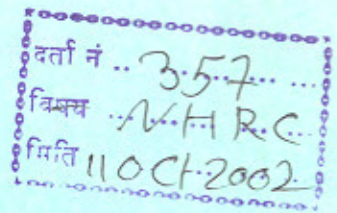


Kathmandu University
School of Science
Department of Pharmacy
Dhulikhel, Nepal



**"An open, prospective comparison of
Beta-2 agonist (Salbutamol) given via
Nebulizer or Metered dose inhaler
In
Inpatients with airflow obstruction"**



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MPharm III semester

In Partial fulfillment of requirement

For

Master of Pharmacy Degree in Pharmaceutical care

2002



ACKNOWLEDGEMENT

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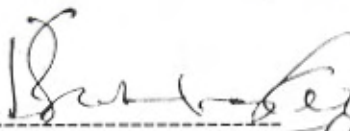
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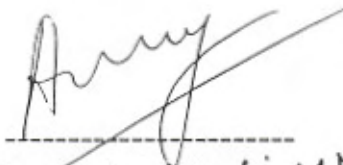
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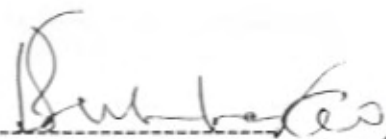
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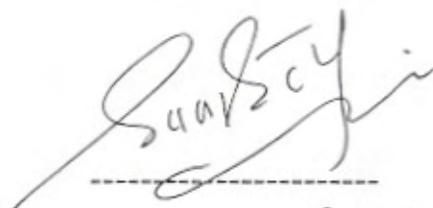
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ABSTRACT

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Asthma and chronic obstructive pulmonary disease (COPD) are growing problems in developing countries including in Nepal. Many patients suffering from obstructive lung diseases are of poor economical status, mostly illiterate. Therefore has a direct bearing on patient compliance.

Inhalation is preferred route of β -agonist administration for treating airflow obstruction. Researches have shown therapeutic equivalence between MDI and Nebulizer. In addition, the MDI is more practical, portable, less costly and associated with a lower risk of infection.

This research was designed to compare bronchodilatory effect of two dosage forms (nebulizers and MDI) in inpatients with airflow obstruction. The therapeutic equivalence, improvement in MDI technique and cost difference was the outcome measurements of this study. And it was hypothesized that there would be no difference between these two groups in their outcome variables. Patients diagnosed clinically as COPD and admitted during 28th December 2001 to 20th march, 2002 in Dhulikhel hospital were selected for the study. They were randomized in to two groups.

There were significant improvements in lung function measured after bronchodilator therapy than that of baseline values ($p=0.00$). Percentage improvement of lung function parameters was found for MDI (%PEF 23.93, %FVC 13.63 and %FEV₁ 18.29) and for Nebulizer (%PEF 20.97, %FVC 18.51 and %FEV₁ 22.07). Overall there were no significant differences in improvement of lung function parameters between these two groups.

The regular use of metered dose inhaler during hospitalization improved patient's MDI use technique. Though there was no significant difference in baseline placebo score ($P=0.6073$), the final score of MDI technique has significant improvement ($P=0.0017$) (8.64 ± 1.64 for MDI versus 5.2 ± 1.7 for NEB).

The cost of treatment for MDI in rupees during hospitalization has been found to be much less than that of nebulizer (Rs 285.48 versus Rs 443.45) by decreasing length of hospital stay (4.5 ± 2.5 days versus 5.2 ± 1.7 days).

Overall evidences argues against any clinically important potency difference between MDI or nebulizer, the further long term study including large population will be beneficial for evaluating clinical and pharmacoeconomic equivalence along with patient's life quality.

LIST OF ABBREVIATIONS

AIDS	Acquired Immuno Deficiency Syndrome
ATS	American Thoracic Society
BTS	British Thoracic Society
CBA	Cost benefit analysis
CMA	Cost minimization analysis
COPD	Chronic obstructive pulmonary disease
Dr.	Doctor
e.g.	Example
ERS	European Respiratory Society
et al	and colleagues
FEV _{0.75}	Forced expiratory volume 75% of FVC
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HIV	Human Immuno virus
KU	Kathmandu University
L/min	Liter per minute
L	Liter
Ltd	Limited
LTOT	Long term oxygen therapy
MBBS	Bachelor of Medicine bachelor of surgery
MD	Doctor of Medicine
mg	Milligram
ml	Milliliter
MMAD	Mass medium aerodynamic diameter
mmHg	Millimeter of mercury
n	Number
NEB	Nebulizers
No	Number
OPD	Outpatients department
P	P-Value
PEF	Peak expiratory flow
Q	Question.
S	supplement
S	Second
SD	Standard deviation
Suppl	Supplement
UK	United Kingdom
WHO	World Health Organization
µg	Micro gram
µm	Micrometer

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CHAPTER 1: INTRODUCTION

1.1 BACKGROUNDS

Respiratory diseases are threatening problems worldwide. Respiratory diseases kill 2.6 million people every year around the world ^(1,2). In UK, diseases of the respiratory system are the causes of one in four deaths and in 1992 there were 26033 deaths in England and Wales attributed to COPD, chronic bronchitis and emphysema, that accounted for 6.4% of males and 3.9% of females deaths ⁽¹⁾. Similarly in the United States, morbidity caused by COPD is 4% ⁽³⁾. Internationally, there is substantial variation in death rates possibly reflecting smoking behavior, type and processing of tobacco, pollution, climate, respiratory management and genetic factor ⁽³⁾. In developing nations a 4-6% burden of ARI and COPD (mortality and morbidity) is attributed to use of solid fuels in adult women and young children, who jointly receive the highest exposures because of their household roles ⁽⁴⁾. Even in Nepal, in female nonsmokers and smokers and past smokers, chronic bronchitis was significantly associated with increasing exposure to domestic smoke ⁽⁵⁾.

Table 1.1: Annual health service workload due to chronic respiratory disease in an average UK health district.

Chronic respiratory diseases	Hospital admissions	Inpatients bed days	General practice consultations
Chronic bronchitis, emphysema and COPD	680	9600	14200
Asthma	410	1800	11900

Source: BTS ⁽⁶⁾

Asthma and COPD (Chronic obstructive pulmonary disease) are two main causes of deaths due to respiratory diseases. These have lifelong disabling consequences and are growing problems in developing countries. In Nepal – A high prevalence of COPD is reported and many patients suffering from this are of poor economical status, mostly illiterate ^(2,5). There is also less facilities and manpower in our health sectors.

It is found that, patients of developing nations like Nepal are not treated properly due to lack of various drugs or due to low economical status ⁽⁷⁾. It is also seen that health-care sectors do not provide long-term supportive care services for severely disabled individuals in most of the developing nations, COPD may force the patient and care taker to leave the workplace ⁽⁸⁾. Thus selection of method of treatment and cost reduction is very important for short term and long-term treatment.

Table 1.2: Five leading causes of mortality estimated for 1999.
(Mortality in all members states)

Disease	Rank	% Total	(000)
Ischemic heart disease*	1	12.7	7089
Cerebrovascular disease*	2	9.9	5544
Acute lower respiratory infections	3	7.1	3963
HIV/ AIDS	4	4.8	2673
Chronic obstructive pulmonary disease*	5	4.8	2660

* Non-communicable diseases.

Source: WHO ⁽²⁾.

β - agonist, which is main drug for treating airflow obstruction, may be administered orally, subcutaneously, intravenously or via inhalation. However, inhalation is the preferred route since aerosolized agents have more rapid onset of action along with reduced systemic side effect as compared with oral route ^(6,9). Drugs for inhalation may be delivered by a variety of devices including the wet nebulizer, dry powder devices and the pressurized metered dose inhaler (MDI) with or without a large volume

spacer. Of these, the MDI tends to be prescribed for outpatients, whereas nebulizers have traditionally been recommended to be used in hospital for treating patients with acute exacerbation requiring hospital visit and/or hospitalization ^(10,11). However, studies have demonstrated therapeutic equivalence between the two forms of delivery ⁽⁹⁻¹⁵⁾. In addition, the MDI is more practical, portable, less costly and associated with a lower risk of infection ^(16,17,18). In view of such findings, the current widespread use of nebulizer is questionable. Hence this study, to compare the cost and benefit between nebulizer and MDI use, for patients with COPD, in hospital setting is important.

1.2 Research objectives

1. To evaluate the prescribing pattern of salbutamol by the physicians for treating patients with airflow obstruction.
2. To estimate the overall improvement in peak expiratory flow (PEF), forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) of the patients using two different methods of delivery.
3. To estimate the pharmacoeconomics by considering total direct cost of treatment.
4. To evaluate possible improvement in patient's use of MDI, at the time of discharge after being hospitalized.

1.3 Research hypothesis

There will be no difference in lung function parameters, cost of treatment and MDI use technique among patients hospitalized for COPD exacerbation receiving β_2 agonist (Salbutamol) via MDI or Nebulizer method.

CHAPTER 2: LITERATURE REVIEW

2.1 COPD management and Bronchodilator Therapy

Chronic obstructive pulmonary disease is characterized by airflow limitation and is associated with history of smoking. According to the British thoracic guidelines ⁽⁶⁾, COPD can be diagnosed by assessing the physical parameters like dyspnea, wheeze, sputum volume, and chest tightness, and with history of smoking (>20 pack years). General classification, diagnosis and management of COPD are shown in table 2.1.

Despite the lack of significant reversibility, patients often report symptomatic improvement with short acting β_2 agonists. These agents are widely used and are recommended for use in management guidelines for COPD (American Thoracic Society; ATS, European Respiratory Society; ERS, British Thoracic Society; BTS). They are used both on an "as required" or "regular plus as required basis" and also in conjunction with other bronchodilators such as ipratropium and methylxanthines. Short-acting β_2 bronchodilators are used in both the chronic stable management of COPD and in acute exacerbations. Short-acting β_2 agonist can be delivered in several ways, e.g. by metered dose inhalers, dry powder inhalers, nebulizers or by tablets.

Bronchodilators are the cornerstone of symptomatic treatment for the reversible component of airway obstruction. They probably act by reducing bronchomotor tone and hence airway resistance in patients with COPD and reducing the level of pulmonary over inflation. Inhaled agents given in small doses are as efficacious as oral preparations, having fewer side effects and therefore the preferred ones (6,9,18).

Table 2.1 Classification, diagnosis and management of COPD*

Types	Clinical state	Results of measurements	Use of health care resources
Mild	Smoker's cough, but little or no breathlessness. No abnormal signs.	FEV ₁ 60-79% predicted, FEV ₁ /FVC and other indices of expiratory flow mildly reduced.	Unknown-presymptomatic within the community.
Moderate	Breathlessness (+/- wheeze) on exertion, cough (+/- sputum) and abnormal signs.	FEV ₁ 40-59% predicted, often with increased FRC and reduced TLCO. Some patients are hypoxaemic but not hypercapnic.	Known to GP with intermittent complains.
Severe	Breathlessness on any exertion. Wheeze, cough prominent. Clinical overinflation usual, plus cyanosis, peripheral edema and polycythaemia in some.	FEV ₁ <40% predicted with marked overinflation. TLCO variable but often low. Hypoxemic usual and hypercapnia in some.	Likely to be known to hospital and by GP, with frequent problems and hospital admissions.

* Source: BTS Guidelines ⁽⁶⁾

2.1.1 Selection of dosage forms

For domiciliary purpose nebulizer is recommended but it may be costlier than MDI ⁽¹⁹⁾. The major disadvantage of the MDI is the lack of proper technique of using it ⁽²⁰⁾. The study carried out for evaluating the prescribing habit of physicians also proved that the patients do not know the ideal technique of using MDI ⁽²¹⁾. Many patients with COPD perceive nebulization as the most effective delivery method for inhaled bronchodilators when their disease is symptomatic. This may be

related to the routine use of nebulizers in many hospitals worldwide for the delivery of bronchodilators in COPD exacerbation ⁽²²⁾. The easy availability of compressed air and oxygen in hospitals means that it is cheap to use nebulized beta-agonists to provide patients attending casualty. This advantage, however, rapidly disappears when patients are treated in the community, since the cost of a compressor and the drugs used in nebulized form is higher than treatment with an MDI and spacer ⁽²²⁾. The clinical role and necessity of nebulized therapy in the chronic domiciliary setting needs to be established and few treatment guidelines already addressed the issue.

2.1.2 Nebulization therapy

Nebulizers are widely used throughout the world in adults and pediatric medical practice, both for emergency and acute treatment, and for domiciliary long term treatment for a variety of respiratory diseases, most commonly airflow obstruction ⁽¹⁶⁾. In 1994 the standards of Care Committee of the British Thoracic Society initiated to review Nebulizer treatment in all its aspects and published a set of guidelines for Nebulizer treatment ⁽¹⁷⁾. According to the guidelines:

2.1.2.1 Aim of Nebulization

The aim of Nebulizer therapy is to deliver a therapeutic dose of desired drug in the form of irrespirable particles within a fairly short period of time, usually 5-10 minutes ⁽¹⁷⁾. The general indications for Nebulizer use are as in table 2.2.

