Original Article

Lack of efficacy of pre bronchoscopy inhaled salbutamol on symptoms and lung functions in patients with pre-existing airway obstruction

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ABSTRACT

Background: Fiberoptic bronchoscopy (FOB) may exaggerate symptoms and lung functions in patients with pre-existing airway obstruction. Interventions which can alleviate or minimize this procedure-related bronchospasm, especially in this high-risk group are, therefore, required. **Methods:** A double-blinded randomized controlled trial was conducted to evaluate the efficacy of 400 µg of inhaled salbutamol on patients with spirometric evidence of airflow obstruction planned for FOB. Patient's dyspnea, procedure tolerability, and change in spirometry were assessed before and after the procedure. **Results:** A total of 50 patients were enrolled (78% males), with a mean (standard deviation) age of 49.8 (6.2) years. There was a significant fall in % predicted FEV_1 within each group compared to their respective pre-bronchoscopy values. However, no significant difference in the % predicted or absolute FEV_1 level was observed between the two groups. Similarly, although both groups experienced increased dyspnea immediately following FOB, this difference was not significant between the two groups either on the Borg or visual analog scale scales. Pre-FOB anxiety levels and the tolerability of the procedure as assessed by the bronchoscopist were similar in both groups. **Conclusion:** FOB in patients with pre-existing airway obstruction aggravates cough and dyspnea, with a concomitant decline in FEV_1 and FVC. The administration of pre-FOB inhaled salbutamol does not have any significant beneficial effect on procedure-related outcomes.

KEY WORDS: Bronchoscopy, salbutamol, spirometry

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INTRODUCTION

Fiberoptic bronchoscopy (FOB) is a critical tool for the evaluation and treatment of respiratory disorders and the indications for its use are steadily increasing. Although FOB is generally a safe procedure, some degree of morbidity and complications such as laryngospasm (0.6%), vomiting (0.1%), vasovagal syncope (0.05%), epistaxis (0.02%), and bronchospasm (0.02%) are well known.[1] Major complications such as respiratory failure (0.2%), pneumothorax (0.16%), hemorrhage (0.12%), airway obstruction, cardio-respiratory arrest, arrhythmias, pulmonary edema, and pneumonia have also been reported.[1-11]

Within the airways, FOB results in mild increase in airway obstruction,[12] airway resistance, and thereby hypoxemia that is usually transient.[13] However, in patients with pre-existing airway obstruction/airflow limitation such as chronic obstructive pulmonary disease (COPD), the hypoxia may be severe and persistent, with consequently

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higher morbidity.[12,14] In this scenario, interventions which can alleviate or minimize this procedure-related bronchospasm, especially in this high-risk group are, therefore required.

Various sedatives,[15,16] antitussives,[17-19] topical anesthetics,[17-19] and anticholinergics[20-22] have been tried in an attempt to improve bronchoscopy-related outcomes, with variable success. However, sparse data are available on use of inhaled short-acting bronchodilator agents (SABA) such as salbutamol, especially in patients with airway obstruction undergoing bronchoscopy. The direct effects of inhaled SABA on procedure-related outcomes are not very well defined. This study was therefore conducted to determine whether administration of inhaled SABAs before bronchoscopy in patients with underlying airway obstruction has any effect on procedure-related outcomes.

METHODS

This double-blinded randomized controlled trial was conducted at the All India Institute of Medical Sciences, New Delhi. Patients undergoing FOB were screened using spirometry and those having evidence of airway obstruction i.e., $FEV_1/FVC < 70\%$ were recruited after obtaining informed consent. Spirometry was done within 24 h prior to bronchoscopy as per the American Thoracic Society guidelines using a microprocessor-driven pneumotachometer manufactured by Morgan India Pvt. Ltd. (UK), 2001.[23] Patients planned for trans-bronchial lung biopsy were excluded due to concerns of pneumothorax in case of post-procedure spirometry.

