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RESEARCH ARTICLE

UNIQUE ANTI-INFLAMMATORY APPROACH OF ATORVASTATIN IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT

Atorvastatin is most effective cholesterol lowering agent. Most recently it was found that apart from their primary actions on HMG-CoA reductase enzyme this can also modulates the immune functions and inflammatory processes by their effects on expression of signaling proteins most importantly Rho, Rac and Ras. Therefore atorvastatin may have beneficiary effects of different inflammatorydiseases and autoimmune diseases. Out of theses chronic obstructive pulmonary disease (COPD) is most common public health problem and its accounts for about 3rd leading cause of death worldwide. The main burden of COPD associated morbidity were due to its systemic complications and frequent exacerbations. Current therapy cannot efficiently decreases its systemic complications. Thus in this research project we evaluating the beneficial effects of Atorvastatin in COPD patients and compare it with standard anti-inflammatory drug which was Budesonide. This shows that Atorvastatin can effectively improve the Spirometric finding, also having positive impact on health related quality of life as assessed by BODE index and SGRQ and effectively decreases the chances of exacerbations. Thus Atorvastatin can becomes the mainstay adjuvant therapy beside of their cardiovascular protective effects in COPD patients by modulating the inflammatory processes.

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INTRODUCTION

Chronic obstructive pulmonary disease is the main foremost cause of indisposition and humanity worldwide (Lawes et al., 2012). COPD is characterize by progressive airway limitations and currently COPD is not consider as disease merely restricted to airway but COPD now cogitate as systemic disease involving the multiple systems including specially cardiovascular system (Mroz et al., 2015). Main causes of COPD related deaths occurred due to frequent exacerbations and their systemic complications such as myocardial infarction (Barnes, 2010). The pathogenesis behind systemic complications of COPD is due to stumble of inflammatory mediators from respiratory tract to systemic circulation. Reduced Spirometric findings as indicated by reduced forced expiratory volume in one second (FEV1) is a prevailing marker for cardiovascular complications in COPD patients which was second to smoking as clairvoyant for cardiovascular disease (CVD) related mortality in COPD patients (Falk et al., 2008). Current therapy of COPD could not efficaciously cure the disease and also ineffective in decreases the chances of exacerbations of disease. Because main drawback of current therapies are that poor compliance and most of the agents can increases the chances of systemic complications associated with COPD (Altose, 2003). Therefore there should more concern about effective oral agent that can having effects on both respiratory and systemic complications associated with COPD (Wagner and Kenreigh, 2005). Statins are the effective agents that reduces the cholesterol biosynthesis by their inhibiting effects of HMG CoA reductase enzyme. Currently it was found that Atorva statin have several pleiotropic effects alongside of their primary cholesterol lowering effects (Ghobadi et al., 2014). These includes specially anti-inflammatory and immunomodulatory effects. Statins can modulates the inflammation by inhibiting the release of chemokines, cytokines and chemotaxis factors that involved during inflammation. Statins can have these effects by inhibiting the intermediate isoprenoids by their inhibiting effects on mevalonate pathway. These isoprenoids are important in prenylation of Rho, Ras and Rac (Hothersall et al., 2008). These intermediate signaling proteins are involve in expression of chemokines and cytokines thus promoting inflammation (Keddissi et al., 2007). Therefore by decreasing the expression of these signaling proteins constraining the inflammation. Hence because of these effects statins can be useful in varieties of inflammatory diseases such as psoriasis, COPD, and even in Alzheimer'sdisease (Young et al., 2009). In

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COPD Statin can decreasing the respiratory inflammation and in turn also inhibiting the systemic spillover of inflammatory mediators. Consequently because of these effects statins can decrease the incidences of exacerbations and mortality of COPD patients (Fabbri et al., 2008). The objective of this research project was to evaluate the dual cardiopulmonary protective effects of Atorvastatin in COPD patients, which may become the mainstay of therapy in prevention of exacerbation of COPD, cardiovascular events and improvement in major pulmonary functional capacities.