TABLE 2.2: GENERAL INDICATIONS FOR TREATMENT WITH NEBULIZERS

Absolute Indications:

1. Too sick or incapable of managing hand held inhalers.
2. Drug not available in hand held inhalers.
3. Need to target treatment to particular generations of bronchi or the alveoli.

Relative Indications:

1. Need for a large drug dose.
2. Patients' preference.
3. Practical convenience.

Source: Muers MF⁽¹⁶⁾.

2.1.2.2 Types of Nebulizers

1. *Jet nebulizer*: it consists of a nebulizing chamber in which an aerosol is generated with a flow of gas provided either by an electrical compressor or compressed gas (air or oxygen).
2. *Ultrasonic nebulizers*: They are self-contained electrical devices in which an aerosol is generated by vibrating fluid placed within them. They can nebulize larger volumes of fluid and are quiet.

2.1.2.3 Factors affecting drug output⁽²³⁾

Driving gas flow rate: most jet nebulizers are now designed to work at a flow rate of 6-10 L/min. The flow required would depend upon the nebulizer design, the dimension of the connecting tubing and, to lesser extent, the drug used.

Nebulizer chamber design: Increasing the fraction of droplets intercepted by the internal baffles in a standard jet nebulizer will decrease particles size but increase nebulization time.

Residual volume: this is the volume of liquid remaining in the nebulizer reservoir when nebulization has ceased. It will affect the drug output from a given fill volume. If the residual volume is less than 1.0ml, a fill volume of 2.0-2.5ml may be adequate; nebulizers with residual volumes of more than 1.0ml generally require fill volumes of about 4ml.

Fill volumes: Nebulizer chambers have different fill volume and it must be known to fill maximum volume of drug.

Physical properties of drug solution or suspension: Simple drug solutions, such as commonly used bronchodilators, have a similar nebulizer volume output and particle size distribution to that of 0.9% sodium chloride; the volume output of drug preparations with a higher viscosity or a different surface tension will differ.

Breathing pattern of the patient: this may have a profound effect on the mass of drug delivered to the lungs. It is a particularly important consideration in infants or young children. Steady normal breathing interspersed with occasional deep breaths is likely to be optimal.

Table 2.3 Factors affecting output of drug solutions from jet nebulizers

<i>Factor</i>	<i>Positive effect</i>	<i>Negative effect</i>
Increase driving gas compressor flow /compressor rating	Smaller particle size, shorter nebulization time	More expensive
Increases fill volume	Greater proportion of drug nebulized	longer nebulization time
Decrease residual Volume.	Greater proportion of Drug nebulized	longer nebulization time
Increase baffles	smaller particle size	Longer nebulization time
Decrease solution Viscosity (e.g. warm solution).	smaller particle size	Minor effect
Use an "open vent" Nebuliser.	Shorter nebulization time	Nebuliser cost
Use nebulizer with manual interrupter/ assisted "open vent"	No drug wasted in expiration. Increased dose to patient	Coordination required. Longer treatment time
Use "breath assisted open vent" nebuliser.	Greater (twice or more) drug delivery to patient.	Effectiveness has only been shown in adults using bronchodilator solutions.

Source: O' Callghan C⁽²³⁾.

2.1.2.4 Nebulizer for COPD

The use of nebulized bronchodilators for COPD should be consistent with the British Thoracic Society guidelines for the management of COPD (1997) and with the European Respiratory Society (1995) and the American Thoracic Society (1995). For the acute exacerbation of COPD following recommendations are given by thoracic society guidelines:

- Nebulized bronchodilators are indicated for acute exacerbation of COPD if treatment with hand held inhaler is insufficient. Beta agonist and anticholinergics may be used and combination should be considered in more severe cases, especially if the patient has had poor response to either type of drug alone.
- For mild exacerbation hand held inhaler (MDI) should be used by giving 200-400µg salbutamol or 500 - 1000µg terbutaline.
- In more severe cases nebulized salbutamol (2.5- 5mg) or terbutaline (5- 10mg) or ipratropium bromide (500µg) should be given 4- 6 hourly for 24 – 48 hours or until the patient is improving clinically.
- Combined nebulized treatment (2.5-10mg of β_2 agonist with 250-500µg ipratropium bromide) should be considered for more severe cases, especially if patient has had poor response to either treatment given alone.
- If the patient is very ill and requires hospital admission, arterial blood gas tension should always be measured to avoid carbon dioxide retention. In general practice nebulization should be given with compressed air.
- Nebulizer bronchodilator treatment should be changed to treatment with hand held inhaler and patients should be observed for 24- 48 hours before discharge from hospital.

- Patients should be advised to use nebulized bronchodilator treatment as needed, up to four times per day. (In practice, most patients choose four times daily treatment)

2.1.2.5 Nebulization in elderly

Patients aged over 65 years nebulizers are mostly used to deliver high dose bronchodilator medication in those with severe COPD or asthma^(10,16). They will also be needed for patients with milder disease who are unable to use hand held inhalers. Relatively high proportion of elderly patients may not be able to use metered dose inhalers satisfactorily due to impaired cognitive function or memory loss, weak fingers, and poor coordination⁽²⁴⁾. Beta agonists are likely to cause tremor in the elderly. So, high dose should be avoided unless necessary.

2.2 Spirometric evaluation

According to the guidelines of British Thoracic Society and American Thoracic society, spirometric evaluation is an important parameter for diagnosing and monitoring the COPD patients. We can determine the peak expiratory flow, forced vital capacity and forced expiratory volume in one second by using spirometer. The main variable recommended for the spirometric evaluation of COPD patients is forced expiratory volume in one second (FEV₁)^(7,25,26,28). Reduction on this spirometric indicator primarily reflect obstruction in the larger and medium sized airways, and may be poor indicators of small airway dysfunction which has been proposed as an early stage in the natural history of COPD^(7,26,28). Similarly, a change in FEV₁ that is both a >15% increase and more than 200ml over pre-bronchodilator levels indicates some reversibility but COPD patients with small changes are still likely to benefit from bronchodilator therapy symptomatically⁽²⁸⁾. Summarized criteria for identifying bronchodilator responses with the help of spirometry, are given in table 2.4 along with references.

Table 2.4: Criteria for identifying bronchodilator responses

Criteria	% Change before and after bronchodilator therapy	References
Repeat measurements on one day:		
FEV ₁	> 15% of baseline.	ATS.
FEV ₁	> 9% of baseline.	Dales RE, et al.
FEV ₁ and FVC	> 200ml.	Tweeddale PM, et al.
FEV ₁ and FVC	>12% of baseline and >200ml.(absolute volume)	ATS.
FEV ₁ and FVC	>12% of predicted and >200l	European Respiratory Society.
	PEF >60ml.	Dekker FW, et al.
Repeat PEF over several	Measurements days:	
	>20% baseline, mean 7 days.	Mitchell DM, et al.
Corticosteroid Trials	> 15% baseline, mean 7days.	Wardman AG, et al.
Nebulizer assessments.		Goldman JM, et al.
Reproducibility (PEF)	>15% baseline, mean 7 days.	Weir DC, et al.
Best two measures within 20 l/ min		

Source: Muers MF⁽¹⁶⁾.

Table 2.5: Measuring the efficacy of Nebulizers treatment:

Drug	Problem	Objective	Usual measurements	Agreed criteria for response
Bronchodilator	Acute airway obstruction	Rapid bronchodilation	PEF, FEV ₁	+
Bronchodilators	Chronic air flow limitation	Decrease disability	PEF, Exercise test, Validated questionnaires.	+/-
Steroids	Chronic airflow limitation	Bronchodilation, Decrease oral dose	PEF, oral dose	+/-

Source: MF Muers ⁽¹⁶⁾.

2.2.1 Interpretation of spirometric readings

FEV₁ is strongly recommended as the measurement of choice in COPD because of its reproducibility and precision for supporting evidence of the disease progression ^(7,26,28). PEF data may underestimate the degree of airway obstruction. One of the major problems of PEF in COPD is its poor relationship with FEV₁ and hence not possible to predict FEV₁ from the PEF or vice versa ⁽²⁷⁾.

The interpretation of the spirometric values should be done after satisfying the following criteria ⁽⁶⁾:

1. There are at least three technically satisfactory readings;
2. The expiratory volume/time traces are smooth, convex upward, and free from irregularities that suggest either variable sub maximal effort or coughing;
3. There are at least two readings of FEV₁ that are within 100 ml or 5% of the other; (Initially it was 200ml and 10% as 1987 ATS guidelines)

4. The recording has been continued long enough for a volume plateau to be reached on the volume -time plot. This can take up to 15 seconds in patients with severe COPD. Abbreviated efforts will underestimate FVC.

2.3 Smoking history

The smoking history should include both the number smoked, for how long, and an estimate of total pack-year of smoking. One pack of 20 cigarettes smoked per day for one year = One pack-year.

(No. Cigarettes smoked/day)	
Total pack-year =	_____ * No. Years of smoking.
	20

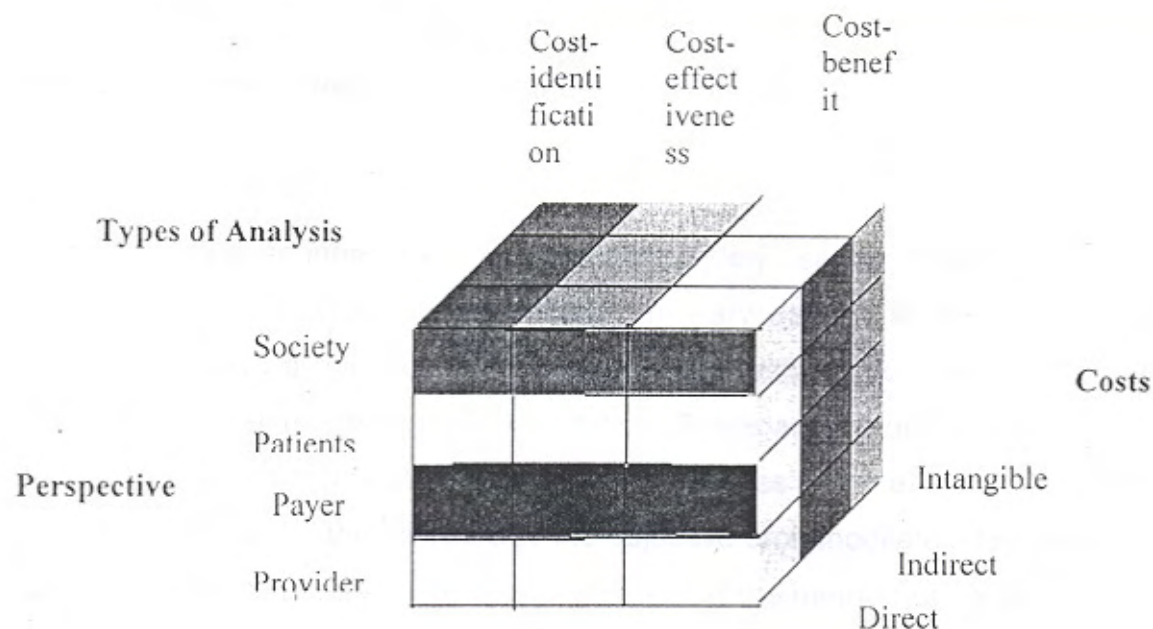
Source: BTS guideline ⁽⁶⁾.

2.4 Pharmacoeconomics

A relatively new discipline of health economics related to medicines is usually called 'Pharmacoeconomics' is being used nowadays. It can be defined as – 'the application of methods for evaluating relative patient and social benefits in terms of therapeutic and economic effectiveness and quality of life ⁽²⁹⁾. According to six European congresses of Biopharmaceutics and Pharmacokinetics, Athens 1996, there are different types of studies according to the way in which the effects are measured:

1. Cost Minimization Analysis (CMA): In CMA effects are assumed to be 'comparative' and therefore not really evaluated.
2. Cost-Benefit Analysis (CBA): In CBA the benefits are expressed in monetary terms (e.g. Savings in terms of morbidity, productivity, etc.)
3. Cost-effective Analysis (CEA): In CEA effects are measured as natural entities, such as result in clinical parameters, reduced loss of work etc.
4. Cost-Utility Analysis (CUA): In CUA outcomes are expressed as utilities compared to e.g. Quality adjusted life years.

Fig: 2.1 Health Economic Analysis



Source: adopted from Eisenberg and Bambar, 1964

Because COPD is highly prevalent and can be severely disabling, medical expenditures for treating COPD can represent as substantial economic burden for societies and for public and private health insurers worldwide ^(1,4,8). Nevertheless, very little economic information concerning COPD is available in the literature today. Studies of economic burden of illness have been conducted in only a few developed countries. Although studies of direct medical-care cost may be less relevant to the developing world, one might hypothesize that the indirect burden of COPD in developing nations may be substantial and important because the health care sectors do not provide long-term supportive-care services for severely disabled individual ⁽⁸⁾. Thus every aspect of treatment is important and it must reduce the economic burden of patients to manage for long-term treatment.