Baseline evaluation
A detailed history including the presenting complaints, smoking or indoor biomass exposure, occupation, associated comorbidities, and past illnesses was elicited, followed by a thorough clinical examination. Current smokers were defined as all patients currently smoking or those having quit within 3 months. All subjects were asked to grade their level of dyspnea and cough prior to the procedure using the modified Borg scale[24,25] and a visual analog scale (VAS).[26-28]

Bronchoscopy procedure
All the screened subjects were asked not to use short acting β_2 agonists 4–6 h prior to FOB. Randomization was done through arbitrary allocation based on a computer-generated random list of numbers to divide the subjects into two groups—the intervention group (salbutamol) and the placebo group.

To the intervention group, 400 µg of salbutamol was administered using a metered dose inhaler (MDI) with a spacer; to the placebo group, an identical looking placebo was administered 15 min before bronchoscopy by a staff nurse in a double-blinded fashion, with both the investigators and subjects being unaware of the contents of the inhaler. The identical placebo contained the Propellant HFA 134a, i.e., it contained only the propellant used in a standard MDI without the medication. FOB was performed by the same physician throughout the period of study, who also graded the degree of cough, pre-procedure anxiety, and overall patient's tolerability of the procedure on the VAS, before and after FOB. As per our bronchoscopy protocol, no injectable sedatives are administered to any patient unless specifically indicated. All procedures were performed using 2% topical lignocaine as throat sprays and "spray as you go" technique during scope insertion.

Post procedure
Post-FOB, the subjects were observed for any immediate complications and were asked to grade the severity of their dyspnea and cough post procedure on a Borg scale and a VAS. Spirometry was repeated within 2 h following the procedure. Figure 1 depicts the method of recruitment, intervention, and outcome measurements.

Statistical analysis
Post-FOB, deterioration in predicted $FEV_1 \geq 5\%$ compared to the pre-FOB value was taken as the primary outcome. All data were managed on an excel spreadsheet. Statistical analysis was done using StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP software. Two-tailed $P < 0.05$ was considered statistically significant. Results were expressed as frequencies and percentages for binary and categorical variables and as mean (standard deviation [SD])/median with interquartile range for continuous variables. Comparison between two groups was done using Student's *t*-test and Rank-sum test
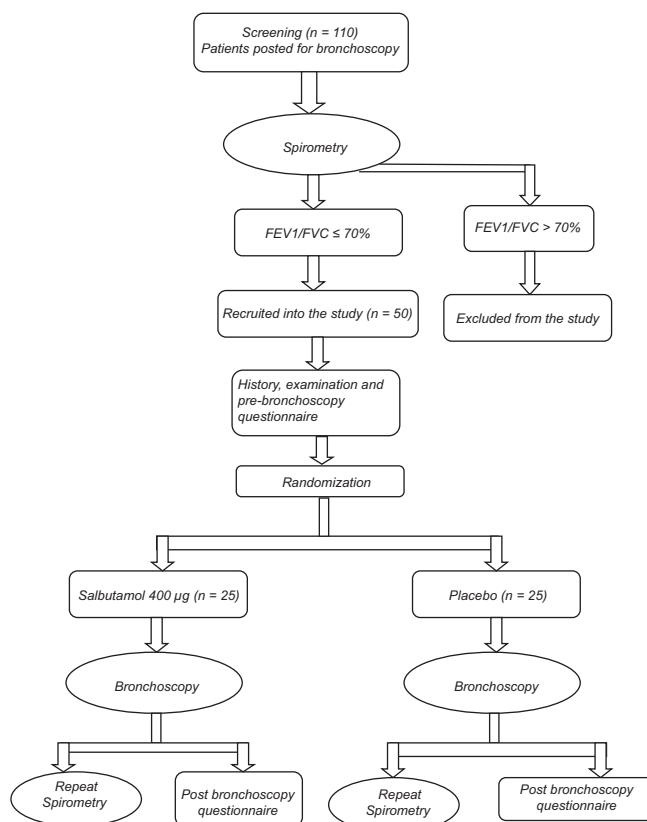

Figure 1: Representation of the study methodology and design

for quantitative variables and Chi-square test for qualitative variables.