MATERIALS AND METHODS

This was open label clinical trial carried out in Department of Pharmacology and Therapeutic at Basic Medical Sciences Institute in collaboration with Department of chest medicine, JPMC, Karachi. The ethical committee of this institution approved the study protocol. We basically enrolled clinically diagnosed cases of moderate COPD age ranges between 35-65 years of either sex with C-reactive protein levels ≥3mg/lit. The following were our exclusion criteria:

- Unstable COPD patients
- Patients already on Statin therapy
- Previous Statin sensitivity or myopathy or myositis
- On any medications known to interacts with Statin
- Pregnant and lactating mothers
- Active and chronic liver disease
- Renal compromised patients
- Other immunological disorders
- Respiratory infection defined as fever, nasal/sinus congestion, fatigue, cough, antibiotic use or yellow/green sputum within 4 weeks prior to study
- Pneumonia

The extent of study was 6months (Dec 2010 to May 2011) with specific study period were of 90 days with 5 follow up visits. The sample size 105 patients were registered in this trial and distributed equally into 3 groups designated group A, B and C. 35 patients per group was enrolled as per criteria mentioned above. Group A was assigned to receive tab. Atorvastatin 20mg/day once a day for 12 weeks. Group B was assigned to inhale Budesonide twice a day for 12 weeks. While group C was assigned for inhaled Budesonide twice a day along with Atorvastatin 20mg once a day for 12 weeks. The primary outcomes for assessing the improvement were done by Spirometry, impact on quality of life by BODE index and SGRQ, exacerbation rate. The exacerbation rate assessed by clinical COPD questionnaire card specially designed for this project.

Statistical Analysis

SPSS (statistical Package for Social Sciences) ver 11.5 was used for data feeding and analysis. Frequencies and percentages were calculated for qualitative variables (gender, smoking history, sputum production, family history, etc.) while mean ± S.E.M for quantitative variables (age, PEFR, FEV1, FVC, FEV1/FVC ratio, Liver function test (LFT), lipid profile, etc). Paired sample Student t-test (paired) was used for comparison of quantitative data from baseline (day-0) to day-30, day-60 and day-90.

RESULTS

Pulmonary functional capacity which was assessed by Spirometric findings shows that as compare to single group of Atorvastatin and Budesonide the combination group more efficiently improve the Spirometric findings. As compare to baseline % change of FEV1 were 11.1%, 14.2% and 19.3% in Atorvastatin, Budesonide and combination group respectively. Likewise % change of FVC were 3.4% in Atorvastatingroup, 5.7 % in Budesonide group and 11% in combination group. As illustrated in table 1Aand figure 1A. Likewise clinical improvement were assess in respect to average % improvement of component of pulmonary functional capacity which was FEV1 and clinical disability score which was assess by MMRC dyspnea score. This shows that mean reduction of MMRC dyspnea score were 15.2 ± 3.21, 11.4 ± 3.22 and 18.5 ± 3.63 in Atorvastatin alone, Budesonide and combination group respectively. This shows that in all treated groups infirmity due to dyspnea was significantlyabridged but more efficiently in combination group. Likewise mean improvement of FEV1 was 15.6 ± 0.99 in Atorvastatin group, 13.9 ± 0.79 in Budesonide treated group and 19.7 ± 0.96 in combination group. As publicized in table 1A, 1B and figures 1A, 1B &1C.
In comparison of sway on the health related quality of life in COPD patients which was assessed by SGRQ, and impact on exercise capacity which was assess by BODE index shows that there was momentous difference were noted between the all treated groups and combination therapy was more effective in improving the domains of SGRQ and BODE index then the either treatment alone. The main components of SGRQ are symptom score, activity score and impact score. The mean symptom score were significantly reduced in all treated groups. In Atorvastatin mean symptom score at baseline was 66.2 ± 1.06, which was reduced to 54.4 ±1.31 (17.9%) at the end of the study. Similarly in Budesonide group the mean symptom score was 67.7 ± 0.86 which was reduced to 51.9 ±0.95 (20.4%) and in combination group mean symptom score was 65.8 ± 0.88 which was reduce to 44.6 ±0.84 (32.3%) at day 90 which was highly significant. Likewise at baseline the activity score impact score and total score were 60.4 ± 1.64, 60.6 ± 0.87 and 61.6 ± 0.73 respectively in atorvastatin group which were decreases to 51.6 ±1.35(14.6%), 51.6 ±1.26(14.9%) and 54.9 ±0.60 (10.9%) respectively at the end of the study. In combination group at the end of the study, % improvement of activity score, impact score and total score were 29.6%, 30.4% and 30.8%. As depicted in table 2A & 2B.
The impact of treatment on exercise capacity can assess by 6MWT shows that there were significant improvement in all treated groups. In combination group at baseline mean 6MWT was 214 ± 6.7 which was improve up to 271 ± 6.5(26.6%) at the end of the study. In respect to reduction of exacerbation rate there were no significant difference were noted between all treated groups. The exacerbation rate can assess by clinical COPD questionnaire card. As depicted in Table 3 and Figure 2.