2.5 Comparison of Nebulizer and MDI

2.5.1 Effect on lung function

Both Metered dose inhaler and Nebulizer are widely used for treating patients with airflow obstruction. They are used for domiciliary as well as for hospital-based care. It is always a question of discussion on, whether Nebulizer or MDI is best suitable for Inpatients with airflow limitation. There are various studies that have been carried out which justify- both has more or less same efficacy. According to Mendelberg et al ⁽¹³⁾, the clinical and the objective bronchodilator responses to the administration of salbutamol were independent of the method of delivery: MDI with large spacer vs wet nebulizer. He has conducted randomized, double blind, placebo-controlled trial for unselected group of patients in emergency department. Similar study conducted in unselected very young children in pediatric emergency department using MDI with non-electrostatic spacer device (NESP) was found to be as effective as the nebulized wet aerosol ⁽³⁰⁾. Other studies by Mestitz et al ⁽¹¹⁾ and Turner et al ⁽¹²⁾ also proved therapeutic equivalence of both dosage forms. Apart from the above findings, other studies suggested that patient with acute asthma or COPD might respond better to nebulizer than metered dose inhaler ⁽³¹⁾. The recent review article by Catec CJ ⁽¹⁵⁾ is important for concluding therapeutic equivalence of MDI with nebulizer, which had included 16 similar trials for asthmatic patients.

Rebuck et al ⁽³²⁾ found (in 51 patients with COPD) that the mean peak flow increased from 70 l/min to 95 l/min (36% rise) ninety minutes after treatment with nebulized bronchodilator. Later a study by O'Driscoll et al ⁽¹⁸⁾ reported a rise of 19% in peak flow from 113 l/min in 47 patients with COPD after nebulized bronchodilator.

The selection of dose regimen differs from study to study. Mendelberg et al ⁽¹³⁾ used cumulative drug regimen giving 200 microgram MDI or 0.5 ml nebulizer for

three dosages with interval of 15 minutes and then doing spirometry evaluation after 15 minutes of each dose. Here total dose becomes 600 micrograms for MDI and 1.5mg for nebulizer. Similarly Anders et al ⁽³³⁾ used cumulative dose for both MDI and nebulizer, at thirty minutes interval for five times. In both cases high concentration of drugs were used. Even low concentration of drugs may be used to assess bronchodilator effect ^(17,34). BTS guidelines ^(7,28) suggest that even 2.5 to 5 mg of salbutamol are enough for reversibility testing. 5mg of nebulized salbutamol and 400 microgram of salbutamol MDI were being used by Thiadens et al ⁽³⁵⁾ to assess bronchodilatory response. Similarly, Campbell et al ⁽³⁶⁾ used 5mg-nebulized salbutamol, 5mg terbutaline nebulizer and 200-microgram salbutamol pressurized MDI in emergency department. Time for assessing bronchodilator response has been suggested between 15 to 30 minutes after, by various researchers and thoracic guidelines ^(10-15,28,34).

2.5.2 Economical analysis

The total economic cost of COPD morbidity and mortality in the United States were estimated at \$23.9 billion in 1993 ⁽⁸⁾. Sixty-eight percentages of medical expenditures in persons with COPD were for inpatient hospitalization ⁽⁴⁾. The cost of administration and the total cost of manpower and materials are also important besides cost of hospitalization. Generally MDI is supposed to be expensive than nebulizers for hospital setting, if we do not consider the cost of accessories required for nebulizers ^(13,22). But in community settings nebulizer may be expensive than MDI. Mendelberg et al ⁽¹³⁾ proved that the cost of Nebulizer is significantly more than the cost of MDI. Turner et al ⁽²²⁾ did the cost benefit analysis of MDI with wet nebulizer for hospitalized patients with airflow obstruction and proved equivalent cost of treatment for both groups.

Cost benefit analysis for two dosage forms of same therapeutic effect, can be done by considering total cost for treatment of individual drug and comparing it with outcomes ^(29,37).

2.5.3 Patients' knowledge for MDI use

The technique of MDI use is considered to be more difficult than nebulizer. Most patients use their MDI, incorrectly; females of all ages are much more likely to have improper MDI technique than are males ⁽³⁸⁾. Improper use of MDI may decrease its therapeutic value. Even Physicians are not willing to prescribe MDI considering the less knowledge of patients about the technique of using it. It is suggested that paramedical personnel such as pharmacist could address this problem by serving as patient educator (39).

Armitage et al ⁽²⁰⁾ proved age as a major factor when assessing patients' ability to use MDI correctly, and patients under the age of 65 can use significantly better than older patients. Thachil et al ⁽²¹⁾ surveyed 40 asthmatic patients for evaluating the technique of MDI considering 10-point technique. His selected patients were using MDI at least two times before. His findings for accurate technique were 80%, which suggested existence of problems on MDI technique. These researches were done in developed nations where literacy is high. Different findings may be obtained in illiterate patient, which is common in Nepal.

CHAPTER 3: METHODOLOGY

3.1 Survey of physicians

Survey of physicians was done to estimate prescribing pattern of bronchodilators for treating COPD. Aims of this survey were to evaluate practices of prescribing MDI, nebulizer and tablet of salbutamol and to compare it with BTS and ATS guidelines. Four major hospitals of Kathmandu (Bir hospital, Patan hospital, Military hospital, Kathmandu Medical College Teaching Hospital) and two hospitals outside the Kathmandu (Dhulikhel Hospital and Sheer Memorial Hospital) were selected for the survey.

Pre-constructed questionnaire (Annex 2) was used for the survey. Physicians were requested to fill the questionnaire by direct interview.

3.2 Selection of patients:

Selection of patient for the comparative study was done after the clinical diagnosis of airflow limitation. After reviewing the patient's medical record, the patients documented with COPD were selected for the study. Diagnosis of COPD was done by clinical symptoms and physical examination recommended by British Thoracic Guidelines and American Thoracic Guidelines.

3.2.1 Inclusion criteria

Patients were included in this study if they:

1. Were admitted to Inpatients ward.
2. Had documented diagnosis of COPD.
3. Were prescribed salbutamol.
4. Were fully conscious.

3.2.2 Exclusion criteria

Patients were excluded if they were:

1. Were unwilling to participate.
2. Were diagnosed for pneumothorax or operative cases.
3. Were unconscious.

3.2.3 Randomization and Selection Procedure

Patients were selected according to the selection criteria. The inpatient registration book was the main source for grouping the patients in to two main groups (viz. MDI and NEB). Patients' admission numbers were considered for randomization. Randomization was done by lottery method. Four slips numbering MDI group and four slips numbering NEB group was mixed in a box and four slips were withdrawn. Slips obtained in each attempt were marked for final patient selection. By this, the group of four obtained was NEB 01, NEB 02, MDI 01, NEB 03. It was followed by systemic sampling. The next group of patients was alternative to the first group (i.e. MDI 02, MDI 03, NEB 04 and MDI 04). Thus there were two groups of four individual patients. Further selection and grouping was done in the similar manner.

3.3 Drug strength and dosing frequency

Metered dose inhaler: ASTHALIN ®

Manufactured by CIPLA, INDIA

200-metered dose and each puff contain 100 microgram of salbutamol.

Respiratory solution: ASTHALIN ®

Manufactured by CIPLA, INDIA.

15ml, each ml contains 5 mg of salbutamol

The dose and dosing frequency of MDI and Nebulizer were:

1. MDI

Dose of Metered dose inhaler prescribed for every patient was:

Four puff each time for four times a day. Each puff was given in one-minute interval (as per MDI score technique, Annex 3).

Those patients, not knowing the MDI technique (as explained in section 3.5), were prescribed for spacer drive (750ml of CIPLA).

2. Nebulizer

Nebulizer was given by positive pressure of oxygen. Nebulizer was given according to the common practices found in Nepal i.e. 5mg of salbutamol (1ml respiratory solution+2ml normal saline). Flow of oxygen was kept for 2 L / min and the usual time of nebulization (administration time) were considered for 12 minutes.

3.4 Patients' Information

After grouping the selected patients, every patient was asked for information about as specified in the patient's informant (Annex 2). Other information was collected from the patients' medical record. The habits of the patients and socioeconomic status were also asked as mentioned in patients' informant (Annex 2). Written consent (Annex 4) for every patient was taken before enrolling in the study.

3.5 MDI score technique

Patients were first trained for MDI by using placebo inhaler (Asthalin® - CIPLA). The demonstration was done for once, after which patients were asked whether they understood or not. If they did not understand that, and then second demonstration was done. After that patient was asked to perform inhalation by using placebo inhaler and technique scoring was done. Demonstration and

evaluation were done by using ten-point score technique ⁽⁴⁰⁾ (Annex 3). The MDI group was then provided with MDI and Nebulizer group with nebulizer. At the time of discharging, every patient was evaluated again by using placebo-inhaler. This reflected the knowledge of patients about the use MDI at discharge. Data were collected and tabulated as Placebo-score and Discharge-score.

The MDI group was provided with MDI alone when the patient obtained MDI score not less than 7 or any step (6, 7, 8, and 9) was not missing. Other wise the patient was supplied with spacer device.

3.6 Spirometry evaluation

The Spirometer (Spirotron 2: DRAGER) used was of open type pneumatic, automatic spirometer with thermal print as hardcopy facility that printed all efforts (PF, FVC and FEV (0.5, 1 and 3 seconds)).

Spirometry evaluations of each patient were done after grouping the patients in separate group. Spirometry was performed before and after 25 minutes of bronchodilator therapy. This was done two times a day- morning (9 to 10 am) and evening (4 to 5 pm). Generally five maneuvers were recorded for each patient. If patient was not performing satisfactory maneuvers then maximum eight readings were taken. Highest spirometric values were considered though they were of different maneuvers. At least three pre and post bronchodilator therapy spirometric values were obtained for one patient and mean of these was calculated to estimate bronchodilatory effect.

3.6.1 Method of spirometry evaluation

Patients were asked to perform forced expiration. First they were asked to take deep inspiration and then forced expiration with mouthpiece inside mouth. There should be no coughing or any hindrance in first second of maneuver. Coughing in first second will mislead actual volume of forced expiratory volume and forced vital capacity.

3.6.2 Standardization of maneuver

Standardization of forced expiratory maneuver was done according to the BTS and ATS guidelines. Following points were considered:

- ❖ There should be no coughing during the first second.
- ❖ The graph should be convex upward in first second.
- ❖ The expiration should be of forceful expiration.

Only those graphs obeying the standardized criteria were considered for evaluation.

3.7 Pharmacoeconomics

Mainly direct cost was considered for pharmacoeconomics.

Direct costs:

- ❖ Acquisition cost of the drug (drug price)
- ❖ Costs for preparation and administration
- ❖ Personnel salaries (nurse)
- ❖ Equipment and supplies (syringe, Nebulizer chamber, oxygen cylinder, spacer device)
- ❖ Other costs:
- ❖ Hospital costs

Indirect costs were not estimated because it was difficult quantifying cost of illness and lost labor time. It may need to follow the patients after discharge. Similarly, intangible cost such as quality of life was also not estimated. The cost determined was mainly the direct cost to compare hospital cost of two different therapies. Material costs for nebulized and MDI administrations were obtained from pharmacy of the hospital.

The time required for administration of nebulized β -2 agonists was estimated by timing the procedure three times. This included the time taken to prepare the medicine, teaching time and the time taken to administer. Similarly time required administering via an MDI and Spacer was also estimated.

After determining the direct cost, the cost benefit analysis was performed for both the groups. Science spacer and nebulizer mask, were used for different patients, the possible cost of Spacer and Nebulizer mask were determined by respective frequency of use. The difference of MDI cost with or without spacer was also compared. The cost of oxygen was not considered because both groups were receiving oxygen according to the standard protocol.

3.8 Statistical analysis

Statistical analysis was performed by using statlets program (Version 2.01, April 7, 2000, stat point LLC, Englewood cliffs, N.J.). Data were classified in different independent variables and analysis was done by using student t-test. The lung function parameters (after and before) were compared by using two-tailed paired t-test at the 5% level of significance. The MDI technique scores were compared for the values at the time of discharge and at the time of placebo by using paired t-test at the 5% level of significance. One-tailed and two-tailed t-tests were used for suitable data. Same parameters for different groups were compared by two-sample t-test for independent samples at the 5% significance level. The data were significant for $p < 0.05$.

Graphs were plotted by using EXCEL-98.

CHAPTER 4: RESULTS

4.1 Survey of physicians

Total 77 physicians from five different hospitals were surveyed in which 11 were MD and 61 were MBBS. There were 2 Pulmonary Medicine Specialists.

The questionnaire used for the survey is as shown in Annex 1.

Table No: 4.1.1 survey results showing preference of dosage forms.

