COMPARISON OF BRONCHODILATOR EFFECT OF SALBUTAMOL DELIVERED VIA MDI AND DPI IN COPD PATIENTS

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ABSTRACT

Introduction : Chronic Obstructive Pulmonary Disease (COPD) is one of the leading problems affecting majority of population all over the world which diminishes the quality of life of the individual and create extra burden to the society as well as country. Inhaled bronchodilator therapy is the mainstay of treatment in the management of COPD. Various inhaled [e.g. metered dose inhaler (MDI) /dry powder inhaler (DPI)] formulations are available and are widely used among the COPD patients in Nepal.

Methodology : This is cross sectional prospective study, designed to compare the bronchodilating effect produced when salbutamol is delivered via two devices: MDI (Asthalin® from Cipla) and DPI (Asthalin® rotacap delivered via Rotahaler® from Cipla), in patients with stable COPD. It is proven by previous studies that intervention is necessary to improve the compliance of the patients; all subjects (total n=60; 30 in each group) are counseled and trained to follow correct inhaling technique through particular device. Then their improvements in lung function were measured with reference to the pulmonary function test based on spirometry.

Results : Patients enrolled in each group were not statistically different regarding to age (P=0.318), weight (P=0.324) & BMI (P=0.836). Among the total subjects 87% had smoking history and 2% were still smoking and there was no significant difference in smoking habit between the two groups (p-value 0.544 > 0.05). Similarly 91.6 % of the total had exposure to indoor air pollution which had been the major risk factor for COPD. Most of the patients were on stage II COPD (62%). Salbutamol was found to have no effect on vital statistics of patients. Study showed there was no significant difference in the improvement of forced expiratory volume in one second (FEV1) (p=0.802), FVC (p= 0.693), FEV1 % (p=1) and PEF (p=0.448) between MDI and Rotahaler groups. Major side effect associated with the MDI users is headache (79%) while those among Rotahaler users were muscle cramps (79%). Even though intervention improved the inhaler using technique among the patients in both the groups, it was found even after counseling, DPI seemed to be better understood by the patients in comparison to MDI (p=0.003 & 0.00). In addition DPI was preferred by most of the patients who were familiar with both delivery systems. It was also found to be cheaper than the MDI.

Conclusion : Overall evidence suggests that although both MDI & DPI improve the lung function of COPD patients to similar extent, DPI is cheaper and more preferred and can be easily handled by the patients which can result in reduction of non-compliance.

Keyword : COPD. Salbutamol, DPI, MDI, Spirometry

INTRODUCTION

COPD stands for Chronic Obstructive Pulmonary Disease.[1] Chronic obstructive pulmonary disease is a lung ailment that is characterized by a persistent blockage of airflow from the lungs which is an under-diagnosed, life-threatening lung disease that interferes with normal breathing and is not fully reversible.[2] COPD is not one single disease but an umbrella term used to describe chronic lung diseases that cause limitations in lung airflow; the more familiar terms are 'chronic bronchitis' and 'emphysema'.[3]

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According to the latest WHO estimates (2007), currently 210 million people have COPD and 3 million people died of COPD in 2005. WHO predicts that COPD will become the third leading cause of death worldwide by 2030.[3]

In Nepal, a combination of asthma and bronchitis constitutes a major cause of mortality.[4] It is estimated that about 7500 people, most of whom are children, lose their lives each year in Nepal due to indoor air pollution (IAP) related Acute Lower Respiratory Infections (ALRI) and COPD.[5]

COPD can not be cured, but it can be controlled.[1] Prevention of disease progression, improvement of symptoms, exercise tolerance and health status and decrease in exacerbations and mortality are the goals of management.[6]

The inhaled route is preferred in the therapy of COPD as small doses of drugs are delivered direct to their site of action, leading to a rapid onset of action and a low incidence of side effects.[7] The airways are treated but less drug reach to the other parts of the body.[8] Inhaled medications are intended to exert localized, site-specific therapeutic effects on the bronchioles.[9] Thus inhaled bronchodilator therapy is the mainstay of treatment in the management of COPD. Inhaled short acting bronchodilator is recommended for symptoms in mild disease, whereas inhaled long acting bronchodilator is recommended for maintenance therapy of daily symptoms.[6]