DISCUSSION

COPD is the main public health problem worldwide and now this disease is considered as systemic disease with involvement of cardiovascular and musculoskeletal system (Chung, 2006). The frequent hospitalizations due to COPD produces most significant burden on public health (Keddissi et al., 2007). In search of ideal oral therapy to avoid the compliance related problems associated with inhaled medications used in COPD as well as decreases the incidences of systemic complications of disease we were evaluated the therapeutic evaluation of atorvastatin in COPD patients by its inhibitory effects on inflammatory process. In the present study a total of 105 patients of both sexes were enrolled and were divided into three groups; designated as Group A, Group B and Group C.

Table 1A. Comparison of effectiveness of improving the pulmonary functional capacity in all treated groups

Variables	Group A (n=33) Mean± SEM	Group B (n=34) Mean± SEM	Group C (n=34) Mean± SEM	P-value
Baseline (Day-0)				
FEV1	2.16 ± 0.07	2.12 ± 0.05	2.18 ± 0.03	0.613
FVC	3.57 ± 0.11	3.51 ± 0.08	3.54 ± 0.05	0.263
FEV1/FVC ratio	0.59 ± 0.01	0.60 ± 0.01	0.59 ± 0.01	0.095
PEFR	163 ± 2.44	166 ± 2.66	168 ± 2.40	0.351
Day – 30				
FEV1	2.25 ± 0.06(4.2%)	2.24 ± 0.05(5.7%)	2.28 ± 0.06(4.6%)	0.861
FVC	3.62 ± 0.11 (1.4%)	3.59 ± 0.08(2.3%)	3.71 ± 0.10(4.8%)	0.614
FEV1/FVC ratio	0.61 ± 0.01(3.4%)	0.63 ± 0.01(5%)	0.63 ± 0.01(6.8%)	0.054
PEFR	178 ±2.49(9.2%)	189± 2.54(13.9%)	207±2.56(23.2%)	0.002**
Day – 60				
FEV1	2.35 ± 0.06(8.8%)	2.31 ± 0.04(9%)	2.45 ± 0.04(13%)	0.032*
FVC	3.65 ± 0.11 (2.2%)	3.68± 0.11(4.2%)	3.82 ± 0.07(8%)	0.428
FEV1/FVC ratio	0.62 ± 0.01(5.1%)	0.64 ± 0.01(6.7%)	0.66 ± 0.01(11.9%)	0.021*
PEFR	187 ±2.52(14.7%)	198± 2.65(19.3%)	216±2.67(28.6%)	0.002**
Day – 90				
FEV1	2.48± 0.06(11.1%)	2.40 ± 0.04 (14.2%)	2.60 ± 0.04(19.3%)	0.020*
FVC	3.69 ± 0.08 (3.4%)	3.71 ± 0.11(5.7%)	3.94 ± 0.07(11%)	0.047*
FEV1/FVC ratio	0.64 ± 0.01(8.4%)	0.66 ± 0.01(10%)	0.68 ± 0.01(15.3%)	0.021 *
PEFR	210± 2.57(28.8%)	227 ±2.76(36.7%)	232±2.71(38.1%)	0.001**

*= p<0.05 significant from the day 0
**= p<0.01, highly significant from the day 0
%=Percentage changes in parenthesis

Table 1B. Comparision of efficacy of tablet atorvastatin and inhaled budenoside in improving the pulmonary functional capacity in chronic obstructive pulmonary disease patients

	Average % from baseline (Day-0)		
Clinically Assessed	Group A	Group B	Group C
Improvement in FEV1			
Day 30	4.4 ± 0.62	6.2 ± 0.32	6.1 ± 0.43
Day 60	9.2 ± 0.86	9.5 ± 0.64**	10.3 ± 0.53**
Day 90	15.6 ± 0.99**	13.9 ± 0.79**	19.7 ± 0.96**
Reduction in MMRC Dyspnea score			
Day 30	3.0 ± 1.95	4.5 ± 1.70	3.5 ± 1.25
Day 60	8.1 ± 2.67	7.1 ± 2.32	10.3 ± 2.87*
Day 90	15.2 ± 3.21*	11.4 ± 3.22**	18.5 ± 3.63**

