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ORIGINAL ARTICLE

Evaluation of Efficacy and Safety in between Inhaled Levosalbutamol and Inhaled Salbutamol along with Conventional therapy in Severe Asthma patients

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Abstract:

Background: *Levosalbutamol causes more bronchodilatation with less side effects as compared to salbutamol in asthma patients during acute relief of asthma symptoms, symptoms relieve during maintenance treatment of asthma and protection against exercise -induced asthma. Aims: To explore the efficacy and safety of Inhaled Levosalbutamol (group A) 300 µg/day (50µg 2 puffs thrice daily) compared with Inhaled Salbutamol (group B) 600µg/day (100µg 2 puffs thrice daily) along with Conventional therapy in case of treatment of severe asthma patients. Methods: This interventional study was carried out in the Department of Respiratory Medicine in NIDCH, Mohakhali, Dhaka, during November, 2016 to October, 2017. Severe (FEV1=<50 to 30% predicted) Asthma patients with agee"12years, both sexes, non smoker, who are not known case of COPD, Bronchiectasis, GERD were enrolled in this study. A total no. of 85 patients were included in this study. Among them 43 patients were treated with Levosalbutamol inhaler and 42 patients were treated with Salbutamol inhaler along with conventional therapy for severe Asthma. Results: In this study, in case of severe asthma, in group A (Levosalbutamol inhaler 300µg/day), FEV1 was increased from 38.84 ± 5.52 to 49.53 ± 7.63 (p<.001) and in group B (Salbutamol inhaler 600µg/day), FEV1 was increased from 37.22 ± 5.13 to 43.71 ± 6.79 (p<.001), which were highly significant but group A showed significant improvement than group B (p<0.05). In group A, FVC was increased from 52.61 ± 6.96 to 63.93 ± 8.33 (p<.001) and In group B, FVC was increased from 49.24 ± 6.52 to 57.28 ±7.87 (p<.001) which were highly significant but group A showed significant improvement than group B (p<0.05). In group A, Heart rate was increased from 78.56 ± 10.56 to 86.42 ± 9.21 (p<.001) and in group B, Heart rate was increased from 77.06 ± 9.46 to 93.71 ±8.18 (p<.001) which were highly significant but group B(Salbutamol) showed more tachycardia*

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than group A(Levosalbutamol) (p<0.05). In group A, Tremor was increased from 4.20 ± 1.56 to 5.73 ± 2.07 (p<.001) and in group B, Tremor was increased from 3.80 ± 1.48 to 7.65 ± 2.63 (p<.001) which were highly significant but group B(Salbutamol) showed more tremor than group A(Levosalbutamol) (p<0.05). In group A, Serum potassium level was decreased from 4.02 ± .42 to 3.79 ± .36 (p<.001) and in group B, Serum potassium level was decreased from 4.14 ± .51 to 3.38 ± .56 (p<.001) which were highly significant but group B(Salbutamol) showed more hypokalemia than group A (Levosalbutamol) (p<0.05). Conclusion: The present study concluded that Levosalbutamol inhaler appears to be more efficacious than Salbutamol inhaler in terms of improvement in lung functions (FEV1 and FVC) while adverse events like tachycardia, tremor and hypokalemia are seen less with Levosalbutamol inhaler than Salbutamol inhaler in case of severe asthma patients.

Keywords: Levosalbutamol, Salbutamol, FEV_1, FVC , Heart rate, Tremor, Serum potassium(S. K+).

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Introduction:

Asthma is a common and potentially serious chronic disease that imposes a substantial burden on patients, their families and the community. It causes respiratory symptoms, limitation of activity, and exacerbation that require urgent health care and may be fatal if not addressed properly. Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in occurence, frequency and intensity. These symptoms are associated with variable expiratory airflow,i.e. difficulty in breathing air out of the lungs due to bronchoconstriction, airway wall thickening, and increased mucus.[1] β_2-Agonists drugs are the most commonly used bronchodilators for the treatment of asthma to relieve bronchospasm.[2,3] Bronchodilation may be the result of β_2-receptor stimulation as induced by a β_2-receptor agonist. Salbutamol is the most widely used short-acting ^{2}2-agonist in the symptomatic relief of asthma.[4,5]

