5mg) alone, whereas Group B received a combination of nebulized salbutamol (5mg) and ipratropium bromide (0.5mg). These nebulized drugs were administered thrice daily. Improvement in Respiratory rate, cough and sputum production was noted. Length of stay in hospital was also noted.

Data were analyzed using SPSS version 22. Quantitative variables like age, length of stay in hospital, respiratory rate was described as Mean±SD. Frequency and percentages were calculated for categorical variables like gender. The mean changes for length of stay amongst patients from both these groups were compared using independent samples t-test. *p*-values ≤0.05 was considered significant. Post-strati-fication independent sample t-test was applied. The *p*- value ≤0.05 was taken as significant.

RESULTS

A total of 300 patients (150 in each group) were taken during the study period. Group A received nebulized salbutamol (5mg) alone. Group B received a combination of nebulized salbutamol (5mg) and ipratropium bromide (0.5mg).

Table-I: Comparison of mean length of stay (Days) in Hospital between Group-A and Group-B (n=300)

Group	Mean	S.D
Group-A (Nebulized Salbutamol alone)	5.0	0.5
Group-B (Combination of nebulized Salbutamol and ipratropium)	4.3	0.6
t-value	10.203	
p-value	*p*<0.001	

Table-II: Stratification for Gender (n=300)

Gender	Group	Length of Stay in Hospital		*p*-value
		Mean	S.D	
Male	Group-A	5.00	0.54	0.001
	Group-B	4.31	0.66	
Female	Group-A	5.07	0.26	0.001
	Group-B	4.22	0.65	

Mean age of the patients was 66.4±6.4 and 65.7±6.8 in group-A and B, respectively. In group-A, there were 136(90.7%) and in group B 134(89.3%) were males while 14(9.3%) and 16(10.7%) were females in group- A and B, respectively. Mean duration of disease in group A was 5.2±2.4 and in group-B 6.0±1.6 years.

Table-III: Stratification for Duration of Disease (n=300)

Duration (Year)	Group	Length of Stay in Hospital		*p*-value
		Mean	S.D	
1-5	Group-A	5.01	0.52	0.001
	Group-B	4.35	0.61	
6-12	Group-A	5.00	0.53	0.001
	Group-B	4.26	0.70	

Comparison of mean length of stay (days) revealed in hospital between nebulized salbutamol alone (5.0±0.5) with combination of nebulized salbutamol and ipratropium (4.3±0.6) with *p*-value <0.001.

Stratification with regard to age, gender, duration of disease and symptoms was also carried out.

Table-IV: Stratification for Purulent Sputum (n=300)

Purulent Sputum	Group	Length of Stay in Hospital		*p*-value
		Mean	S.D	
Yes	Group-A	5.00	0.52	0.001
	Group-B	4.30	0.66	
No	Group-A	5.25	0.50	0.028
	Group-B	4.00	0.70	

Table-V: Stratification for Cough (n=300)

Cough	Group	Length of Stay in Hospital		*p*-value
		Mean	S.D	
Yes	Group-A	5.00	0.53	0.001
	Group-B	4.30	0.66	
No	Group-A	5.00	0.00	0.111
	Group-B	4.14	0.80	

DISCUSSION

P 2 agonist have been usual mode of treatment for patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) and admitted in the respiratory unit as part of their management plan. Ipratropium bromide though increase the cost of management but still widely used along with P2 agonist to manage the COPD patients in acute phase. They basically inhibit vagally mediated bronchomotor tone as their mechanism of action and provide an additional benefit to such patients as described by Saab *et al.* in 2020.[7] Studies done bu Hunag *et al*. in 2019 and Tashkin *et al*. in 2016 have suggested that long term management plans should include ipratropium bromide as it seems to provide long term benefit both in cases of COPD.[8,9] Hashmi *et al*. demonstrated same effect of ipratropium in acute severe asthma.[10] The possible mechanism of action of ipratropium bromide as published by Gosens *et al*. in 2018 suggest that it may have more role to play in prolonging the remission phase of airway disease instead to providing immediate relief in acute phase of illness.[11]

Researchers and clinicians have been doing work on this aspect of management of COPD as combination drugs may provide relief but also prone individuals to more side effects. Most of the studies suggest that combination of ipratropium and salbutamol has no added benefit in terms of efficacy when compared with salbutamol alone. All the long term, short term, clinical and laboratory parameters were more or less equal in both the groups generating the results in favor of using salbutamol alone instead of combination for the acute phase of treatment. Research done on stable out-patients in most part of the world has generated results opposite to the ones generated for acute phase of illness. Combination treatment has proven to be more effective in prevention of relapse as compared to salbutamol alone as described by Calzetta et al. in 2018, Zheng *et al*. in 2018 and Conolly *et al*. in 1987.[12-14] Improvement extent may not be very large but still combination treatment is somewhat superior in stable patients of COPD as published by Braun *et al*. in 1989.[15] Though ipratropium alone has not been used in routine as primary management agent but some trials have suggested that it alone is as effective as combination or salbutamol alone.[16,17] Though this was not scope of our study but future studies may take up this challenge.

O'Driscoll *et al*.[17] did an interesting study back in 1989 and evaluated the patients one hour after the treatment. They concluded that one hour benefit in respiratory symptoms was equal in both the combination group and salbutamol group so no short term benefit of combination was elicited in their study.