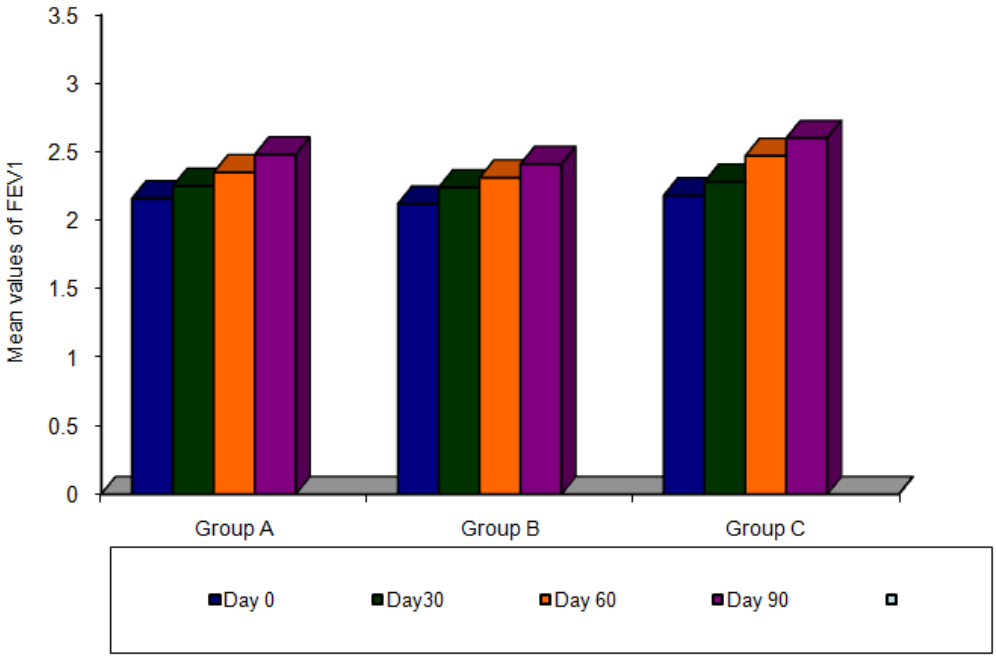

Figure 1A. Comparison of effectiveness of improving the forced expiratory volume in one second (FEV1) in all treated groups

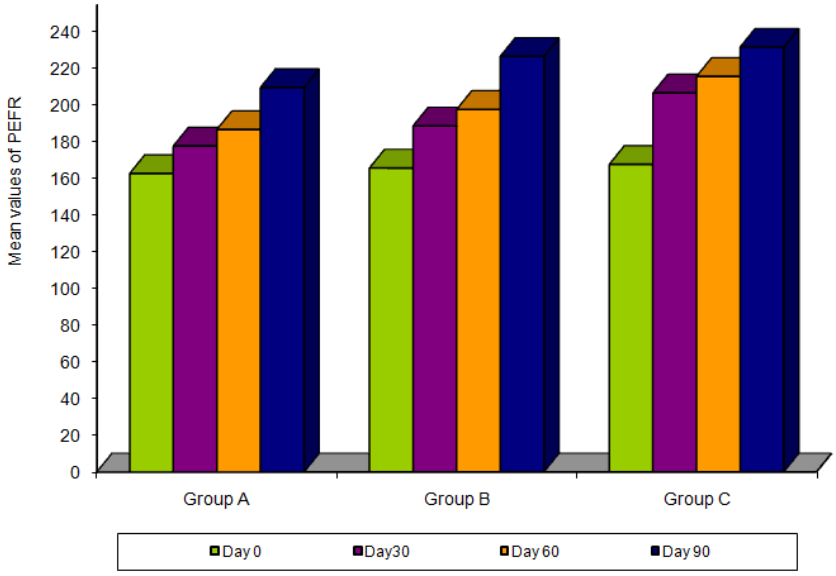

Figure 1B. Comparison of PEFR following treatment in group A (Atorvastatin),Group B (Budesonide) and Group C (combination thetapy) in COPD patients