Q: 1 Preferred dosage forms for treating Inpatients (n =76)	
A: Nebulizer	90.8%
B: Metered Dose Inhaler	6.6%
C: Tablets	2.6%
Q: 2 Preferred dosage forms to prescribe on discharge (n = 75)	
A: MDI	48%
B: Tablets	48%
C: None	4%
Q: 3 Best therapeutic value- for long-term treatment. (n = 76)	
A: Tablets	31.58%
B: MDI	67.1%
C: No difference	1.32
Q: 9 Recommended dosage forms- if patients were supposed to know MDI technique (n = 76)	
A: MDI	90.8%
B: Tablets	1.32%
C: Sometimes	7.9%

Results are in Percentage.

90.8% physicians preferred Nebulizer for treating Inpatients with airflow obstruction while only 6.6 % preferred MDI and 2.6% preferred tablets.

Table: 4.1.2 survey results showing reasons behind not using MDI.

Q: 8: Reasons behind not practicing MDI for COPD patients in comparison with Nebulizer.	
A: MDI more expensive than Nebulizer	39.7%
B: MDI is less effective than Nebulizer	38.4%
C: MDI is less convenient to use by health workers	15.1%
D: Patients not know appropriate technique of MDI	63.4%

The percentage of physicians recommending MDI (48%) and Tablets (48%) were same though 67.1% of physicians thought MDI was of better therapeutic value than Tablets (31.58%). Only 1.32 % of physicians thought that MDI and Tablets have same therapeutic value (table 4.1.1).

Many physicians (90.8%) preferred Nebulizer for treating the inpatients with airflow obstruction. Among them, 53% were using positive pressure of oxygen while 47% were using air compressor. The main reason for not using MDI in Inpatients' department was found as lack of patients' knowledge of using MDI (63.4%). Other reasons were high cost of MDI (39.7%), less effectiveness of MDI than Nebulizers (38.4%) and inconvenience MDI by health workers (15.1%) (As in table 4.1.2). It was found that 90.8% of physicians recommended MDI if they felt that the patients could use it properly (table 4.1.1).

The usual dose recommended by the physicians for prescribing MDI or Nebulizer was found as in table 4.1.3. There was a high variation in prescribing pattern. This variation might be due to non-availability of Nepalese standard guidelines. Most of Physicians were practicing by their own experience and by consulting international guidelines. Though BTS recommended use of pressurized air for nebulizing COPD patients, 53% physicians were found using positive pressure of oxygen.

Table: 4.1.3 survey results showing pattern of salbutamol use.

	Nebulizer			Metered dose Inhaler	
	Asthalin® (ml)	Normal Saline (ml)	Oxygen (Liter/Minute)	Asthaline ® (µgm)	Times a day.
	(N = 69)			(N = 62)	
Mean	1.16	2.66	2.76	219.35	3.58
S.D	0.4	1.17	1.30	84.63	1.13
Mode	1	2	2	200	4

Figure 4.1 Survey of physicians (Q: 1,2,3 &9)

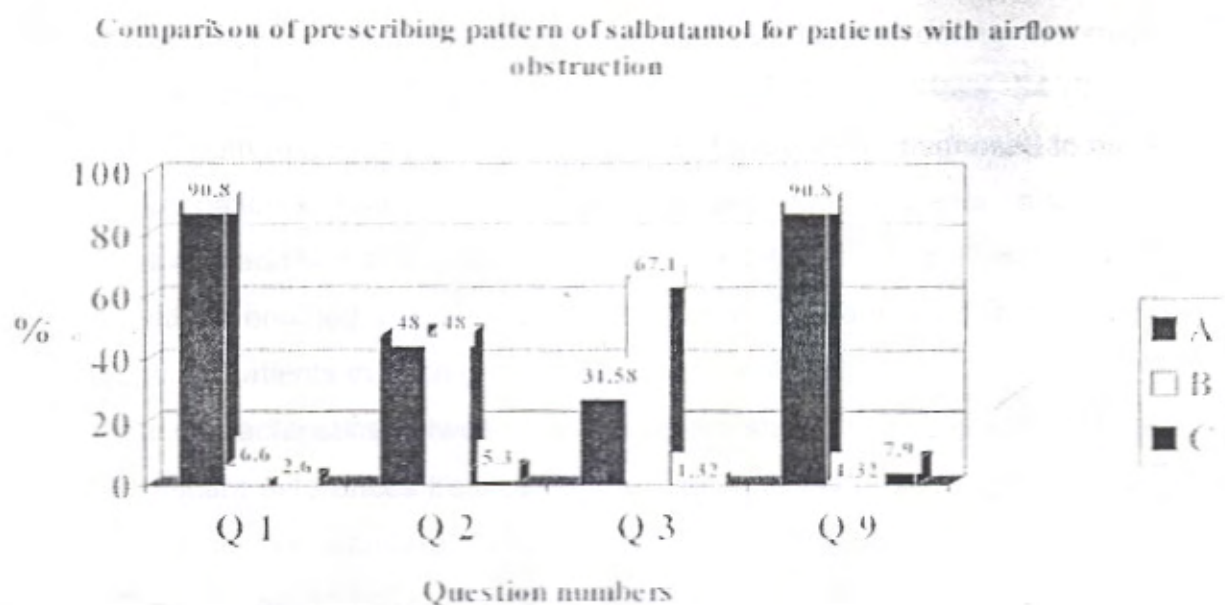
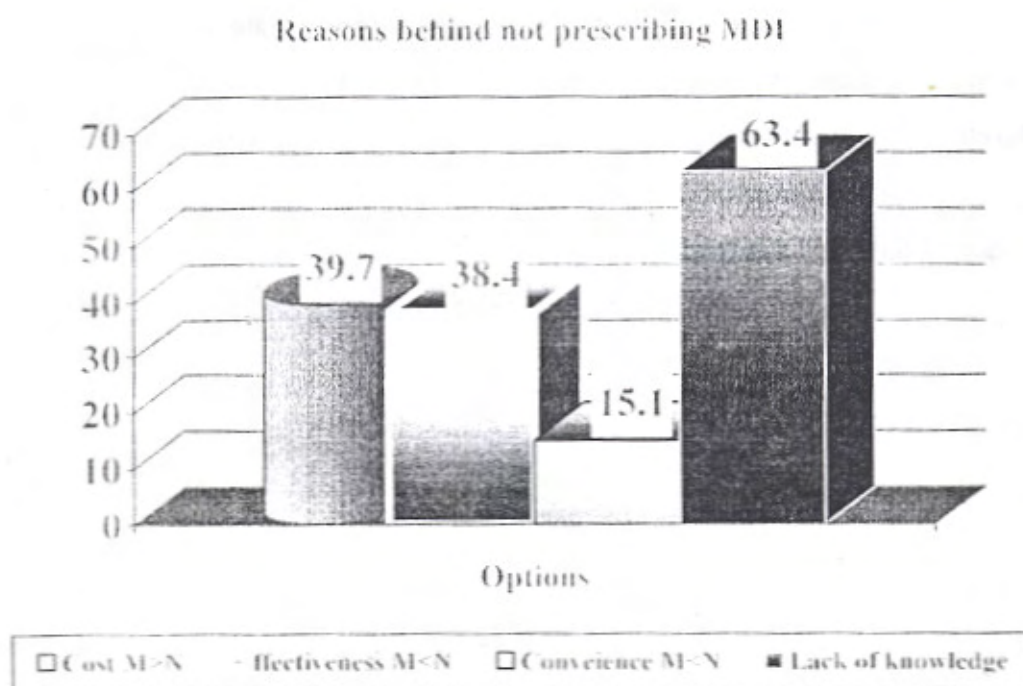


Figure 4.2 Survey of physicians (Q: 8)



4.2 Comparative analysis

A total of 620 patients were hospitalized in Dhulikhel Hospital during the study period from December 28th, 2001 to March 20th, 2002. Out of these, 54 (8.7%) were suffering from respiratory problems, and 36 of them were diagnosed to have COPD. Two patients had nasogastric tube and four patients also had pneumothorax in addition to COPD. Hence, only a total of 30 (83.3% of COPD) patients could be enrolled in the study. All consented to participate in the study resulting total 15 patients in each group (MDI and Nebulizer).

The baseline characteristics between the groups are shown in Table: 4.2.1. There were no significant differences between the groups in terms of sex, age and body weight. There is no standard lung function reference value for Nepalese population, which would have helped to come up with predicted lung function value. Hence height measurement was not done. Therefore, the percentage predicted value could not be mentioned.

As compared to baseline, especially FEV1 and FVC were found significantly improved in after bronchodilator therapy in MDI and nebulizer groups. Similar improvement is also seen in peak expiratory flow measurement ($P = 0.00$). The statistical analysis of the lung function data of pre and post bronchodilator treatment treatments was done at 5% significance level. The results showed significant improvement in lung function after bronchodilator therapy.

There was an improvement in MDI score technique for the MDI group, which was found to be significantly greater than that of nebulizer group.

Table: 4.2.1 Base-line characteristics of study participants *

CHARACTERS	MDI Group (n = 15)	NEB Group (n = 15)	P-value
Sex			
Male	7	7	
Female	8	8	
Age	58.66 ± 8.68	61.666 ± 10.81	0.4091
Weight	43.04 ± 9.56	41.73 ± 8.76	0.6992
Blood pressure			
Systolic	104 ± 13.39	107 ± 15.09	0.5693
Diastolic (mmHg)	70.33 ± 13.42	75.33 ± 13.55	0.3187
Breathing per minute	22.53 ± 2.32	24.66 ± 2.44	0.0209
Temperature (°c)	36.38 ± 0.85	36.06 ± 0.65	0.2493
Pulse (per minute)	85.8 ± 14.56	86.4 ± 14.13	0.9096
Smoking			
Pack- years	18.16 ± 10.45	23.36 ± 9.74	0.00001
Occupation (%farmer)	100	100	
Education (% Less than 5 class)	93	100	
Label Understanding (% Not understand)	100	100	
Family members (Per patient)	5.93 ± 2.63	6.0 ± 1.65	0.0009

* Data were in Mean ± SD, unless otherwise explained.

Table: 4.2.2 Outcome Measures*

Measure	MDI Group (n = 15)	Nebulizer Group (n = 15)	P-Value
FEV₁			
Base line FEV ₁ (L)	0.82 ± 0.40	0.77 ± 0.31	0.7049
FEV ₁ after bronchodilator (L)	0.97 ± 0.43	0.94 ± 0.41	0.8464
% Change in FEV ₁	18.29	22.07	
FVC			
Baseline FVC (L)	1.10 ± 0.51	1.08 ± 0.45	0.9101
FVC after bronchodilator (L)	1.25 ± 0.54	1.28 ± 0.5	0.8757
%Change in FVC	13.63	18.51	
PEF			
Baseline PEF (L)	2.34 ± 1.29	2.67 ± 0.98	0.4368
PEF after bronchodilator(L)	2.90 ± 1.69	3.23 ± 1.44	0.5695
%Change in PEF	23.93	20.97	
MDI Technique Score **			
Placebo Score	7.43 ± 1.34	7.13 ± 1.68	0.6073
Final Score	8.64 ± 1.64	6.4 ± 1.80	0.0017
Difference	1.21 ± 1.72	-0.73 ± 1.71	0.0050

* Data were in Mean ± SD, unless otherwise explained.