The effectiveness of inhaled bronchodilator in individual patients is assessed by comparing measurements from pulmonary function tests made before and after administration of the drugs.[10,11] Generally, forced expiratory volume in one second (FEV1) is the marker used, in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[12,13]

Various inhaled formulations [metered dose inhaler (MDI) / dry powder inhaler (DPI) or Nebulizer] are available but it is the MDI, which is most commonly prescribed.[14] Although nebulizers are frequently used to deliver COPD treatment, particularly to less mobile patients, most current designs are bulky and inconvenient, and treatment times are longer. Therefore, they are better categorized as fallback devices for most COPD patients. They are not true competitors to pressurized metered-dose inhalers (pMDIs) and DPIs for outpatient use.[15]

There is no perfect inhaler, and each has advantages and disadvantages, but there is increasing recognition that a successful clinical outcome is determined as much by choice of an appropriate inhaler device as by the drugs that go in them.[16] Drug delivery from all inhaler devices depends on how the patient prepares the device and then inhales from it. The best device for COPD patients is arguably one for which both these steps can be performed successfully without major challenges.

There is evidence that a patient is most likely to use correctly an inhaler that he or she prefers.[17] Choice of an inhaler device should therefore take into account the likelihood that patients will be able to use a particular device correctly, cost-effectiveness, preference and likely compliance.

This is significantly important to compare the cost and benefit between MDI and DPI for patient with COPD to achieve the definite therapeutic outcome. Hence the study is mostly focused on to analyze the device preference of the patients and their capability of producing improvement in pulmonary function.

METHODS

Study Design

This was cross sectional prospective study.

Study Site and duration

The study was conducted in Dhulikhel Hospital, Kathmandu University Teaching Hospital, Dhulikhel from Dec 2007 to June 2008.

Sample selection criteria

Patients from out patient department as well as from in patient department who had age above 15 years with the documented diagnosis of COPD and prescribed with salbutamol inhaler (200 µg dose) were included in the sample. However patients with following criteria were excluded in the sample.

- Unstable angina
- Recent pneumothorax
- Recent heart attack or stroke
- Recent eye or abdominal surgery
- Coughed up blood recently and the cause is notknown
- Patient prescribed with corticosteroids

Sample size

Sixty (n=60) consecutive patients who fulfilled the inclusion criteria were included in the study. All patients were then further divided into MDI and DPI groups (thirty in each group) according to the type of salbutamol inhaler they were prescribed with as well as on their own preference if they were familiar with both inhalers.

Each patient of MDI group (n=30) received 200 µg (two puffs in one minute interval) salbutamol four times a day via a MDI (ASTHALIN CFC free inhaler, Manufactured by CIPLA, Ltd. INDIA containing 200 Metered dose and each puff containing 100 µg of Salbutamol) as per MDI score technique .While patients of DPI group (n=30) received 200 µg of salbutamol via Rotahaler (ASTHALIN Rotacap, Manufactured by CIPLA, Ltd. INDIA; each Rotacap containing 200 µg of Salbutamol for use with Rotahaler) four times a day as per DPI scores technique.

Data Collection

At first, patients who met the inclusion criterias, were told about the study being done and about their contribution in this study. After taking informed consent from the patients, they were directly interviewed using structured questionnaire. The key data information included age, sex, literacy, occupation, races, smoking/ alcohol habit and exposure to any air outdoor or indoor air pollution. Additional information about date of diagnosis of COPD, drug treatment for COPD and other concomitant diseases and abnormal clinical findings were recorded from medical case record.

Patients were counseled about how to use the inhaler they were prescribed with, for those who were using inhaler for the first time. For those who were already using inhaler, knowledge about using technique of particular inhaler (MDI or DPI) was checked. If they did wrong they were counseled and demonstrated (using device without active ingredient) how to use it correctly. The improvement in inhaler using technique was evaluated by scoring each correct step using Rotahaler/ Meter Dose Inhaler Technique Score Chart just after counseling and also on follow up.