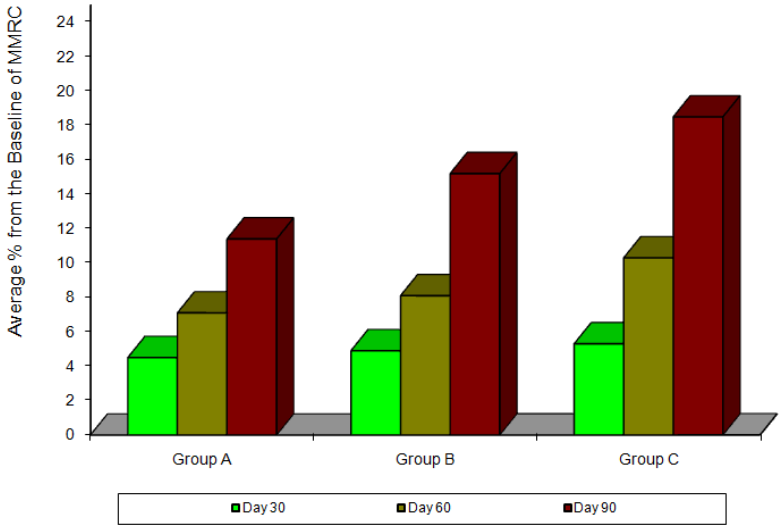

Figure 1C. Comparision of efficacy of tablet atorvastatin and inhaled Budesonide in improving the pulmonary functional capacity in chronic obstructive pulmonary disease

Table 2A. Comparison of effects on SGRQ in all treated groups

Variables	Group A (n=33) Mean± SEM	Group B (n=34) Mean± SEM	Group C (n=34) Mean± SEM	P-value
Baseline (Day-0)				
Symptoms score	66.2 ± 1.06	67.7 ± 0.86	65.8 ± 0.88	0.294
Activity score	60.4 ± 1.64	61.1 ± 1.44	59.9 ± 1.92	0.883
Impact score	60.6 ± 0.87	60.7 ±0.94	59.7 ± 0.53	0.604
Total score	61.6 ± 0.73	63.2 ±0.69	61.8 ± 0.63	0.192
Day – 30				
Symptoms score	63.4 ± 1.12(4.3%)	63.7 ± 0.91(6%)	59.2 ± 0.88(10.1%)	0.002 **
Activity score	59.5 ± 1.57(1.5%)	57.4 ± 1.44(6.1%)	53.9 ± 1.97(10.1%)	0.063
Impact score	59.9 ± 0.84(1.2%)	56.1 ± 0.91(7.6%)	53.9 ± 0.78(9.8%)	0.001 **
Total score	62.3 ± 0.66(1.2%)	59.1 ± 0.70(6.5%)	55.6 ± 0.72(10.1%)	0.001 **
Day – 60				
Symptoms score	61.8 ± 1.08(4.3%)	59.0 ±0.93(12.9%)	47.4 ± 0.90(28%)	0.001 **
Activity score	57.7 ± 1.46(4.5%)	51.6 ±1.41(12.3%)	47.3 ± 1.78(21.1%)	0.001 **
Impact score	58.6 ± 0.85(3.3%)	51.7 ±0.89(14.9%)	46.9 ± 0.76(21.5%)	0.001 **
Total score	59.4 ± 0.72(3.6%)	54.8 ±0.66(13.3%)	47.2 ± 0.74(23.7%)	0.001 **
Day – 90				
Symptoms score	54.4 ±1.31(17.9%)	51.9 ±0.95(20.4%)	44.6 ±0.84(32.3%)	0.001 **
Activity score	51.6 ±1.35(14.6%)	48.9 ± 1.43(20%)	42.2 ±1.64(29.6%)	0.001 **
Impact score	51.6 ±1.26(14.9%)	47.2 ±0.90(22.3%)	41.6 ±0.76(30.4%)	0.001 **
Total score	54.9 ±0.60(10.9%)	50.0 ±0.71(20.9%)	42.8 ±0.69(30.8%)	0.001 **

*= p<0.05 significant from the day 0
** =p<0.01, highly significant from the day 0
%=Percentage changes in parenthesis