Racemic Salbutamol has been the mainstay of treatment for bronchial smooth muscle contraction since 1982. Salbutamol are racemic drugs containing both 'R' (Levo) and 'S' (Dextro) optical isomers. Only R-isomer fits into three-dimensional conformation of β_2-adrenoceptor Proteins.[4-6] So (R)- and RS- salbutamol have a 2:1 potency ratio for improvement in FEV1 in asthmatic patients and shows that (S)-salbutamol is clinically inactive or little active. Because the RS - salbutamol mixture contains only 50% (R)-salbutamol, it is clear that the clinical effect of salbutamol resides with the (R)-enantiomer. [7,8] Consequently, "Levosalbutamol" was approved by FDA (Food and Drug Administration) in 1999 as a purified single isomer for clinical use in asthma patients.[5] Moreover, (S)-salbutamol appears to be preferentially retained in the lungs in comparison with (R)–salbutamol.[4] So, that this slower metabolism increases the proportion of (S)–salbutamol than levosalbutamol in vivo and exposes the patient to relatively more potential adverse effects of (S)–salbutamol than levosalbutamol like hypokalemia, tremor, tachycardia.[6,8,9,10,11,12] So, the efficacy and safety of Levosalbutamol Inhaler is better than Salbutamol Inhaler in asthma patients.This study will be undertaken to test this hypothesis.

Materials & Methods:

This was a randomized Clinical Trial carried out in inpatient department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from November, 2016 to October, 2017 for one year. All patients over 12 years of both sexes suffering from asthma were taken as study population and those who fulfill the inclusion and exclusion criteria were recruited as study sample.

A total number of 96 patients were taken as study sample that means severe (FEV1=<50 to 30% predicted) asthma. A semi-structured questionnaire was followed by face to face interview on the basis of objective of study. Eligible patients were allocated randomly into

two groups. Of them 48 patients were in group A and 48 patients were in group B. Group A was treated with Levosalbutamol inhaler (300µg/day) 50 µg 2 puffs thrice daily and group B was treated with Salbutamol inhaler (600µg/day) 100 µg 2 puffs thrice daily for 4 weeks along with other with conventional therapy for asthma.

Each subject was evaluated with history and symptoms regarding the presentation. Patients age, occupation, working environment, smoking history, past medical history, current medications were asked. Patients were asked about the dyspnoea, wheezing, chest tightness, cough, sputum production, daytime symptoms, night time symptoms, triggering factor, activity level, associated diseases. They were examined and spirometry, in addition, to the other necessary baseline investigation (including CBC with ESR, Serum electrolytes, Chest X-ray P/A view, RBS, ECG, Sputum for AFB, Sputum for eosinophil count etc.) were done.

Baseline Lung function tests ($FEV_{1,}$ FVC), ECG (Heart rate), Tremor assessment, Serum potassium level (S. K+) were obtained before the day of discharge after cessation of the fol-lowing respiratory medications: oxygen therapy, nebulization and other injectable medications.These parameters were again done during follow up after 4 weeks. Tremor assessment was observed by TRG (Tremor research group) Essential Tremor Rating Assessment Scale (TETRAS) which was the performance measures of head, upper limb and lower limb tremor.

In group A ,1 patient did not come to follow up, 2 patient need Levosalbutamol inhaler more than thrice daily and 2 patient need less than thrice daily. In group B, 2 patient did not come to follow up, 2 patient need Salbutamol inhaler more than thrice daily and 2 patient need less than thrice daily.

Finally total 85 patients were included(43 patients in group A and 42 patients in group B). All the informations were properly documented in the prescribed forms. All interviewed questionnaire were checked for completeness, accuracy and consistency to exclude missing or inconsistent data. Data were checked, cleaned and edited properly. Quantitative data were expressed as mean and standard deviation and comparison done by paired and unpaired t-test. Qualitative data were expressed as frequency and percentage and comparison was carried by Chi-square ($Ç^2$) test. 95% confidence limit was taken. A probability value (p) of less than 0.05 was considered to indicate statistical significance. All patients/legal guardians were briefed about the study. Informed and written consent were taken from all study population.