After counseling, spirometric test was performed in each patient by using the spirometer (Vitalograph) to find out the baseline lung functions. If the patient was already using the salbutamol inhaler, after consultation with the physician, the patient was made to escape the dose of the medicines 6 hrs before the spirometry evaluation to get the baseline results.

During the spirometric test each patient was asked to take the deepest breath he/she could, and then to exhale into the sensor as forcefully as possible and for as long as possible. During the test, soft nose clip was used to prevent air escaping through the nose. The present lung functions of the patients were displayed in terms of FVC (Forced Vital Capacity) (Liters), FEV1 (Liters) and PEF (Liters/ second). Standard values for each patient differ according to their height, age, sex, and sometimes race and weight. After the baseline evaluation, the usual dose i.e. 200 µg of salbutamol was given to the patients at the same time his/her inhalation technique was also checked and then spirometric analysis was repeated as follow up to find out the improvement in lung function.

The blood pressure (BP), respiration rate (RR), pulse rate (PR) and potassium level were also assessed before and after the use of bronchodilator to find out if there was any change. The spirometric test, vital statistics (BP, RR, PR), potassium level, understanding of inhalation technique, health problems they faced during therapy were again investigated in follow up visit after two weeks (usually 14-20 days) of each patients of both groups.

Data analysis

The data collected by using structured questionnaire and reviewing medical record forms were entered into a computer file and were expressed into codes for the purpose of analysis. The data with qualitative variables were summarized and expressed as frequency and percentage. The data with quantitative variables were expressed as mean and standard deviation (SD) and were analyzed by using statistical tests.

Patient's age, weight, height and BMI were compared using Mann-Whitney U test. Change in Vital Statistics (BP, RR, PR), potassium level and improvement in lung function parameters (FVC, FEV1, FEV1%, PEF) after using salbutamol via particular inhaler (MDI or DPI) were analyzed by Wilcoxon Signed Ranks Test. While comparison of same variables including oxygen saturation between two different groups was carried out by using Mann-Whitney U test. MDI and DPI scores were compared for the values before counseling, after 30 min of bronchodilator and after two weeks of starting bronchodilator by using Mann-Whitney U

test. All data were analyzed at the 5% significance level. The data were significant for p<0.05. All analysis was done by using statistical software SPSS 15 and graphs were plotted in Excel 2003 and 2007.

RESULTS

Table 1: Demographic Characteristics

Variables	Characteristics	MDI (n=30)	DPI (n=30)	p-value
Age, years (Mean ± SD)		61.20 ± 13.52	59.00 ± 11.03	0.318
Age group, years	<40	1	1	
	40-49	3	4	
	50-59	9	10	
	60-69	6	9	
	70-79	10	5	
	>=80	1	1	
Gender	Female	28	23	
	Male	2	7	
Ethnic Group	Magar	5	4	
	Newar	8	11	
	Chettri	6	3	
	Brahmin	8	9	
	Others+	3	3	
Education	Literate	2	6	
	Illiterate	28	24	
Employment	Farmer	17	22	
	Housewife	11	6	
	Service	1	0	
	Shopkeeper	0	1	
	Other++	1	1	

Others+: Rokka, Giri, Pariyar, Lohala, Shanker, Thokar; Other++: Masson, Student

Table 2: Anthropometric Measurements

Variables	MDI (n=30)	DPI (n=30)	P-value
Weight (Kg)	44.83 ± 9.27	46.57 ± 7.22	0.324
Height (cm)	148.77 ± 6.17	152.6 ± 7.11	0.049
BMI status (kg/ m^2)	20.27 ± 3.97	19.77 ± 2.81	0.836
Under weight (BMI <18.5)	11	10	
Normal weight(BMI 18.5-24.9)	16	18	
Overweight(BMI 25-29.9)	1	2	
Obese(BMI ≥ 30)	2	0	