Table 2B. Comparison of eeftcs on BODEX index in all treated COPD patients

Variables	Group A (n=33) Mean± SEM	Group B (n=34) Mean± SEM	Group C (n=34) Mean± SEM	P-value
FEV1				
Day – 0	2.16 ± 0.07	2.12 ± 0.05	2.18 ± 0.03	0.613
Day – 30	2.25 ± 0.06(4.2%)	2.24 ± 0.05(5.7%)	2.28 ± 0.06(4.6%)	0.351
Day – 60	2.35 ± 0.06(8.8%)	2.31 ± 0.04(9%)	2.47 ± 0.04(13%)	0.378
Day – 90	2.48 ± 0.06(14.9%)	2.40 ±0.04(14.2%)	2.60 ±0.04(19.3%)	0.020 *
6 minutes walk test (6MWD) test				
Day – 0	217±5.7	219 ± 5.5	214 ± 6.7	0.349
Day – 30	221± 5.9(1.9%)	223 ± 5.4(1.9%)	243 ± 6.6(13.5%)	0.018*
Day – 60	231 ± 6.4(6.5%)	237 ± 5.8(8.2%)	262± 6.9(22.4%)	0.001**
Day – 90	243± 5.6(12%)	248 ± 5.5(13.2%)	271 ± 6.5(26.6%)	0.003**
MMRC (Dyspnea score)				
Day – 0	2.82 ± 0.13	2.88 ± 0.11	2.89 ± 0.12	0.188
Day – 30	2.77 ± 0.10(1.8%)	2.68 ± 0.11(7%)	2.56 ± 0.10(11.4%)	0.844
Day – 60	2.69± 0.08(5%)	2.47 ± 0.07(14.2%)	2.36 ± 0.08(18.3%)	0.010*
Day – 90	2.52± 0.08(13.1%)	2.41 ± 0.07(16.3%)	2.20± 0.07(23.8%)	0.022*
BMI (Body Mass Index)				
Day – 0	20.0 ± 0.37	19.9 ± 0.35	20.3 ± 0.19	0.781
Day – 30	20.3 ± 0.19(1.5%)	19.9 ± 0.35(2.6%)	20.2 ± 0.19(0.5%)	0.570
Day – 60	20.4 ± 0.18(2%)	20.2 ± 0.34(1.6%)	20.6 ± 0.17(1.5%)	0.495
Day – 90	20.6 ± 0.17(3%)	20.0 ± 0.35(0.6%)	20.7 ± 0.16(2%)	0.076
Total points				
Day – 0	6.33 ±0.20	6.39±0.14	6.37±0.14	0.698
Day – 30	6.18±0.15(2.4%)	6.18±0.14(3.2%)	6.09±0.13(4.3%)	0.570
Day – 60	6.00±0.15(5.3%)	5.94±0.14(7.1%)	5.81±0.13(8.7%)	0.456
Day – 90	5.94±0.17(6.2%)	5.85±0.14(8.5%)	5.67±0.14(11%)	0.005**

*= p<0.05 significant from the day 0
** p<0.01, highly significant from the day 0
%=Percentage changes in parenthesis

Table 3. Comparison of effects on reducing the exacerbation rate in all treated groups

Reduction in exacerbation	Group A (n=33) No. (%)	Group B (n=34) No. (%)	Group C (n=34) No. (%)	P-value
Day – 15	10 (3.03%)	8 (23.5%)	8(23.5%)	0.311
Day – 30	5(9.1%)	4 (5.9%)	1 (2.9%)	0.041*
Day – 60	2 (6.1%)	3(5.9%)	-	0.726
Day – 90	2 (6.1%)	1 (2.9%)	-	0.344