** For MDI technique score, sample size for MDI group was 14 and for Nebulizer group was 15.

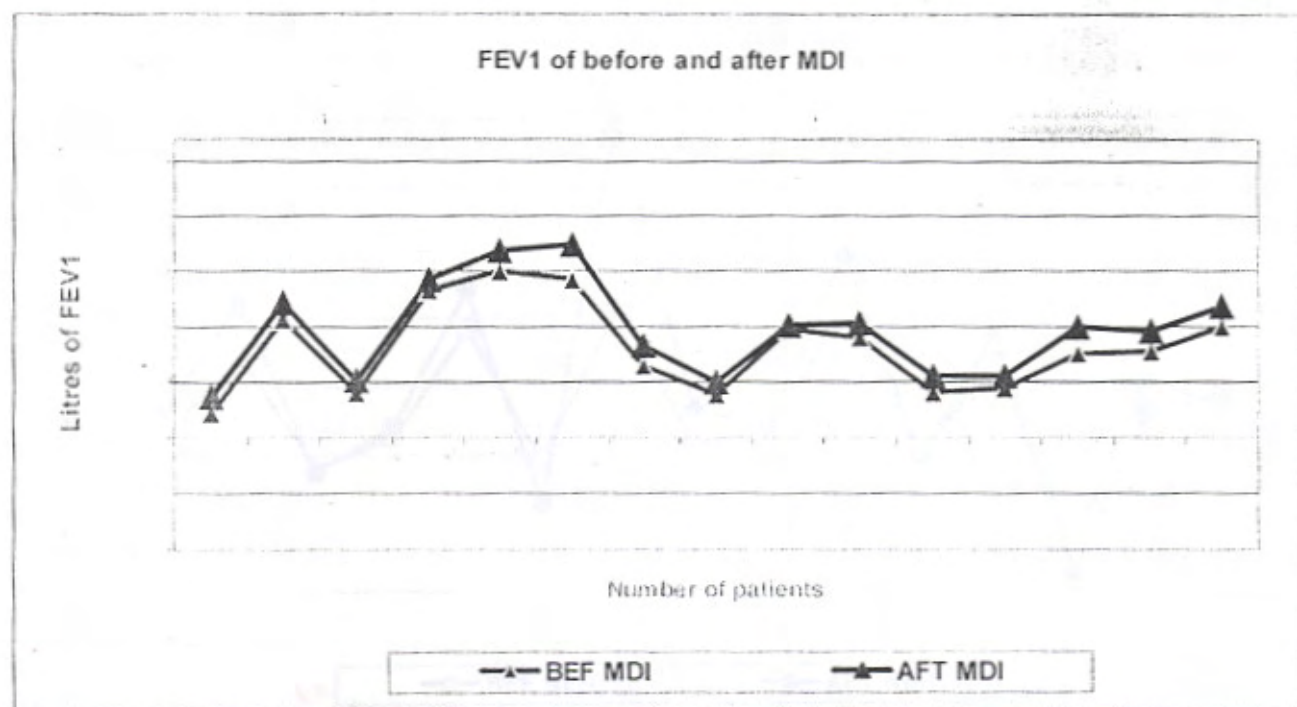
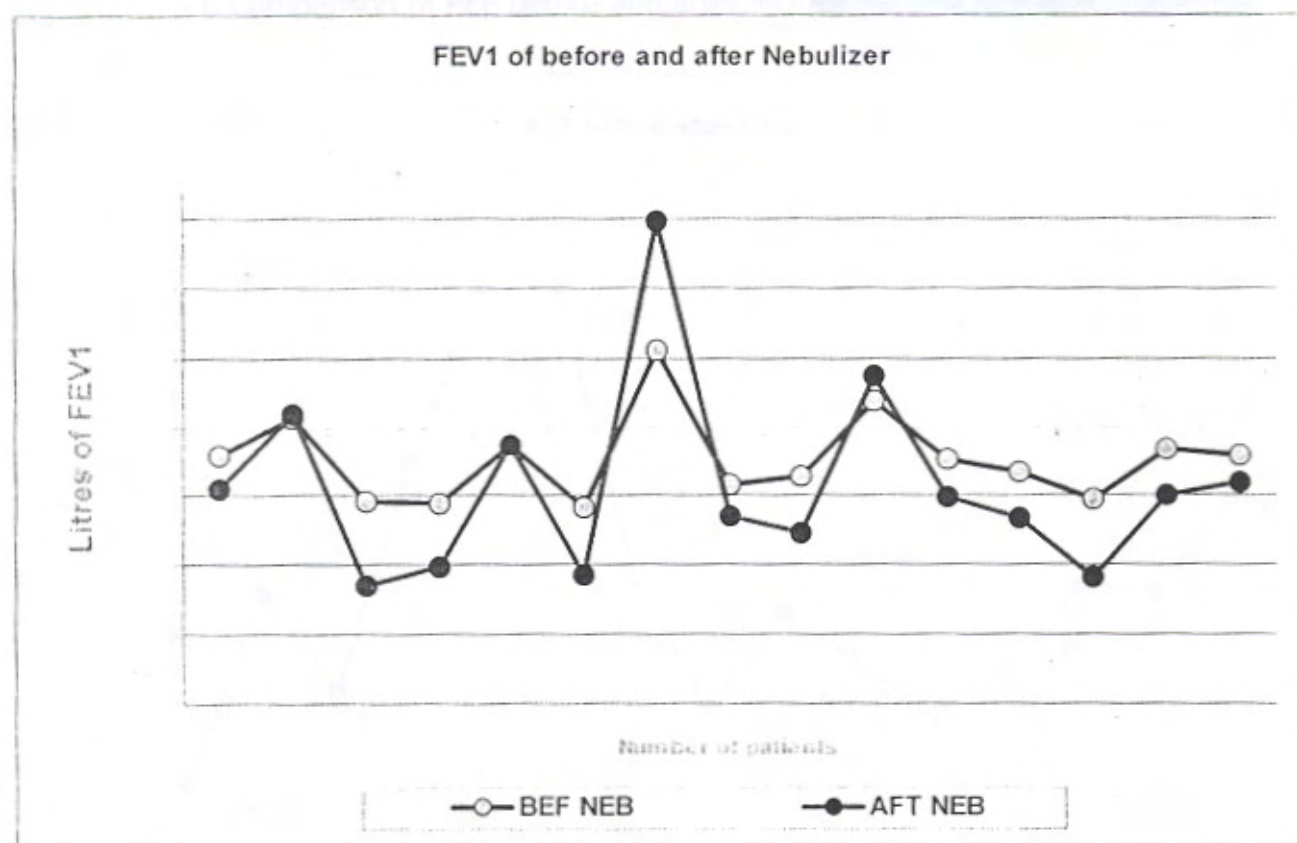
Figure: 4.3 Comparison of FEV₁ for MDIFigure: 4.4 Comparison of FEV₁ for Nebulizers

Figure: 4.5 Comparison of PEF before and after of Nebulizer

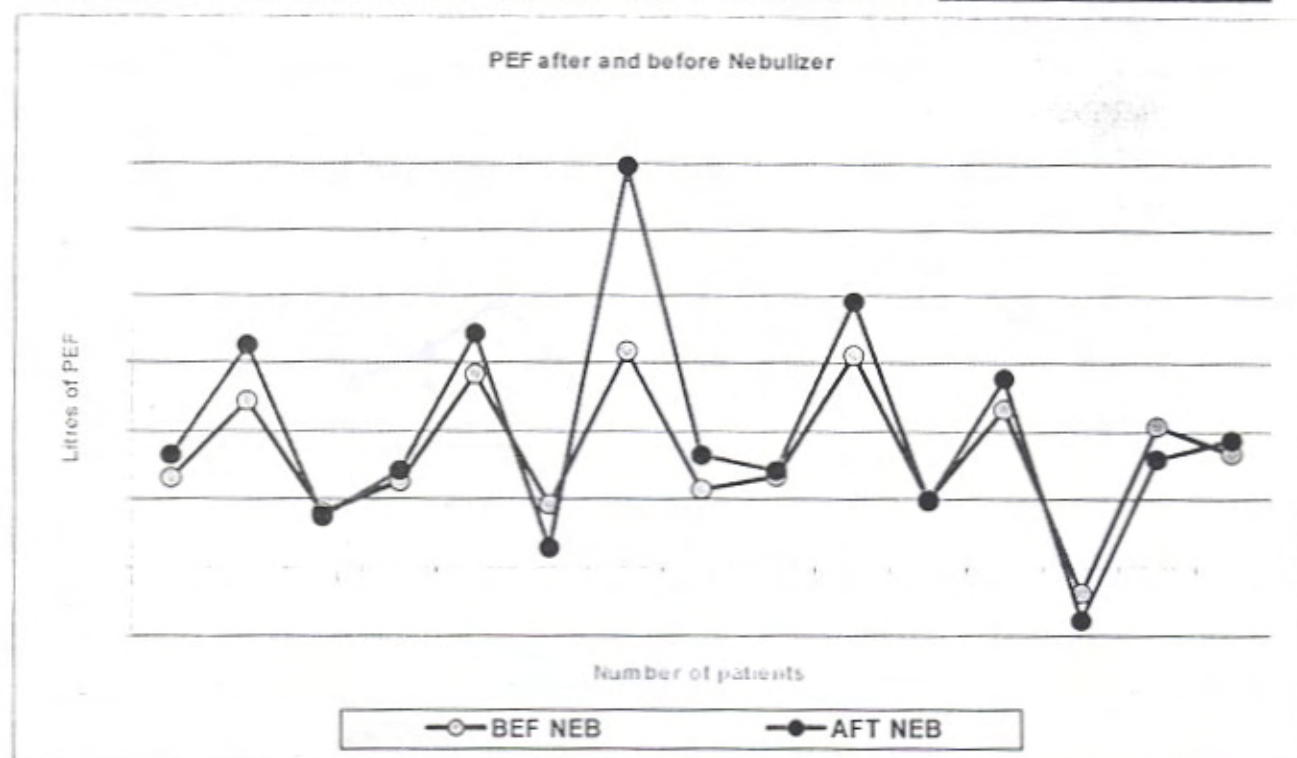


Figure: 4.6 Comparison of PEF before and after MDI

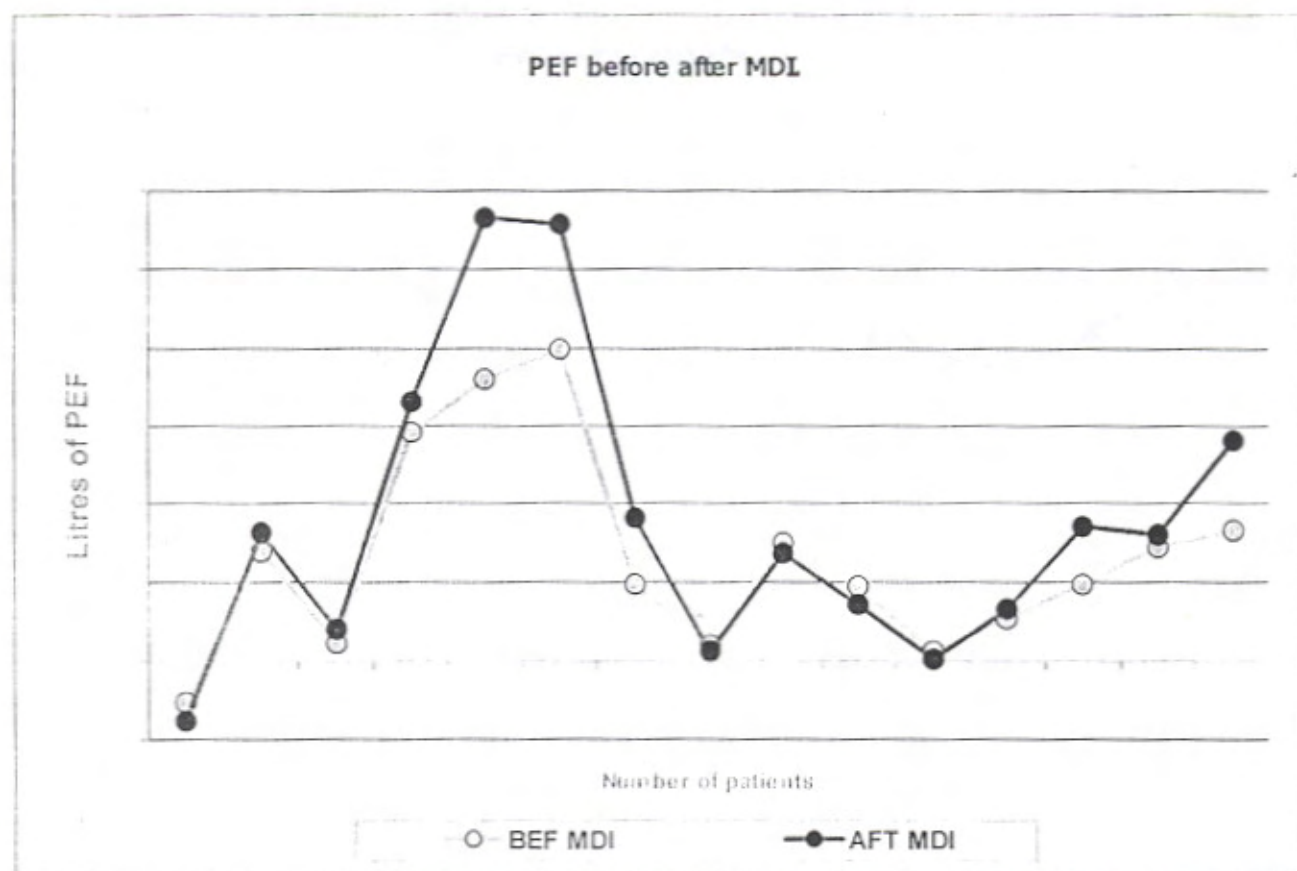


Figure: 4.7 Comparison of FVC before and after Nebulizer.