RESULTS

A total of 50 patients were enrolled (78% males), with a mean (SD) age of 49.8 (6.2) years. Of these, 35 patients (70%) were current smokers. Thirteen subjects (26%) were on regular inhaled medications (long-acting β_2 agonists and inhaled anticholinergics in combination with steroids or alone) [Table 1].

There was a significant fall in % predicted FEV1 within each group compared to their respective pre-bronchoscopy

Table 1: Baseline characteristics of the study group

Variable	Salbutamol group (*n*=25)	Placebo group (*n*=25)	*P*
Age (years)	50.7 (11.5)	48.9 (13.2)	0.6
Males/females	20/5	19/6	0.5
Inhaled medication use (%)	7 (28)	6 (24)	-
Baseline pulmonary function			
FVC (L)	3.8 (0.6)	2.8 (0.8)	0.6
FEV_1/FVC	61 (6)	60 (9)	0.6
FEV_1 (L)	2.1 (0.6)	1.7 (0.7)	0.1
% predicted FEV_1	59 (52-67)	55 (47-61)	0.4
Current smokers (%)	19 (76)	16 (64)	
Comorbidities			
Chronic kidney disease	1	1	-
Diabetes mellitus	2	1	-
Hypertension	4	2	-
Hypothyroidism	0	2	-

All values expressed as mean (SD), median (IQR) or number (%). SD: Standard deviation, IQR: Interquartile range, FEV_1: Forced expiratory volume in the first second, FVC: Forced vital capacity

Table 2: Comparison of various parameters between salbutamol and placebo groups

Parameter	Salbutamol group (*n*=25)	Placebo group (*n*=25)	*P*
% predicted FEV_1			
Pre-FOB	59 (52-67)	55 (47-61)	0.6
Post-FOB	51 (45-59)	45 (36-54)	0.1
Change post-FOB	8 (6-10)	10 (7-11)	0.1
Dyspnea Borg scale			
Pre-FOB	2.4 (1.1)	2.4 (0.9)	0.9
Post-FOB	5.2 (1.6)	5.8 (1.7)	0.4
Change post-FOB	2.8 (1.5)	3.3 (1.2)	0.2
Dyspnea VAS score			
Pre-FOB	24.3 (10.8)	25.6 (8.8)	0.6
Post-FOB	50.9 (20.9)	58.1 (15.9)	0.2
Change post-FOB	26.0 (15.0)	32.5 (12.1)	0.1
Cough severity in VAS			
Pre-FOB	21.2 (11.6)	23.7 (5.4)	0.3
During procedure	38.5 (10.4)	40.2 (8.4)	0.5
Post-FOB	38.9 (20.3)	45 (15.2)	0.2
Change post-FOB	17.8 (17.6)	21.3 (14.5)	0.4
Preprocedure patient anxiety (VAS)	20.5 (6.1)	22.7 (6.2)	0.2
Tolerability of procedure (VAS)	73.3 (4.5)	74.5 (4.4)	0.3
Duration of bronchoscopy (min)	12.9 (3.5)	11.6 (2.7)	0.1
Lignocaine quantity (ml)	17.6 (4.1)	18.2 (4.3)	0.7

All values expressed as mean (SD) or median (IQR). FVC: Forced vital capacity, FEV_1: Forced expiratory volume in the first second, SD: Standard deviation, IQR: Interquartile range, FOB: Fibreoptic bronchoscopy, VAS: Visual analog scale

values. However, no significant difference in the % predicted or absolute FEV_1 level was observed between the two groups. Similarly, although both groups experienced increased dyspnea immediately following FOB, this difference was not significant between the two groups either on the Borg or VAS scales. Pre-FOB anxiety levels and the tolerability of the procedure as assessed by the bronchoscopist were similar in both groups [Table 2].