*=p<0.05 significant from the day 0
%= percentage of patients

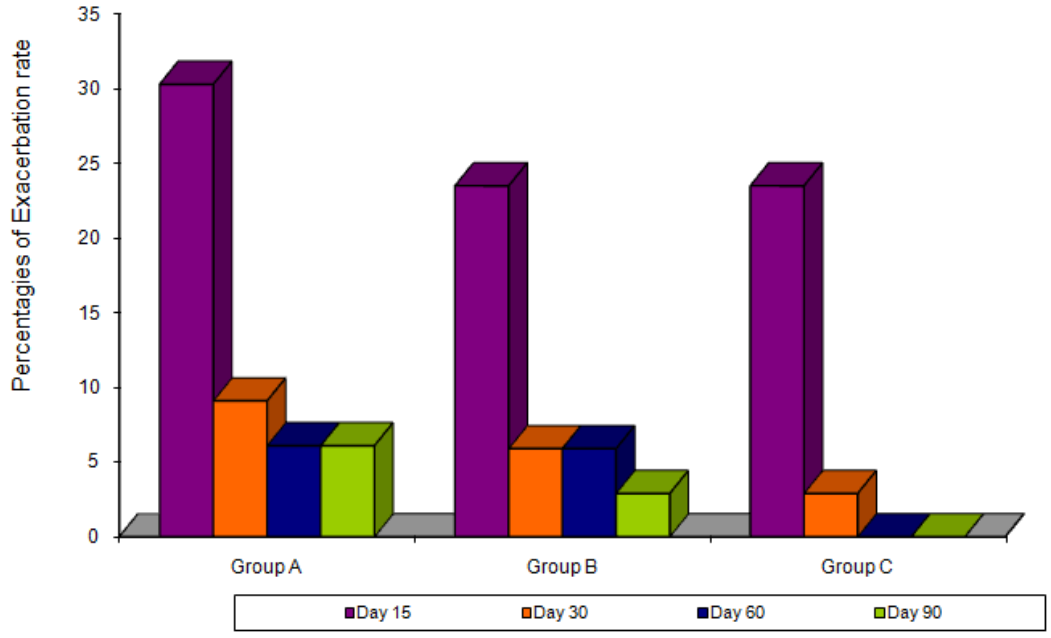

Figure 2. Effectiveness of atorvastatin and inhaled Budesonide in reducing the exacerbation rate in COPD patients

Each group having 35 patients; all the patients were registered on prescribed Performa especially designed for this study. There was no significant difference in gender and age distribution in all three. The final analysis of the study applied to 101 patients (33 in Group A, 34 in Group B and 34 in Group C), who were completed the study. There was clinically significant improvement of pulmonary functional capacities as assess by spirometry in all treated group. There was also significant decrease of disability due to dyspnea by MMRC dyspnea score and exacerbation rate. This was in line with the study conducted by Keddissi *et al*. (Bartziokas et al., 2011). showed that use of Statin was associated with atempereddecay in lung function and a lesserprevalence of respiratory related emergency department visits and/or hospitalization in patients with obstructive lung disease implies that Statin may have a direct disease amendingoutcome on COPD. Our study concluded that the Statin can improve the Health related quality of life (HRQoL) in COPD patients, which were evaluated by the effects of Atorvastatin on the domains of the SGRQ. Our result was matched with the study conducted by the Bartiziakas *et al.* (Bartziokas et al., 2011). They Bartziokas conducted prospective studies on 245 patients admitted to hospital for exacerbations of COPD (ECOPD) with scheduledappraisals for one year on Statin users. They determined that the usage of Statins in patients hospitalized for ECOPD was allied with a lesserperil for ensuing ECOPD and improved health related quality of life (SGRQ). Effects of Statin on exercise capacity as assessed by component of BODE index which was 6MWT and MMRC dyspnea score in our study was in line with the study conducted by Lee *et al.* (Soyseth et al., 2007). as they appraised the effects of pravastatin on COPD patients with pulmonary hypertension. Accordance to Lee *et al*. pravastatin can increased the exercise capacity significantly about 52% and there were also significant improvement in dyspnea score. The Combination of the HMG-CoA reductase inhibitors and a Glucocorticoids given in chorus may potentiate the effects of either component or also crop a superior effect than conventional COPD treatments. The therapeutics consequence can experiential with respect to the fast decline in the lung function that is a hallmark of COPD, and effects may be observed regarding the systemic inflammation that is also characteristics of COPD. The most preferred combinations are budesonide can combine either with Atorvastatin or Rouvastatin (Pritchett, 2001). Combined therapy of Statin with inhaled steroids has more favorable effects on all outcomes in our study as compare to the either treatment alone. This was consistent with the study conducted by Moneechatesuwan *et al.* (Chung, 2006). They appraised that which evertallying of Statin augments anti-inflammatory properties of steroids in asthmatic patients. They clinched that a Statin boosts the anti-inflammatory effect of inhaled steroids in asthma and this was mediated through the modification of indoleamine 2, 3-dioxygenase (IDD) commotion in macrophages. Statin in addition may bidcertainfortification against having osteonecrosis ripen when systemic steroid treatment is essential because of osteonecrosis is a overwhelmingimpediment of systemic steroid use. Asextended steroid use produces a hyperlipidemia state in most patients and put them at risk of osteonecrosis and osteoporosis (Pritchett, 2001).

Conclusion

This study demonstrated that Atorvastatin have additional potential to improving the pulmonary functional capacities and improve health related quality of life in chronic obstructive pulmonary disease beside of their primary cholesterol lowering effects.

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