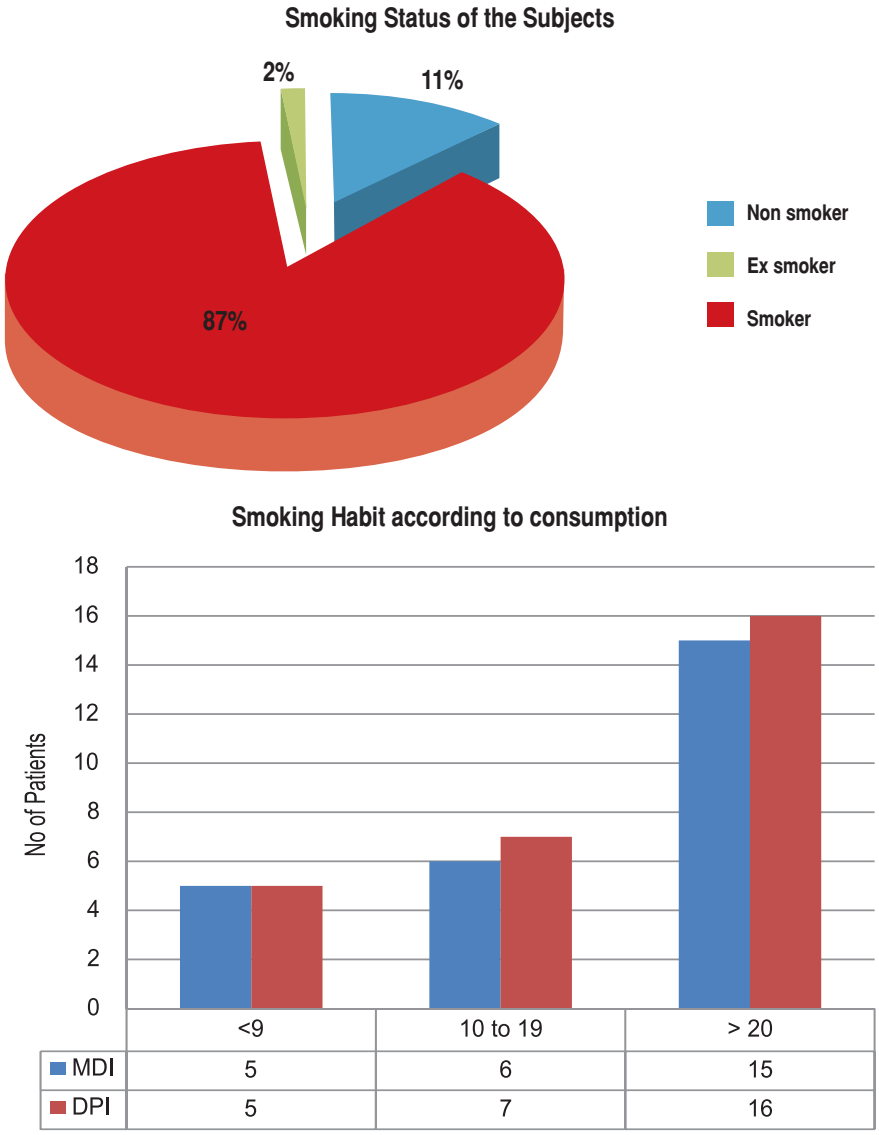

Figure 1: Smoking habit

Study of vital statistics of the participants

Table 3: Comparison of vital statistics and oxygen saturation of the participants between two groups i.e. MDI & DPI (Mann-Whitney U)

Measures	MDI - P-values	DPI - P-values
Δ SBP (after 30 mins) from baseline	0.227	0.414
Δ SBP (after two weeks) from baseline	0.068	0.157
Δ DBP (after 30 mins) from baseline	0.234	0.107
Δ DBP (after two weeks) from baseline	0.36	0.19
Δ RR (after 30 mins) from baseline	0.395	0.011
Δ RR (after two weeks) from baseline	0.011	0.039
Change in mean value of PR	MDI	DPI

Before medication	89.2 ± 14.97	86.23 ± 12.86
After 30 mins	87.87 ± 14.19	85.57 ± 0.58
After two weeks	83.2 ± 8.67	82.6 ± 8.39

Δ = change from baseline after bronchodilator therapy, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, RR = Respiration rate, PR = Pulse rate