Results:

Table-I

Distribution of patients according to Demographic profile (n= 85)

Parameters	Groups: Group A (n=43) (Levosalbutamol Inhaler)	Groups: Group B (n=42) (Salbutamol Inhaler)	p value*
Age	30 ± 8.50	29 ± 7.58	$>0.05^{NS}$
Sex (%)			
Male	21 (48.83)	20 (47.61)	$>0.05^{NS}$
Female	22 (51.17)	22 (52.39)	

— P-value reached from chi square test and student's t test. Age was expressed as mean ± SD (Years). Figure within parentheses indicates in percentage. NS: Not significant

Table-II

Mean ± SD of FEV1 by groups of severe asthma (n-85)

	Groups		
	Group A (n=43) (Levosalbutamol Inhaler)	Group B (n=42) (Salbutamol Inhaler)	p value*
Baseline	38.84 ± 5.52	37.22 ± 5.13	.333 NS
After 4 weeks	49.53 ± 7.63 (p<.001 S)	43.71 ± 6.79 (p<.001 S)	.013 S

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

Table-III

Mean ± SD of FVC by groups of severe asthma (n-85)

	Groups		
	Group A (n=43) (Levosalbutamol Inhaler)	Group B (n=42) (Salbutamol Inhaler)	p value*
Baseline	52.61 ± 6.96	49.24 ± 6.52	.172 NS
After 4 weeks	63.93 ± 8.33 (p<.001 S)	57.28 ±7.87 (p<.001 S)	.012 S

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

Table-IV

Mean ± SDof Heart rate by groups of severe asthma (n-85)

	Groups		
	Group A (n=43) (Levosalbutamol Inhaler)	Group B (n=42) (Salbutamol Inhaler)	p value*
Baseline	78.56 ± 10.56	77.06 ± 9.46	.633 NS
After 4 weeks	86.42 ± 9.21 (p<.001 S)	93.71 ±8.18 (p<.001 S)	.010 S

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

Table-V

Mean ± SD of Tremor by groups of severe asthma (n-85)

	Groups		
	Group A (n=43) (Levosalbutamol Inhaler)	Group B (n=42) (Salbutamol Inhaler)	p value*
Baseline	4.20 ± 1.56	3.80 ± 1.48	.411 NS
After 4 weeks	5.73 ± 2.07 (p<.001 S)	7.65 ± 2.63 (p<.001 S)	.013 S

NS: Not Significant,S: Significant; p value reached from both paired and unpaired t-test.

Table-VI

Mean ± SDof Serum potassium level (S. K+) by groups of severe asthma (n-85)

	Groups		
	Group A (n=43) (Levosalbutamol Inhaler)	Group B (n=42) (Salbutamol Inhaler)	p value*
Baseline	4.02 ± .42	4.14 ± .51	.395 NS
After 4 weeks	3.79 ± .36	3.38 ± .56	.020 S
	(p<.001 S)	(p<.001 S)	

NS: Not Significant,S: Significant; p value reached from both paired and unpaired t-test.

Discussion:

This prospective interventional study was carried out with an aim to explore the efficacy and safety of Inhaled Levosalbutamol compared with Inhaled Salbutamol along with Conventional therapy in case of treatment of severe asthma patients. The patients of either group were evaluated at base line and after 4 weeks. Lung function tests (FEV_1, FVC), Heart rate, Tremor assessment, Serum potassium level (S. K+) level were done at base line and during follow up after 4 weeks. Finally 43 patients in group A and 42 patients in group B were included.

