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ORIGINAL ARTICLE

Efficacy of Indacaterol Versus Salmeterol/ Fluticasone Propionate in the Treatment of Patients with Chronic Obstructive Pulmonary Disease

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Abstract:

Background: *Bronchodilation is the cornerstone in the management of chronic obstructive pulmonary disease (COPD) and is based on regular treatment with long-acting once daily â$_2$agonists (LABAs). A novel bronchodilator, Indacaterol, satisfies the requirements of an efficacious long-acting â$_2$ agonists with faster onset of action.*

Method:*The present study was a prospective, single blind, randomized controlled trial. After fulfilling the exclusion and inclusion criteria with prior written consent, 130 patients suffering from Chronic obstructive disease were recruited by purposive sampling from the patients attending in the outdoor and indoor of National Institute of diseases of the chest and Hospital. Group was allocated randomly and concealed, 50% in Indacaterol group, 50% Salmeterol/fluticasone proprionate group and maintained properly. Following 4 weeks run in and screening period during which baseline variables were assessed and concomitant medications were established. The primary efficacy variable was forced expiratory volume in first second (FEV_1) as a lung function test and secondary efficacy variable was COPD Assessment Test (CAT) score. Then patients were randomized to receive either Indacaterol 150 ìg or Salmeterol/fluticasone proprionate 50/500 ìg. Tiotropium 18ìg in both group was added as concomitant medication. Objective blinded measurement of FEV_1 and subjective measurement of symptoms by COPD assessment Test were done in initial visit and during follow up at 4 weeks, 8 weeks, and at the end of 12 weeks.*

Result:*In the present study, 130 patients were randomized and 44(67.69%) patients in Group A(Indacaterol 150 ìg and 38(58.46) patients in Group B(Salmeterol/fluticasone proprionate 50/500 ìg) completed the study.*

Mean FEV_1 change between two group in 1st visit was 12.57 ml ($p<0.001$), 2nd visit 8.39 ml ($p<0.01$), final visit 20.26 ml ($p<0.04$)that was statistically significant.

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Mean CPOD Assessment Test (CAT) score change between two group in 1st visit was 0.69 (p<0.04), 2nd visit 1.14 (p<0.01), final visit 1.23 (p<0.005)that was statistically significant

Conclusion:*Indacaterol 150ig demonstrated superiority over salmeter/ fluticasone proprionate 50/500ig evidenced by increased FEV_1(p<0.05). Both treatments improved health status, between them favoring Indacaterol.*

Key words: *Indacaterol,Salmeterol/fluticasone proprionate,COPD assessment Test*

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Introduction:

COPD is the 4th leading cause of death worldwide. Prevalence is increasing in our country.[1] Cigarette smoking is the most striking risk factor of COPD. Biomass fuel fires, coal related occupation, outdoor and indoor pollution, recurrent childhood infection are other major risk factors.[2]

Pharmacological therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), inhaled bronchodilators, including β_2 agonists and anti-cholinergics are central to the symptomatic management of chronic obstructive pulmonary diseases).[3]

Currently available inhaled long acting β_2 agonist (LABAs), such as salmeterol and formeterol provide bronchodilation for approximately 12 hours at recommended doses and hence are administered twice daily. Indacaterol, a new drug has the property of rapid onset of action, once daily, long acting bronchodilator(24 hours) in the management of COPD[4] Once daily dosing of indacaterol has been shown to improve a range of clinical outcomes and exacerbations in patients with COPD compared with twice daily Salmeterol/ fluticasone proprionate.[5] Furthermore, patients' compliance with treatment could be improved if regimens are simplified by reducing the dosing frequency.[6]

Materials and Methods:

This present study was a prospective, single-blind randomized controlled trial was carried out in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh from July 2012 to June 2013for a period of one (1) year.130 patients of severe COPD(GOLD stage 3 COPD), age >40 years having a smoking history of > 10 pack year after excluding acute exacerbation of COPD , asthma, bronchial carcinoma,were recruited by purposive sampling from the indoor and outpatients department of National Institute of Diseases of chest & Hospital (NIDCH), Mohakhali, Dhaka.Prior to the commencement of thisstudy, the research protocol were approved by thethical committee of the NIDCH, Dhaka; informedconsents were taken from the respondents.In the present study, during the 4 weeks run-in period, each subject was evaluated with history and symptoms regarding the presentation. They were examined and certain baseline investigations were done. Patient's age, smoking history, past medical history, current medications were asked. Patients were asked about the cough, sputum production, dyspnoea, wheezing, haemoptysis, and chest pain.Lung function test in the form of Forced expiratory volume in 1st second (FEV_1) by Spirometry was done. CAT score was evaluated at screening phase as baseline before starting trial.