Table 4: Spiro-metric analysis

4.1 Analysis of bronchodilating effect of salbutamol within each group (Wilcoxon Rank Test)		
	MDI	DPI
STD FVC	2.14 ± 0.51	2.56 ± 0.52
Baseline FVC	0.92 ± 0.72	0.96 ± 0.47
FVC after 30 mins of bronchodilator	1.16 ± .80	1.18 ± 0.52
FVC after 2 weeks of bronchodilator	1.23 ± 0.65	1.26 ± 0.45
p- value (FVC after30-FVC baseline)	0	0
p- value (FVC after two weeks-FVC baseline)	0	0
Std FEV1	1.78 ± 0.48	2.12 ± 0.4
Baseline FEV1	0.75 ± 0.67	0.75 ± 0.42
FEV1after 30 mins of bronchodilator	0.91± 0.73	0.88 ± 0.41
FEV1after two weeks of bronchodilator	0.95 ± 0.52	0.97 ± 0.40
p- value (FEV1 after30-FEV1 Baseline)	0	0.002
p- value (FEV1 after two weeks-FEV1 Baseline)	0	0
Std PEF	318.93 ± 42.97	349.97± 45.05
Baseline PEF	117.63 ± 96.65	110 ± 76.33
PEF after 30 mins of bronchodilator	121.63 ± 94.65	116.86± 64.11
PEF after 2 weeks of bronchodilator	134.4 ± 82.61	137.35 ± 84.66
p- value (PEF after 30-PEF baseline)	0.066	0.182
p- value (PEF after two weeks-PEF baseline)	0.016	0

Standard values are based on individuals' age, height and gender and automatically displayed by spirometer.

4.2 Comparison of improvement between two groups (Mann Whitney U Test)			
Measures	MDI Group	DPI Group	p-Value
FEV1			
Baseline	0.75 ± 0.67	0.75 ± 0.42	0.268
Improvement after 30 Mins	0.16 ± 0.18	0.13 ± 0.2	0.295
Improvement after 2 weeks	0.21 ± 0.28	0.22 ± 0.24	0.802
FVC			
Baseline	0.92 ± 0.72	0.96 ± 0.47	0.15

Improvement after 30 Mins	0.24 ± 0.21	0.21 ± 0.23	0.705
Improvement after 2 weeks	0.31 ± 0.21	0.30 ± 0.25	0.693
PEF			
Baseline	117.63 ± 96.6	110 ± 76.33	0.988
Improvement after 30 Mins	4 ± 45.3	6.86 ± 28.4	0.802
Improvement after 2 weeks	16.77 ± 41.8	27.34 ± 33.9	0.448

Improvement after 30 mins = Post- bronchodilator values after 30 mins- Baseline values

Improvement after two weeks = Post- bronchodilator values after two weeks - Baseline values

Inhaler using Technique Score

Table 5: Understanding of the patients how to use the particular inhaler

Measures	MDI Group	DPI Group	p- Value
Placebo Score	4.97 ± 2.10	4.87 ± 1.46	0.478
Score after counseling	8.6 ± 0.81	9.23 ± 0.68	0.003
Score in follow up	8.4 ± 0.67	9.47 ± 0.57	0

Table 6 : Side effects associated with a particular device

Measures	MDI (4)	DPI (7)
K-level	3.33 ± 0.09	3.24 ± 0.17
P- value	0.001	0.004

Table 7: Cost comparison of MDI and DPI

	MDI	DPI
Unit price per item (Nepali Rupees)	148.00	27.00
Cost of device	-	119.00
No of administration per package	100	30
Unit cost per administration	1.48	0.9
Cost of device per dose *		0.02
Total cost per administration	1.48	0.92

*Assuming Rotahaler device will last for 5 years.

DISCUSSION

Among the total Newars made up the highest population (32%) followed by Brahmin (28%). It was found that most of the patients were illiterate in both group, only about 7% in MDI and 20% in DPI were literate. Farmer constitutes the more than half of the population (57%) followed by housewife (37%).

The mean age of COPD patients was 61.20±13.52 for MDI and 59.00±11.03 for DPI group respectively. Both MDI and DPI users included in study have similar age as there is no significant difference (p-value 0.318> 0.05; Mann-Whitney U test).