An earlier study done by Rebuck *et al*.[18] revealed that use of alone fenoterol or ipratropium bromide was equally effective in producing the bronchodilator effect in COPD patients after ninety minutes as that of combining the agents. Our results were a bit different as combination treatment emerged as superior ns efficacious option in our analysis.

Studies which have end point in hours and assess very short term benefit in respiratory symptoms cannot be considered appropriate for devising long term management plans as studies of Pratter *et al*. published in 1988 and Taylor *et al*. in 1985.[19,20] Using mean duration of hospital stay as one of the endpoints in our study broadened the horizon and generated results which could be incorporated in making local guidelines.

Though we just looked for the efficacy and mean hospital stay but anticholinergic properties of ipratropium bromide may pose some adverse effects to the patients and whenever option of combination treatment is discussed, possibility of increased side effects should not be ignored.

In present study, mean length of study in hospital was significantly less in nebulized salbutamol alone group when compared with combination of nebulized salbutamol and ipratropium for acute exacerbation of COPD (p<0.001). Study of Moayyedi *et al*.[6] generated results which could be compared with that of ours.

CONCLUSION

In conclusion, management of patients with combination of ipratropium bromide and salbutamol appears to be of more benefit in the treatment of acute exacerbations of COPD and in terms of mean length of hospital stay.

Conflict of Interest: None.

Authors' Contribution

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

MNA & MAK: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

MI & IF: Study design, data interpretation, critical review, approval of the final version to be published.

ZH & LA: Concept, data acquisition, 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. Singh D, Zhu CQ, Sharma S, Church A, Kalberg CJ. Daily variation in lung function in COPD patients with combined albuterol and ipratropium: results from a 4week, randomized, crossover study. Pulm Pharmacol Ther 2015; 31(3): 85-91.
2. Ahmed H, Zaman M. An audit of management of patients with acute exacerbation of COPD at a tertiary care hospital. Pak J Chest Med 2015; 21(1): 68-75.
3. Woldeamanuel GG, Mingude AB, Geta TG. Prevalence of chronic obstructive pulmonary disease (COPD) and its associated factors among adults in Abeshge District, Ethiopia: a cross sectional study. BMC Pulm Med. 2019; 19(1): 181-182. https://doi.org/10.1186/s12890-019-0946-z
4. Ho T, Cusack RP, Chaudhary N, Satia I, Kurmi OP. Under- and over-diagnosis of COPD: a global perspective. Breathe (Sheff). 2019; 15(1): 24-35. https://doi.org/10.1183/20734735.0346-2018
5. Bhatta L, Leivseth L, Mai XM, Henrikson AH, Carslake D, Chen Y et al. GOLD Classifications, COPD Hospitalization, and All-Cause Mortality in Chronic Obstructive Pulmonary Disease: The HUNT Study. Int J Chron Obstruct Pulmon Dis. 2020; 15(3): 225-233. https://doi.org/10.2147/copd.s228958
6. Moayyedi P, Congleton J, Page RL, Pearson SB, Muers MF. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995; 50(1): 834-837.
7. Saab H, Aboeed A. Ipratropium. [Updated 2019 Dec 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544261/
8. Huang K, Guo Y, Kang J, An L. The efficacy of adding budesonide/formoterol to ipratropium plus theophylline in managing severe chronic obstructive pulmonary disease: an open-label, randomized study in China. Ther Adv Respir Dis. 2019; 13(1): 1-5. https://doi.org/10.1177% 2F1753466619853500
9. Tashkin DP. A review of nebulized drug delivery in COPD. Int J Chron Obstruct Pulmon Dis. 2016; 11(3): 2585-2596.
10. Hashmi MF, Tariq M, Cataletto ME. Asthma. [Updated 2020 May 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https:// www.ncbi.nlm.nih.gov/books/NBK430901/
11. Gosens R, Gross N. The mode of action of anticholinergics in asthma. Eur Respir J 2018; 52(4): 1701247.
12. Calzetta L, Matera MG, Cazzola M, Rogliani P. Optimizing the Development Strategy of Combination Therapy in Respiratory Medicine: From Isolated Airways to Patients. Adv Ther. 2019; 36(12): 3291-3298. https://doi.org/10.1007%2Fs15-019-01119-w
13. Zheng Y, Zhu J, Liu Y, Lai W, Lin C, Qiu K et al. Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. BMJ. 2018; 363(1): k4388.
14. Connolly CK, Chan NS. Salbutamol and ipratropium in partially reversible airway obstruction. Br J Dis Chest 1987; 81(4): 55-61.
15. Braun SR, McKenzie WJ. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airways disease. Arch Intern Med 1989; 149(2): 544-547.
16. Easton PA, Jadue C, Dhingra S. A comparison of the bronchodilating effects of a beta-2 adrenergic agent (albeterol) and an anticholinergic agent (ipratropium bromide), given by aerosol alone or in sequence. N Eng J Med 1986; 315(6): 735-739.
17. O'Driscoll BR, Horsley MG, Taylor RJ, Chambers DK, Bernstein A. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. Lancet 1989; 1(8652): 1418-20.
18. Rebuck AS, Chapman KR, Abboud R. Nebulized airways disease in the emergency room. Am J Med 1987; 82(7): 59-64.
19. Pratter MR, Irwin RS. Predicting response to bronchodilator therapy in chronic obstructive pulmonary disease. Arch Intern Med 1988; 148(1): 1909-10.
20. Taylor DR, Buick B, Kinney C, Lowry RC, McDevitt DG. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible airflow obstruction. Am Rev Respir Dis 1985; 131(4): 747-51.