In this study among 85 cases in both Levosalbutamol and salbutamol inhaler groups majority were at or below 35 years of age. Similar study was reported by Chen et al., 2003; Schatz et al., 2006 and mentioned that younger age group are the most prevalent in asthma attack. [13,14] The distribution of the study population according to sex was shown in this study. Females (51.76%) with asthma were a bit predominant than male (48.23%). Similar result was reported by Schatz et al., 2006 and added that female is more commonly affected by asthma than male. [14]

In this study, as shown in table II, base line FEV1 was not statistically significant in both groups (p>0.05). With therapy, after 4 weeks FEV1 were increased to 49.53 ± 7.63 (p<0.05) and 43.71 ± 6.79 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving FEV1 in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more FEV1 improvement than salbutamol Inhaler because the mean differences of improvement between two groups were statistically significant (p<0.05). Nowak et al., 2006; Milgrom et al., 2001 found similar results by some other studies. [9,11] But Rathore K et al., 2012 showed in a study that significant improvement of FEV1 occurred in case of Levosalbutamol Inhaler but improvement of FEV1 in case of salbutamol Inhaler was not statistically significant. [8]

As shown in table III, Base line FVC was not statistically significant in both groups (p>0.05).With therapy,after 4 weeks FVC were increased to 63.93 ± 8.33 (p<0.05) and 57.28 ±7.87 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively. This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving FVC in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more FVC improvement than salbutamol Inhaler because the mean differences of improvement between two groups were statistically significant (p<0.05). Rathore K et al., 2012 found similar results by some other studies. [8]

As shown in table IV, Base line Heart rate was not statistically significant in both groups (p>0.05). With therapy, after 4 weeks Heart rate were increased to 86.42 ± 9.21 (p<0.05) and 93.71 ±8.18 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving Heart rate in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more Heart rate improvement than salbutamol Inhaler because mean the differences of improvement between

two groups were statistically significant ($p<0.05$). This results were consistent with Punj et al., 2009; Lotvall et al., 2001. [6,7] But Rathore K et al., 2012 showed similar result but heart rate differences between two groups were not significant.[8]

As shown in table V, Base line Tremor was not statistically significant in both groups ($p>0.05$). With therapy, after 4 weeks Tremor was increased to 5.73 ± 2.07 ($p<0.05$) and 7.65 ± 2.63 ($p<0.05$) in Levosalbutamol and salbutamol inhaler group respectively. This differences between base line and after 4 weeks were statistically significant. So, both the drugs were responsible for Tremor in asthma patient. Again after 4 weeks it was found that salbutamol Inhaler causes more Tremor than Levosalbutamol Inhaler because the mean differences of increased Tremor between two groups were statistically significant ($p<0.05$). Cazzola et al., 2012 also reported occurrence of tremor in case of using both drugs. [12]

As shown in table VI, Base line Serum potassium level (S. K+) level was not statistically significant in both groups ($p>0.05$).With therapy, after 4 weeks Serum potassium level (S. K+) level were were decreased to $3.79 \pm .36$ ($p<0.05$) and $3.38 \pm .56$ ($p<0.05$) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So,both the drugs were responsible for decreasing Serum potassium level(S. K+) level in asthma patient. Again after 4 weeks it was found that salbutamol Inhaler decreases more Serum potassium level(S. K+) level than Levosalbutamol Inhaler because the mean differences of decreased Serum potassium level (S. K+) level between two groups were statistically significant ($p<0.05$). Similar results were observed by Milgrom et al., 2001; Lotvall et al., 2001; Punj et al., 2009; Rathore K et al., 2012. [6,7,8,11]

Conclusion:

There were significant improvements of FEV_1, FVC in Levosalbutamol inhaler while adverse events like tachycardia, tremor and hypokalemia are seen less with Levosalbutamol inhaler than Salbutamol inhaler in case of severe asthma patients. So treatment with Levosalbutamol inhaler is a better bronchodilator in terms of efficacy and safety than Salbutamol inhaler in patients with severe asthma along with Conventional therapy for symptomatic relief.

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Author Contribution: Dr. Md. Mahabubur Rahman had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Dr. Md. Mahabubur Rahman contributed to study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript and critical revisions of the article.

Prof. Dr. Md. Abdur Rouf, Prof. Dr. Bashir Ahmed, Prof. Dr. Liaquat Ali, Associate Prof. Dr. Bipul Kanti Biswas, Associate Prof. Dr. Mahmud Rahim, Dr. Shahjada Tabrez , Dr. Mohammed Kamrul Hasan contributed to concept and design of the study, interpretation of data, critical revisions and editing of the manuscript.

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