While analyzing among total no of Patients, most of the patients were having normal weight (57%), while some of them (35%) were categorized under underweight group as their BMI was <18.5 which is the prognostic factor for mortality.

Blood pressure, pulse rate, respiration rate and oxygen saturation were checked and analyzed in all patients before and after the use of bronchodilator within and between two groups. Baseline vital signs of both groups were similar (p-value>0.05). There was no significant difference in baseline BP, PR and RR of the patients between two groups. After bronchodilator use, subjects in both groups showed similar BP, PR and RR. No significant difference between the devices was found in terms of vitals (P > 0.05; Mann Whitney Test).

Both delivery systems i.e. MDI and DPI were found equally capable to produce bronchodilating effect of Salbutamol. All parameters FEV1, FVC and FEV1% were significantly improved from baseline as the mean difference of these values between pre and post bronchodilator (after 30 minutes as well as after two weeks) were found significant, (P-values < 0.05, Wilcoxon rank test; table 5.1).

There were no significant differences between two groups in terms of improvement in FEV1, FVC and PEF level (P > 0.05) after bronchodilator therapy. It proved there is the therapeutic equivalence between two delivery systems i.e. MDI and DPI at 200 µg dose of Salbutamol (table 5.2).

Even though about 87% (52 out of 60) were already using the device to deliver the medicine their knowledge about the correct using technique seemed very low; 4.97 ± 2.10 (MDI) & 4.87 ± 1.46 (Rotahaler) when analyzed in Placebo. Most of them were given wrong instruction about the technique from medical shops outside the hospital (e.g. in some cases of Rotahaler, they were instructed to break the capsule by themselves and then poured into the Rotahaler for inhalation) and others who get correct instruction were also making many crucial mistakes. For example in case of MDI, not holding the device in upright position & not closing the mouth properly so that fumes were seemed escaping from mouth were observed in most of the patients. In both groups (MDI as well as Rotahaler) exhalation before inhalation & holding the breath after inhaling the medicine were missing. Studies also showed that many patients fail to hold inhaled medication in their lungs for the full 10 seconds, this final step in the inhaler technique is required for optimal pulmonary absorption of medication, regardless of type of device used.

Drug cost of unit dosage form for DPI was found to be lesser than that of MDI. The socioeconomic status of Nepalese people is low; particularly in the study area (Dhulikhel). The cost analysis would be helpful in recommending the affordable one between two therapeutically equivalent delivery systems. In this case, Rotahaler a simplest DPI was found to be therapeutically equivalent to MDI and is the cheaper one.

CONCLUSION AND RECOMMENDATION

The bronchodilator response was found to be similar irrespective of drug delivery system.[17] It is possible that the DPI deposited the same amount of drug at the site of action as the MDI in patients with COPD. Intervention on inhaler technique improved the patient knowledge which is very crucial to achieve the definite therapeutic outcome. Though all patients showed similar skill at the initial stage (p=0.478), the final score of inhalation technique was significantly improved in case of DPI (p=0.003; 8.6 ± 0.81 for MDI Vs 9.23 ± 0.68 for DPI). Patients using Salbutamol are prone to suffer from hypokalemia in both patterns of delivery (for MDI 3.33 ± 0.09 mol/l; p-value=0.001 and for DPI 3.24 ± 0.17 mol/l; p-value=0.004).

The cost of treatment with DPI is found to be much lesser than that of MDI. Overall evidences from efficacy and cost analysis it seems that treatment of COPD patients with bronchodilator using DPI is more preferable than MDI even though both have similar clinical efficacy.

RECOMMENDATIONS FOR PRACTICE INCLUDE:

- Intervention is essential to improve inhalation technique.
- Nutrition intervention is essential as most of the patients are with BMI <21 kg/m^2 which is the major cause of morbidity.
- Potassium level should be checked in routine intervals there is a chance of hypokalemia.
- Even though both delivery systems have therapeutic equivalence, patient's choice should be given the first preference to improve the compliance.
- As the previous study as well as this study suggests therapeutic efficacy is dose dependent rather than device further research should be conducted at different doses with wide range at large population from two delivery systems.

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