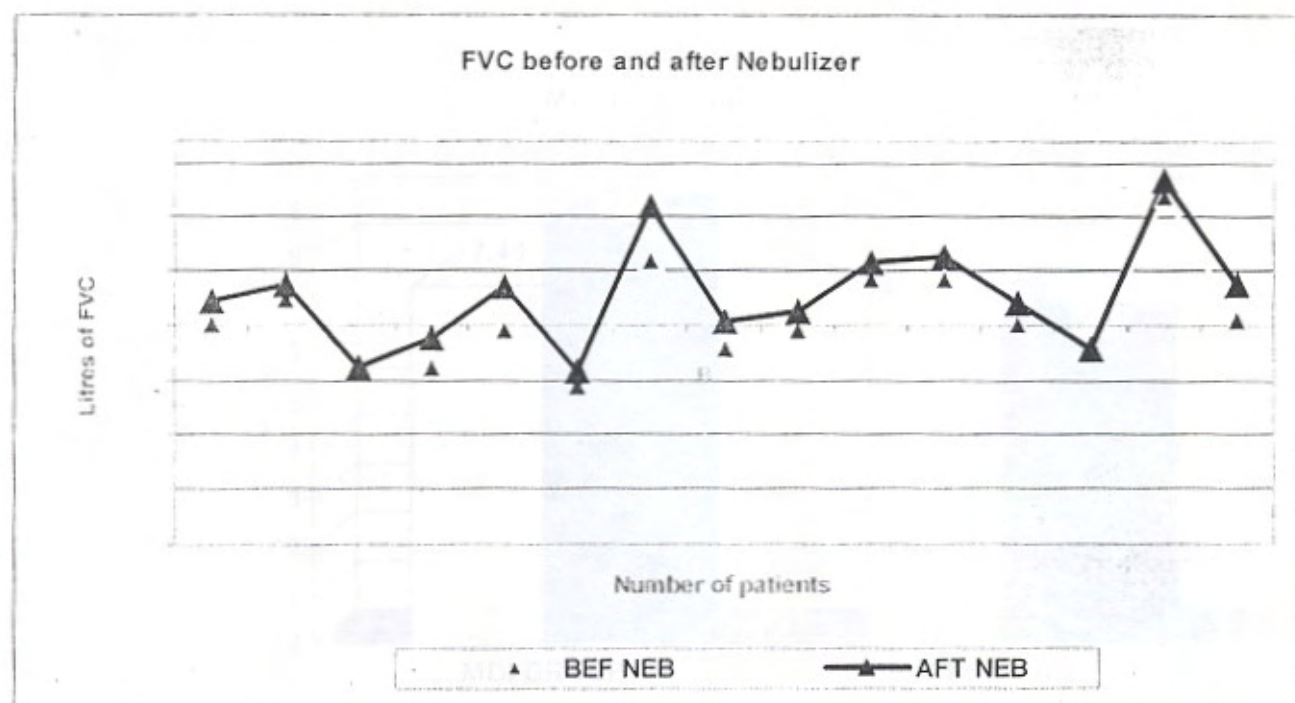


Figure 4.8 Comparison of FVC before and after MDI.

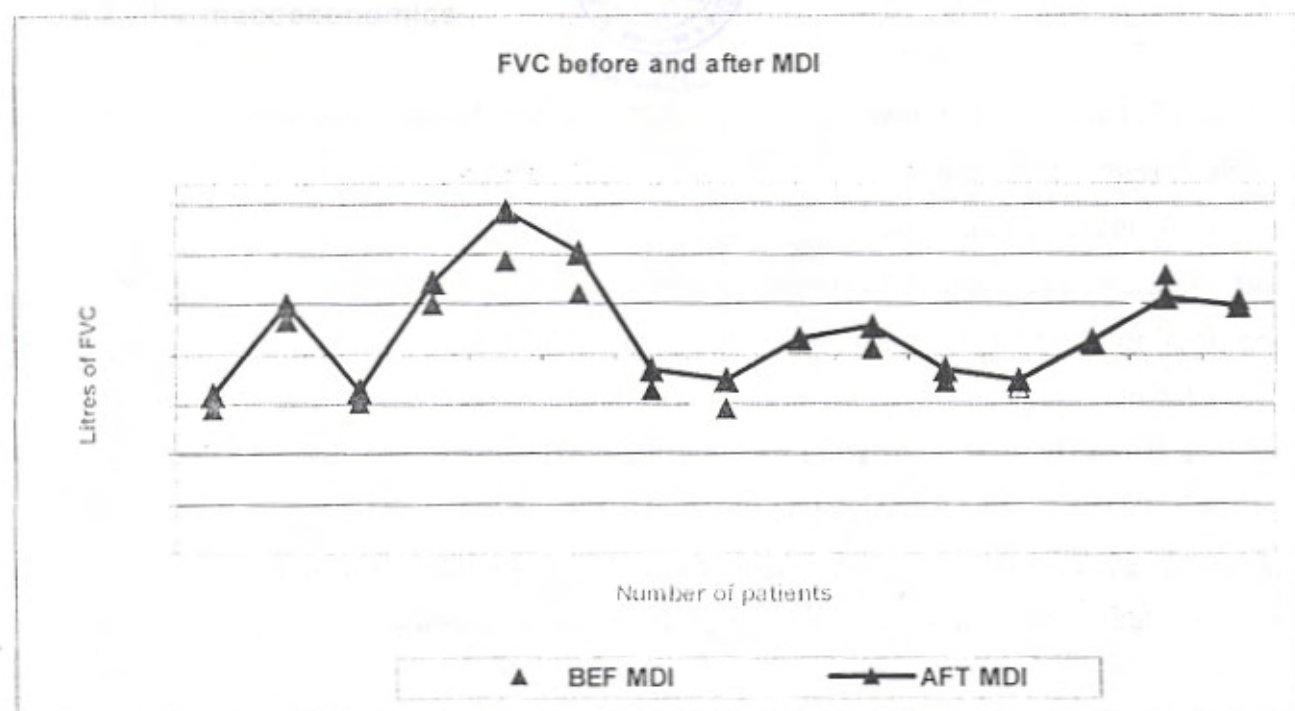
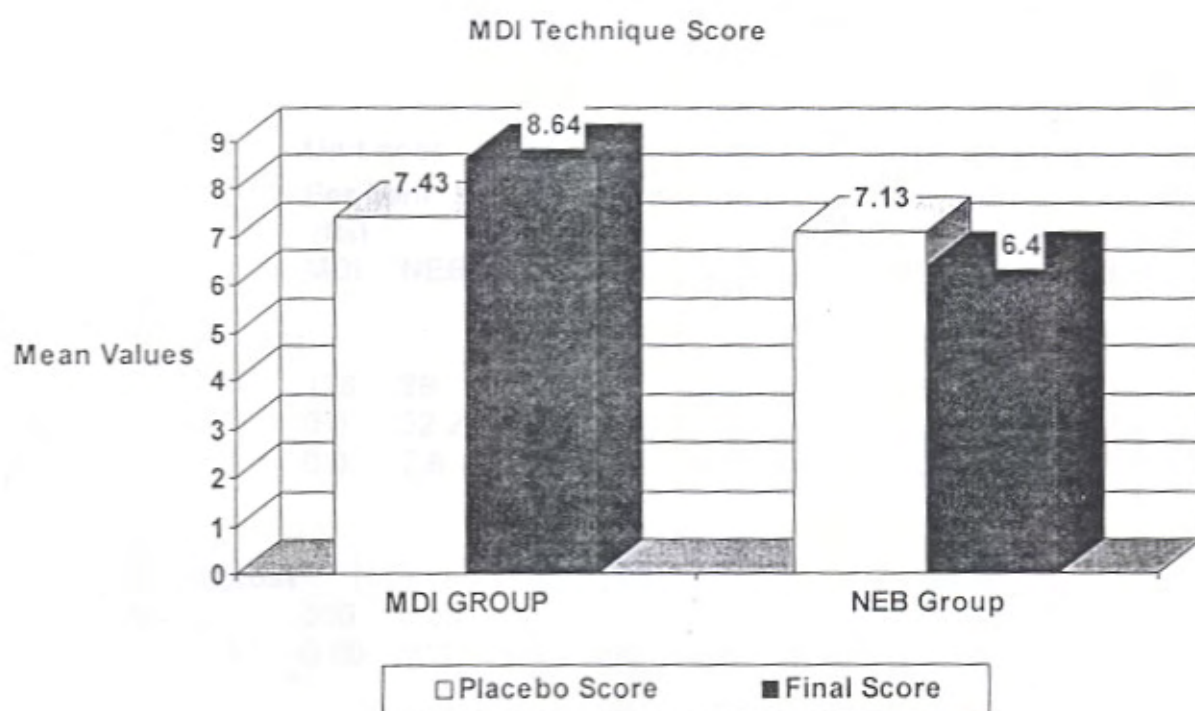


Figure: 4.9 Comparison MDI technique score



4.3 Pharmacoeconomics

The pharmacoeconomics of MDI and Nebulizers is shown in Table 4.3.1. The total treatment cost would include the cost of drugs as well as the cost of administration. Normal saline was used as the vehicle for giving salbutamol as nebulizer. And one bottle of normal saline would last on average five days to treat three patients per day. Similarly, spacer device and nebulizer mask were also used for different patients after washing with soap solution and then with rectified spirit. On average, one spacer or one nebulizer mask was used for thirty days (120 administrations). Also, single syringe was used in four nebulizer administrations.

Nursing care time was estimated by informal observation of their practices. The cost of nursing care was determined according to their average salary, Rs 7000 for eight

hours per day in twenty-six days. The total cost for treatment for both the groups were shown in table 4.3.1.

Table: 4.3.1 COST estimation for MDI and Nebulizer

	Unit cost Per item (Rs)		Number of Administrations		Unit cost per administration (Rs)	
	MDI	NEB	MDI	NEB	MDI	NEB
A: Acquisition cost*						
Salbutamol	128	28	45	14	2.84	2.0
Normal Saline	0.0	32.2	0.0	60	0.0	0.54
Syringes	0.0	7.8	0.0	4.0	0.0	1.95
B: Equipment cost†						
Spacer device	510	0.00	120	0.0	4.25	0.0
Nebulizer	0.00	600	0.0	120	0.0	5.0
C: Cleaning cost						
	0.37	0.62			0.37	0.62
D: Manpower cost ‡ Time (MDI) Time (NEB)						
Preparation time (minutes)	2	5			1.12	2.80
Teaching time (minutes)	6	3			3.36	1.68
Administration time (minutes)	7	12			3.92	6.73
Total cost (Rs)					15.86	21.32
Percentage decrease in unit cost of MDI administration as compared with Nebulizer administration = 34.42 %						

* Acquisition cost is cost of dosage form needed to each administration (For MDI is 400mcg and for Nebulizer is 5mg)

† Equipment cost is cost of spacer or nebulizer chamber considered for 30 days of use for four times a day for one person.

‡ Manpower cost is considered for pay of Rs7000.00 for working hours; 8 hours per day for 26 days.

Table 4.3.2 Cost benefit analysis

Parameters	MDI	NEBULIZER
Cost of each treatment (Rs)	15.86	21.32
Number of treatment per day	4	4
Mean days of hospital stay *	4.5	5.2
Total treatment cost in Rs.	285.48	443.45
% Improvement of FEV1**	18.29	22.07
<u>Benefits of MDI over Nebulizer</u>		
Benefit on cost during treatment		= Rs. 157.97
Decreased hospitalization cost †		= Rs. 77.00
Net benefit of MDI over Nebulizer for each patient		=Rs. 234.97

* For MDI, n =14 and for Nebulizer n =15.

** For both MDI and Nebulizer n = 15.

† Daily hospital charge is Rs. 110.00.

CHAPTER 5 DISCUSSION

5.1 Survey of physicians:

The physician's survey showed a variation on dose selection pattern of salbutamol administration for COPD patients. Nebulizer is the most common delivery method used for treating inpatients and 90.8% physicians preferred it. The dosing pattern of MDI and Nebulizer has a high variation too.

MDI was used less though physician concluded that it has the best therapeutic value among different dosage forms of salbutamol. It is an amazing fact that the less use of MDI was due to lack of proper technique and use would be improved up to 90.8% if patient know it. Only a few physicians supposed MDI is inconvenient to use by health workers and it is expensive than nebulizer. Hence health workers can promote the use of MDI in hospital as well as in domiciliary use by training patients.

5.2 Lung function improvement

The present study included thirty COPD patients in two different groups (MDI and Nebulizer) having fifteen patients in each group. There were similar baseline characters of individual variables (age, sex body weight and vitals) and lung function parameters (FEV1, FVC and PEF). The baseline values of FEV1 and FVC were 0.82 ± 0.4 and 0.77 ± 0.31 respectively for MDI group, and 1.10 ± 0.51 and 1.08 ± 0.45 for nebulizer group. As compared with baseline, the lung function parameters especially FEV1 and FVC were significantly improved in after bronchodilator therapy in MDI or nebulizer groups ($p=0.00$).

Earlier studies comparing salbutamol inhaled via nebulizer or MDI suggest clinical equivalence ⁽¹⁰⁻¹⁵⁾. Mestiz et al ⁽¹¹⁾ thought that this bronchodilator response depends on dose of salbutamol rather than mode of administration. The present study also showed similar bronchodilator efficacy in both groups. Though previous studies compared nebulizer and MDI with spacer, the present study had only fifty-percent patients using spacer device. It suggests that even without spacer device,

patients can use MDI (if he can use effectively) for getting similar bronchodilator therapy as that with nebulizer.

Contrast to the findings of this study, Moss et al ⁽³¹⁾ suggested that patients with acute asthma or COPD might respond better to treatment given via nebulizer than that of via metered dose inhaler.