At the start of the 12-week treatment period, eligiblepatients were randomized in a ratio of 1:1 to receive eitherindacaterol 150 ig once-daily via single-dose dry powderinhaler (taken in the morning) or Salmeterol/fluticasone50/ 500igtwicedaily (morning and evening). Permitted concomitant medication was tiotropium 18 µgin both group.

Follow up was taken monthly for 3 months to determine the forced expiratory volume in first second (FEV_1) as the primary efficacy variable and COPD assessment Test (CAT) score was evaluated to determine the changes in symptoms in COPD patients as secondary efficacy variable.

All the information during run in period and treatment period were collected by a pretested semi-structured questionnaire.Finally 44 patients in group-A and 38 patients in group-B came to final follow-up, 21 patients in group-A and 27 patients in group-B lost in follow-up. All the information were properly documented Data were processed and analyzed using software SPSS (Statistical Package for Social Sciences).

Results:

Comparison between the effect of indacaterol and salmeterol/fluticasone proprionate on Primary outcome variables.

In the present study, Table shows mean FEV_1 change in 1st visit increase 14.20(±16.87) ml were in group A and decrease 1.62(±4.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 15.00(±18.22) ml were in group A and increase 7.85(±14.36) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 24.14(±16.87) ml were in group A and increase 3.88(±15.56) ml were in group B ($p<0.05$) that was statistically significant. Mean difference in both groups is 20.26 ml.

Comparison between the effect of indacaterol and salmeterol/fluticasone proprionate on Secondary outcome variables

In the present study, Table shows mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) ml were in group B ($p>0.05$) that was not statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B ($p<0.05$) that was statistically significant. Mean CAT change in 3rd visit decrease 1.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B ($p<0.05$), total change was 1.23 that was statistically significant.(Table II)

Table-I

Comparison between the effect of indacaterol and salmeterol/ fluticasone proprionate on Primary outcome variables

FEV_1	Group A Mean (±SD) (ml)	Group B Mean (±SD) (ml)	Mean difference (ml)	P value
1st visit	-14.20(±16.87)	-1.62(±4.84)	12.57	<0.001 s
2nd visit	-15.00(±18.22)	-7.85(±14.36)	8.39	0.01 s
3rd visit	-24.14(±16.87)	-3.88(±15.56)	20.26	0.04 s

Group A = Indacaterol 150 ìg
Group B = Salmeterol/fluticasone proprionate 50/500 ìg
P value reached from unpaired t- Test
P value reached from paired t- Test
ns = not significant
s = significant

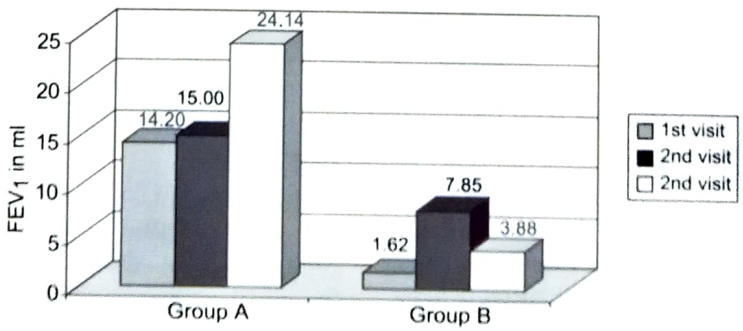

Fig.-1: *Bar diagram showing comparison between the effect of indacaterol and salmeterol/ fluticasone proprionate on Primary outcome variables.*

Table-II

Comparison between the effectof indacaterol and salmeterol / fluticasone proprionate on Secondary outcome variables

CAT score change	Group A Mean (±SD)	Group B Mean (±SD)	Mean difference	P value
CAT 1st visit	0.94(±2.07)	0.25(±1.52)	0.69	0.04 *
CAT 2nd visit	1.56 (±2.28)	0.42(±1.95)	1.14	0.01 *
CAT 3rd visit	1.56 (±2.18)	0.23(±2.0)	1.23	0.005 *

* CAT Score Decrease means improvement of symptoms
Group A = Indacaterol 150 ìg
Group B = Salmeterol/fluticasone proprionate 50/500 ìg
P value reached from unpaired t- Test
P value reached from paired t- Test
ns = not significant
s = significant