Since, the clinical efficacy of salbutamol mainly depends on the dose ^(11-14,19,34), the dose escalation for comparing therapeutic equivalence is important. The basic difference of present study with other studies is the dose selection for MDI or nebulizer. It is found that low dose of salbutamol is also effective but high dose has significant therapeutic outcomes that are easy to measure ^(12,18,34,41). BTS guideline ^(6,17,28) also suggests that 2.5 to 5 mg of salbutamol is enough for reversibility testing. Mendelberg et al ⁽¹³⁾ compared MDI and nebulizer with cumulative drug regimen giving 200 microgram MDI or 0.5 ml nebulizer for three dosages in 15 minutes interval and did spirometry evaluation after 15 minutes of each dose. Here, total dose becomes 600 micrograms for MDI and 1.5mg for nebulizer. Similarly Anders et al also used cumulative dose (3200microgram for MDI) in 30 minutes interval up to 5 times. In both the cases high concentration of drugs were used for comparing therapeutic equivalence than that is used in present study, which is in favor of the present study showing therapeutic equivalence even in low dose. Thiadens et al ⁽³⁵⁾ used similar doses of salbutamol (i.e. 400microgram and 5mg salbutamol) to assess bronchodilatory response and also supported clinical equivalence of MDI and nebulizer. The timing to assess the effects induced by bronchodilator therapy has been supported between 15 to 30 minutes by various researchers and BTS guidelines ^(12,13,18,19,28,41).

5.3 MDI technique Score

Age and education backgrounds of patients are major factors that influence their ability for using MDI correctly ^(20,42). Armitage et al ⁽²⁰⁾ found patient under the age of 65 was using MDI significantly better than older patients. A survey by Thachil et al

⁽²¹⁾, for determining MDI technique considering 10-point technique, suggests problem on MDI technique and only 80% of MDI receiving patients used accurate technique.

Since the present study included patients with similar age distribution and they were all uneducated not understanding the labeling instructions, it is obvious to have low understating in MDI technique. Though there was no significant difference in baseline placebo sore, final score at the time of discharge had significant improvement in MDI group patients than that of nebulizer group. It suggests that regular use of MDI during hospitalization increase patient's skill of MDI use.

5.4 Pharmacoeconomics

The total cost of drug including drug cost, material cost and administration cost, is important to evaluate pharmacoeconomics. Even drug cost of unit dosage form for MDI is higher than that of nebulizer, The total cost per unit administration of Nebulizer has been found to be 34.42% more than that of MDI. It is due to the cost of each administration. Similar study by Turner et al ⁽²²⁾ proved equivalent cost for each group. Even though he used cost can \$1.27 (2puff for MDI) and can \$ 2.62 (2.5 mg for nebulizer) and time for teaching (10 minutes) suggested that the use of spacer device would increase the cost of MDI. The study design of Turner ⁽²²⁾ is not clear about equipment used in nebulizer. A disposable nebulizer may increase nebulization cost and using separate MDI will increase MDI cost. Since the MDI has 200 puffs, considering the cost for hospital stay only; it will definitely increase MDI cost. The current research has different findings than that of Turner because of reuse of MDI, Spacer and Nebulizing chamber. Nursing care cost was more for nebulizer than MDI.

The finding of this research found to be similar to that of Mendelberg et al ⁽¹³⁾, which supported cost of nebulizer, is significantly more than MDI. The use of separate Spacer and disposable nebulizer will dramatically increase the cost of treatment, which may not be affordable for poor patients. The major difference of this study

than other similar ones, it has used same equipment after washing for different patients.

Total cost of bronchodilator therapy for patients with COPD turned out to be Rs 285.48 for MDI group (mean stay 4.5 days $\pm$ 2.5) and Rs 443.45 for Nebulizer group (mean stay 5.2 days $\pm$ 1.74). The net benefit of MDI over nebulizer in terms of cost was Rs 234.97.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Physicians for treating inpatients with airflow obstruction preferred use of nebulizer. Though physicians supposed MDI has best therapeutic value for treating outpatients, its limited use in hospital was due to high cost and difficulty in use.

In randomized groups of COPD patient's bronchodilator therapy using MDI were superior to nebulizer. Though, there was no significant difference in baseline lung functions (FEV₁, FVC and PEF) between the MDI and nebulizer groups, significant improvement of lung function parameters were found in respective groups (For MDI - %PEF= 23.93, %FVC =13.63 and %FEV₁ =18.29 and for Nebulizer -%PEF=20.97, %FVC= 18.51 and %FEV₁ =22.07). The cost of treatment for MDI was found to be much less than that of nebulizer (Rs 285.48 versus Rs 443.45) with mean days of hospitalization 4.5 ± 2.5 days versus 5.2 ± 1.7 days respectively.

The regular use of metered dose inhaler during hospitalization has improved patient's skill for MDI technique. Though all patients showed similar skill at the time of hospitalization ($P=0.6073$), the final score of MDI technique has significant improvement ($P=0.0017$) (8.64 ± 1.64 for MDI versus 5.2 ± 1.7 for NEB).

These data suggests that treatment of COPD patients with bronchodilator (salbutamol) using MDI is more cost effective than nebulizer even though clinical efficacy is similar. Also, hospital use of MDI seems to be useful for improving patient's skill of MDI technique, the regular use of MDI in inpatient department can be recommended.

In summary, we suggest that the overall evidence argues against any clinically important potency difference between salbutamol inhaled via nebulizer or MDI in hospitalized patients with COPD. However, further studies are required to fully understand the dose equivalence of salbutamol given via different inhaler devices in different population of COPD patients. The long-term evaluation for large population will be beneficial for evaluating clinical and pharmacoeconomic equivalence along with patient's life quality.

CHAPTER 7: BIBLIOGRAPHY

- 1) **British Thoracic Society**, 'Burden of lung disease', a statistical report, 2001.
- 2) **WHO**, "Non communicable diseases prevention and management", South East Asia Region, 2001.
- 3) **Hurd S**, 'The impact of COPD on lung health world wide', *Chest* 2000; 117(2): S 1-4.
- 4) **Smith KR**, 'National burden of disease in India from indoor air pollution' *PNAS* 2000; 97(24): 13286-13293.
- 5) **Panday MR**, 'Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal', *Thorax* 1984; 39:337-339.
- 6) **British Thoracic Society (BTS)** guidelines for COPD, *Thorax* 1997; 52(suppl5): S1-S28.
- 7) **Watson J P**, **Lewis R A**, 'Is asthma treatment affordable in developing countries?' *Thorax* 1997; 52(7): 605-607
- 8) **Sullivan Sean D**. PhD, **Ramsay Scott D**. MD PhD and **Lee Todd A**. PharmD, "The economic burden of COPD", *Chest* 2000; 117:5S-9S.
- 9) **Newhouse MT**, **Dolovich MB**, 'Control of asthma by aerosols' *N Engl. J. Med* 1986; 315:870-4.
- 10) **Mestitz H.**, **Copland J M**, **App B**, **Mc Donald C F**, Comparison of outpatient nebulised vs metered dose inhaler terbutaline in chronic air flow obstruction, *Chest* 1989;96: 1237-40.

- 11) **Berry RB**, Shinto RA, Wong FH, Despars JA, Light RW, 'Nebulizer vs spacer for bronchodilator delivery in patients hospitalized for acute exacerbation of COPD', *Chest* 1989; 96:1241-1246.
- 12) **Turner JR**, Corkey KJ, Eckman DE, Gelb AM, Lipavsky A, Sheppard D, "Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction", *Chest* 1988;93:476-81.
- 13) **Mandelberg Avigdor MD**, Erez Chen MD, Natan Noviski MD, and Israel E. Priel MD FCCP, "Nebulized Wet Aerosol Treatment in Emergency Department- Is it Essential?" *Chest* 1997; 112:1501-05.
- 14) **Katsongiannis W**, Despina MM, Sanbrook A, Armour CL, 'Nebuliser versus metered dose inhaler use in hospital', *Aust J Hosp Pharm*, Vol 26, Issue 5, P529-533, Yr 1996.
- 15) **Cates C J**, Rowe B H, "Holding chambers versus nebulisers for beta-agonist treatment of acute asthma, *The Cochrane Library*; 2001: Issue 2.
- 16) **Muers M F**, ' Overview of nebuliser treatment', *Thorax* 1997; 52 (suppl 2): P25-30.
- 17), **British thoracic society**, 'Guideline for Nebuliser treatment', Nebuliser Project Group: 1994.
- 18) **O'Driscoll B R**, 'Nebulisers for chronic obstructive pulmonary disease', *Thorax* 1997; 52 (suppl 2): P49-52.
- 19) **Turner M O**, Patel A, Ginsburg S, Fitzgerald J M, Bronchodilator delivery in acute airflow obstruction, *Arch intern Med*, vol 157, iss15, p1736-1744: Yr 1997.
- 20) **Armitage JM**, Williams SJ, "Inhaler technique in the elderly", *Age and Ageing* 1988; 17:275-278.

- 21) **Rajeev Thachil**, "Patients education on the correct technique of metered dose inhaler: Does it serve the purpose?" *Chest* 2000; 118(suppl4): 1875.
- 22) **Turner MO**, Gafni A, Swan D, FitzGerald M, "A review and economical evaluation of bronchodilator delivery methods in hospitalized patients", *Archives of Internal Medicine*, 1996; 56:2113-2118.
- 23) **O'Callghan C**, Barry P W, 'The science of nebulised drug delivery', *Thorax* 1997; 52 (suppl 2) : P31-44.
- 24) **Stainforth JN**, Lewis RA, and Tattersfield AE, "Dosage and delivery of nebulised beta agonists in hospital", *Thorax* 1983; 38:751-754.
- 25) **American Thoracic Society (ATS)**, Standardization of Spirometry, 1994 Update, *Am J Respir Crit Care Med*, 1995; 152:1107-1136.
- 26) **AARC Clinical Practice Guidline**, Spirometry, 1996 update, Reprinted from *Respir Care* 1996;41(7):629-636.
- 27) **Vincenzo Bella**, Riccardo Pistelli, Filippo Catalano, Raffaele Antonelli-incalzi, Vittorio Grassi, Gaetano Melillo, Dario Olivieri, and Franco Rengo, "Quality control of spirometry in the Elderly, The S.A.R.A. Study", *Am J Respir Crit Care Med*, 2000; 161: 1094-1100.
- 28) **BTS Guidelines**, 'Spirometry in practice' September 2000.
- 29) **Pays F**, 'Pharmacoeconomics: where is the link with pharmacokinetics?' *Pharm World Sci* 1997;19(2):73-81.
- 30) **Mandelberg Avigdor MD**, Sharon Tsechori MD, Sion Houri MD, Ely Gilad MD, and Israel E. Priel MD FCCP, "Is Nebulized Aerosol Treatment Necessary in the Pediatric Emergency Department?" *Chest* 2000; 117:1309-1313.
- 31) **Moss K**, Mc Donald A, Ferrara L, Myles D, Brischetto M, "Metered dose inhaler vs compressor driven nebulizer in the delivery of metaproterenol", *Chest* 1985; 88:53S

- 32) **Rebuck AS**, Chapman KR, Abbound R, Pare PD, Kreisman H, wolkove N, et al, "Nebulised anticholinergic and sympathomimetic treatment of obstructive airways disease in the emergency room", *Am J Med*; 1987:59-64.
- 33) **Anders Mellen**, Peter Arvidsson, Mona Palmqvist and Jan Lotvall, "Equivalent Bronchodilation with salbutamol given via pMDI or Turbuhaler", *Am J Respir Crit Care Med* 1999; 159:1663-1665.
- 34) **Walters EH**, cockroft A, Griffiths T, Rocchiccioli K and Davies BH, "Optimal dose of salbutamol respiratory solution: Comparison of three doses with plasma levels", *Thorax* 1981; 36:625-628.
- 35) **Thiadens H A**, Bock G H De, Houwelingen J C Van, Dekker F W, De Waal M W M, Springer M P, Postma D S, "Can peak flow measurements reliably identify the presence of airflow obstruction and bronchodilator response as assessed by FEV1 in primary care patients presenting with persistent cough?" *Thorax* 1999; 54:1055-1060.
- 36) **Campbell I A**, Colman S B, Mao J H, Prescott R J and Weston C F, An open, prospective comparison of beta-2 agonist via nebuliser, nebuhaler or pressurized inhaler by ambulance crew as emergency treatment. *Thorax* 1995, 50:79-80.
- 37) **MSH**, "Evaluating the Cost of Pharmaceuticals" Rational Pharmaceutical Management Plus Program; May 2001.
- 38) **Goodman DE**, Israel E, Rosenberg M, Johnston, Weiss ST, Drazen JM, 'The influence of age, diagnosis, and gender on proper use of metered dose inhalers', *Am J Respir Crit Care Med* 1994;150(5):1256-1261.
- 39) **Kesten S**, Zive K, Chapman KR, 'Pharmacist knowledge and ability to use inhaled medication delivery systems', *Chest* 1993;104:1737-1742.
- 40) **Walker Roger**, Edwards Clive, 'Clinical Pharmacy and therapeutics', Churchill Livingstone: 1996, p327-362.

- 41) Zainudin BM, Biddiscombe M, Tolfree SE, Short M and Spiro SG, 'Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurized metered dose inhaler, as a dry powder, and as a nebulised solution; Thorax 1990, Vol 45, p 469-473.
- 42) Valerie Jones, Christophe Fernandez, Paul Diggory, "A comparison of large volume spacer, breath-activated and dry powder inhalers in older people", Age and Aging, 1999; 28:481-484.
- 43) Deborah Cook, Gordon Guyatt, Eric Wong, Roger Goldstein, Michel Bedard, Peggy Austin, Helen Ramsdale, Roman Jaeschke and Malcolm Sears, "Regular Versus as needed short-acting inhaled beta-2 agonist therapy for chronic obstructive pulmonary disease", Am J Respir Crit Care Med 2001; 163:85-90.
- 44) Felix S F Ram, Wright John, Brocklebank David, White John E S, "Systematic review of clinical effectiveness of pressurized metered dose inhalers versus other hand held inhaler devices for delivering β_2 agonists bronchodilators in asthma", BMJ 2001; 323:1-7.
- 45) Pierce RJ, McDonald CF, Landau LI, Le Souef PN, Armstrong JG, Mitchell CA, Francis PW, Martin AJ, Musk AW, Antic R, et al. "Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy", Med J Aust 1992 Jun 1; 156 (11): 771-4.
- 46) Summer W, Elston R, Tharpe L, Nelson S, and Haponik EF, "Aerosol bronchodilator delivery methods. Relative impact on pulmonary function and cost of respiratory care", Arch Intern Med 1989 Mar; 149(3): 618-23.

CHAPTER 8: ANNEXES

ANNEX 1 Questionnaire for physician

For evaluating the practice of using Bronchodilators (salbutamol) for the patients of air flow obstructions including asthma:

1) For treating Inpatients with airflow obstruction, which dosage forms (formulation) of the salbutamol will you preferred?

(a) Nebulizer (b) Metered dose inhaler (c) Tablets.

2) On discharging, which of the dosage form of salbutamol would you usually recommend to your patients with airflow obstruction?

(a) Metered dose inhaler (b) Tablets (c) None

3) Which dosage form would you think as better therapeutic agent as well as of lesser side effect for long-term treatment for patients with airflow obstruction?

(a) Tablets (b) Metered dose inhaler (c) No difference.

(4) In your view, what is the practice of giving Nebulisation therapy of salbutamol?

(a) With compressed air (b) With oxygen.

(5) What is the concentration of oxygen used to give Nebulisation therapy, if oxygen is used?

(a) 2L/min (b) 3L/min (c) 4L/min (d) 5L/min (e) 6L/min

(6) What is the normal adult dose of salbutamol given as Nebuliser?

... ml of salbutamol solution + ...ml of normal saline.

Equivalent to----- -mg of salbutamol.

(7) What is the adult dose preferred for Metered Dose Inhaler of Salbutamol?

... mcg salbutamol times a day (24 HOURS)

(8) Generally Metered Dose Inhaler is not practiced in Inpatients.

What might be the reasons?

(You can select one or more options)

(a) MDI is more expensive than Nebulizer, so patient cannot afford.

(b) MDI is less effective than Nebulizer.

- (c) *MDI is less convenient to use by the health workers.*
(d) *Patients not know the appropriate technique of using MDI.*

(9) If you feel patients can use Metered Dose Inhaler properly, will you recommend that on their discharge?

- (a) *Metered Dose Inhaler* (b) *Tablet* (c) *Sometimes*

Special reason if any.....

.....
(10) Do you perform spirometry evaluation of your patient with airflow obstruction?

- (a) *Yes* (b) *No* (c) *Sometimes*

(11) In your opinion, in Nepal, is there any comparative study performed using MDI and Nebulizer, for evaluating improvement of Lung Function?

- (a) *Yes* (b) *No*

Any reference:.....

Degree: -----

Specialization: -----

Hospital/Private clinic: -----

ANNEX 2 Patients informants

NEB NO:

MDI NO:

Randomized¹ Group:

Dhulikhel Hospital
Forms for Research study
Form No: 01

Age:	Sex:	Body Weight:
Educational status: Test pass / SLC / Intermediate / others / None		
Know writing Nepali: Yes / No Know Writing English: Yes/ No		
Understand Labeling instructions: Yes/ No		
Smoking Habits:		
Do you smoke:	Yes/ No	In Past: Yes/ No Pack Year:.....
If left smoking, when: / or/ Before.....years.		
~~Do~~ you take alcohol: Regularly/ sometimes/ No		
Occupation:		
Monthly income of Family: Per month's.....(about)		
No. Of members of Family:.....		
How many members are educated:.....		
Any of them is staying with you: Yes/ No		
Vital status on OPD		
OPD No:	Date:	Time...
BP:.....	Temperature:..... °C	Oxygen saturation:.....%
Pulse:...../min	Breathing Rate:...../min.	
Needs immediate oxygen therapy: Yes/ No		
Needs Immediate Beta-2 agonist: Yes/ No		
Already attended in past: Yes / No		
For same reason: Yes /No		
What might be (if not of same reason):		
Attended By:		
Doctors Name:		
Primary Diagnosis:	Date:	
Confirmatory Diagnosis:	Date:	
(Based on Lung Function Test)		
Needs Admission:		
Yes	No	

Inpatients Admission Date... Time: ...am/ pm

Inpatients admission No:..... Bed No:..... Discharge Date:..... Time:.....

¹ Research forms: By D.K.Aryal: "An open, prospective comparison of Beta-2 agonist given via Nebulizer and MDI in inpatients with airflow obstruction"

ANNEX 3 Metered Dose Inhaler Technique Score Chart

In patient number:

Date:

Group No:

MDI Group	Nebulizer Group

Days:

Date	Fist trial	Discharge day
▼		
SCORE		

S.N.	Steps	P. 1	P. 2	P. 3	D. 1	D. 2	D. 3
1	Shake vigorously						
2	Remove cap						
3	Hold upright						
4	Breath out gently, not fully						
5	Start breathing in slowly and deeply						
6	Actuate during inspiration						
7	Continue slow inhalation.						
8	No aerosol loss is visible						
9	Holds breathe 10 seconds.						
10	Next dose after 1 minute.						
	Total Score:						

- Score 1 for each correct step undertaken.
- This gives a score out of 10 that can be used to monitor a patient's performance and highlight any problem areas.

ANNEX 4: Patients Consent

Volunteer consent form

"An open, prospective comparison of beta-2 agonist (Salbutamol) given via nebulizer and Metered dose inhaler in inpatients with airflow obstruction."

I _____, age _____ having full capacity to consent, hereby volunteer/give consent as legal representative for myself to participate in research 'An open, prospective comparison of beta-2 agonist (Salbutamol) given via nebulizer and Metered dose inhaler in inpatients with airflow obstruction' under the direction of Dipendra Kumar Aryal (principle investigator).

The purpose of this consent form is to document that I am freely volunteering for this study and the information collected will be used for local purposes only. The implications of my voluntary participation; duration and the purpose of the research study; the methods and the means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by an authorized principle investigator whose signature appears below.

The name and results obtained will be kept confidential and I understand that I may, at any time during this study, revoke my consent and withdraw from the study without penalty or loss of benefits, and I may be withdrawn from the study without my consent.

I give my permission for determining Lung function and using MDI or Nebulizer during my treatment in Dhulikhel hospital.

Name of volunteer

Date

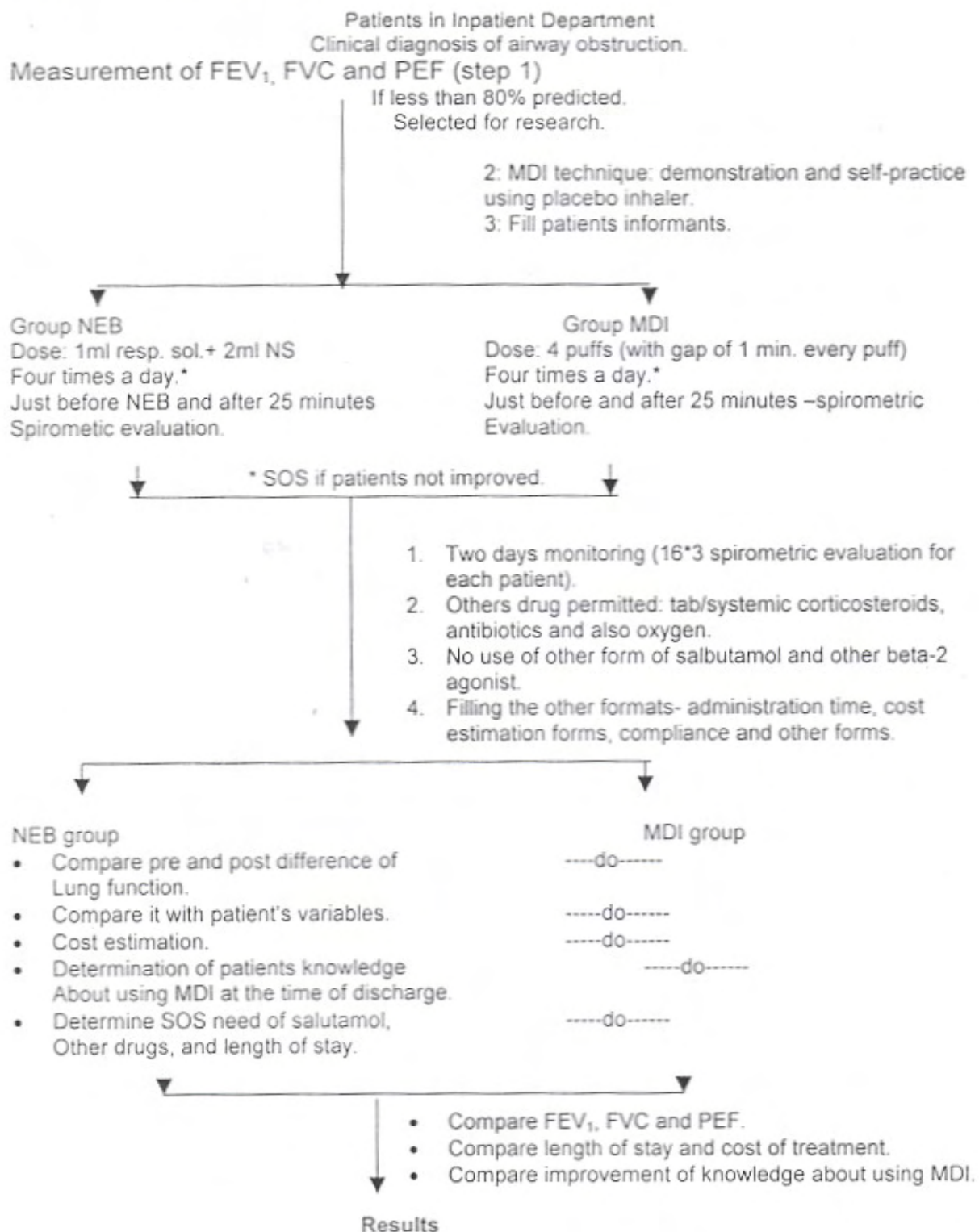
Signature of volunteer

Name of witness

Date

Signature of witness

ANNEX 5 Experiment design flow chart



ANNEX 6: Definitions used in Nebulization therapy

- Aerosol outputs: the mass per minute of particles in aerosol form produced by the nebulizer.
- Respirable particles: particles $<5\ \mu\text{m}$ diameters.
- Respirable fraction: the mass of respirable particles expressed as percentage of the aerosol output.
- Respirable output: the mass of respirable particles produced per minute (aerosol output* respirable fraction).
- Drug output: the mass of drug produced per minute as an aerosol.
- Mass median diameter: the diameter of the particles such that half the mass of the aerosol is contained in smaller diameter particles and half in larger.
- Mass medium aerodynamic diameter (MMAD): the diameter of a sphere of unit density that has the same aerodynamic properties as a particle of median mass from the aerosol.
- Nebulization time: the nebulization time is the time from starting nebulization until continuous nebulization has ceased. The time taken to deliver a drug is important for patient for patient compliance. Nebulization time for bronchodilators should be less than 10 minutes.
- Nebulization end point: 'Dryness' is a difficult end point for patients to recognize. It may be better for patients to be advised to nebulizers for about a minute after 'spluttering' occurs. Patients need to know how long this should take when their equipment is working correctly.

-
- Tapping: tapping the Nebulizers chamber when the solution begins to 'splutter' increase the volume output.
 - Facemasks and mouthpieces: bronchodilator responses are the same whether masks or mouthpieces or mouthpieces are used. The choice should therefore depend upon convenience; for example, masks are better for emergencies – and patient preference. Facemasks should be tight fitting. Patients should breathe with an open mouth. For ipratropium bromide, mouthpieces should be preferred to masks if there is possibility of glaucoma.
 - Cleaning: nebulizers used for bronchodilator therapy should be disassembled, washed in warm water with a little detergent at least once a day, and carefully dried. Then nebulizer should be run empty for a moment or before the next use.
 - Multiple uses: it may be of single use or of single patient use as indicated by manufacturer.