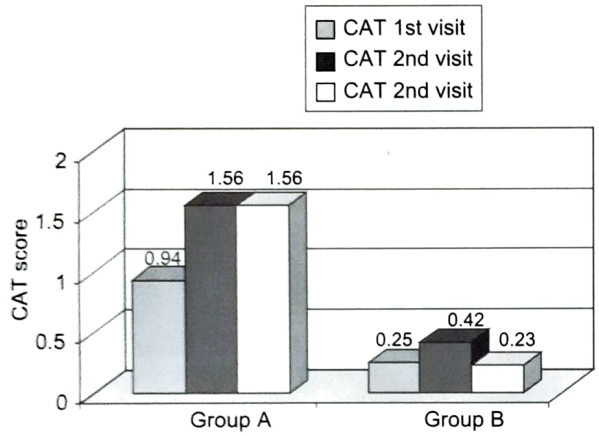

Fig.-2: *Bar diagram showing comparison between the effect of indacaterol and salmeterol / fluticasone proprionate on secondary outcome variables.*

Discussion:

This present study was performed to compare the efficacy of once daily Indacaterol 150 ìg versus twice-daily Salmeterol/fluticasone proprionate 50/500ìg evaluated by forced expiratory volume in 1st second (FEV_1) as lung function test by spirometry and changes of symptoms evaluated by CPOD Assessment Test (CAT) score in patients with severe COPD.

In a recent study, (The INSIST study) Korn S. et al. [7] compared indacaterol 150ìg and salmeterol 50ìg over 12 weeks. Indacaterol 150ìg was statistically superior to salmeterol 50 ìg for the primary endpoint, FEV_1 standardized area under the curve (AUC5 min to 11 h 45 min) at week 12, with an adjusted mean difference of 60 (95% CI 40–80) ml. The percentage of patients with a clinically important improvement (1 point) from baseline in TDI total score at week 12 was statistically higher ($p<0.05$) for indacaterol (69.4%) than salmeterol(62.7%).In this study inhaled steroid was added in salmeterol group. So that the current study agree with the previous study.

In a meta-analysis on 'Comparative efficacy of indacaterol 150 ìg and 300 ìg versus fixed-dose combinations of formoterol + budesonide or salmeterol +fluticasone for the treatment of chronic obstructive pulmonary disease' by Cope S. et al.[8], showed that Indacaterol 150ìg was statistically superior to salmeterol/fluticasone proprionate 50/500ìg for the primary endpoint, FEV_1 at week 12.The current study closely agree with the previous study .

In this present study mean FEV_1 change in 1st visit increase 14.20(±16.87) ml were in group A and decrease 1.62(±4.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 15.00(±18.22) ml were in group A and increase 7.85(±14.36) ml were in group B ($p <0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 24.14(±16.87) ml were in group A and increase 3.88(±15.56) ml were in group B ($p<0.05$) and difference was 20 ml that was statistically significant.

In this present Study, Tritopium was added in both Indacaterol and Salmeterol/ fluticasone proprionate group to stabilize the patient as a concomitant medication. So that 20 ml increase of FEV_1 in indacaterol group over salmeterol/ fluticasone proprionate group was a meaningful difference.

In the present study, CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) were in group B (p>0.05) that was not statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B (p<0.05) that was statistically significant. Mean CAT change in 3rd visit decrease 1.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B (p<0.05) that was statistically significant.

But in the present study, mean improvement in FEV1 is by 20 ml for Indacaterol than Salmeterol fluticasone proprionate at weeks12, it may be because of concomitant triotopium in both Indacaterol and Salmeterol/fluticasone proprionate group. Mean CAT change in 3rd visit decrease 2.53(±2.34) were in group A and decrease 0.58(±1.89) were in group B (p<0.05) that was statistically significant besides poor body build, racial variation, and small group of study population could be another factor for the variation. So the current study closely agreed with the previous 'INSIST' study.

Indacaterol demonstrated statistically superior bronchodilation compared with salmeterol/ fluticasone proprionate in terms of FEV_1 at Weeks 12, improves symptoms and quality of life in terms of CAT score at weeks 12, besides compliance with a once daily bronchodilator indacaterol was higher than with twice-daily bronchodilator salmeterol/ fluticasone proprionate evidenced by decrease dropout rate in indacaterol group than salmeterol/fluticasone proprionate group . Taken together, these imply that once daily dosing with indacaterol could improve compliance compared with twice-daily dosing with salmeterol/ fluticasone proprionate which is also consistent with the previous study: Once-daily indacaterol with twice-daily salmeterol/fluticasone proprionate for COPD.[9]

Conclusion:

In the present randomized controlled trial study, Indacaterol 150µg demonstrated superiority over Salmeterol/fluticasone proprionate 50/500µg evidenced by increased FEV_1which was statistically significant (p<0.05). Both treatments improved health status evidenced by decreased CAT score, between them favoring Indacaterol. Indacaterol 150 µg could be a better option for the first-line treatment of COPD than salmeterol/ fluticasone proprionate 50/500 µg.

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