Among the total bronchoscopic procedures, bronchoalveolar lavage (BAL), bronchial washings, and endobronchial biopsy were performed in 24 (48%), 26 (52%), and 23 (46%) patients, respectively. There were no major complications. Thirteen subjects developed minor complications, such as post-biopsy oozing/hypoxia which neither required termination of bronchoscopy nor hospitalization.

DISCUSSION

Our results suggest that pre-FOB inhaled salbutamol does not prevent the decline in pulmonary functions following bronchoscopy. At baseline, the FEV_1, % predicted FEV_1, FVC, % predicted FVC, and FEV_1/FVC were similar between the two groups. We also observed that although the FEV_1 and % predicted FEV_1 decreased in both groups, the degree of reduction in % predicted FEV_1 was lesser in the intervention group, although insignificantly. Whether this suggests a protective effect of pre-FOB salbutamol on pulmonary functions is difficult to conclude at this juncture. A larger sample size may be able to clarify the reliability of this observation.

We did not observe any significant difference in symptoms such as cough and dyspnea between the two groups before and after FOB, although both groups experienced aggravation of these symptoms following the procedure. Majority of our patients reported aggravation in the severity of dyspnea and cough following FOB. This may be due to the baseline disease characteristics and the fact that the study group had spirometry documented airway obstruction, which aggravated during FOB.

Aggravation of respiratory symptoms following FOB has been reported in previous studies which evaluated patients with pre-existing airway obstruction.[29] In contrast, Clayton *et al.*[30] observed that only 7.8% subjects reported increase in cough post FOB, possibly because they conducted the study on patients with normal spirometry, used atropine as premedication, and recorded only severe cough episodes.

The age and sex distribution were similar in the two groups. Hence, no bias due to the same would have affected the results, since it is known that lung function declines with advancing age.[31] Similarly, smokers were distributed evenly between the two study groups and hence, this factor is unlikely to confound the results.

Following FOB, the % predicted FEV reduced by ≥5% in 48 subjects (96%) (all subjects in the placebo group and 23 (92%) in the intervention group). This figure is higher than that reported in some prior studies,[29,32] probably because we performed the post-bronchoscopy spirometry relatively earlier than other researchers, majority of times within 1–2 h following FOB. Another reason may be the higher proportion of BAL procedures in our study (62%) compared to previous reports.[32] It has been previously demonstrated that BAL is associated with a greater deterioration in pulmonary function and % predicted FEV_1.[29]

The subjects in the salbutamol group found the procedure more tolerable than the placebo group; however, this change did not achieve statistical significance. Furthermore, the inhaled bronchodilator did not significantly affect the total time taken to complete each procedure.

Bronchoscopic procedures have been shown to decrease lung volumes in normal individuals as well.[33-36] The cause of these changes remains speculative. Two studies have demonstrated that lignocaine may induce bronchoconstriction in subjects with hyper-reactive airways, either due to prostaglandin $F_{2\alpha}$ mediation,[37] or due to stimulation of cough, and irritative reflexes in the airway.[38] .Matsushima *et al.*[34] suggested that the reduction in the cross-sectional area of the airways following the insertion of bronchoscope adversely affects pulmonary functions. Salisbury *et al.*[12] demonstrated persistent airway obstruction in patients with chronic airway obstruction by measuring changes in airway conductance (G_{aw}) after the vital capacity, FEV_1, and partial pressure of oxygen (PaO_2) had returned to baseline values. They suggested that bronchospasm itself was the most likely cause of this persistent narrowing of intrapulmonary airways.

The protective effect of other premedications, including aerosolized ipratropium bromide[22] and isoproterenol,[33] on post FOB decline in lung functions and FEV_1 has been demonstrated previously. However, we did not find any significant benefit of giving pre-FOB salbutamol on procedure-related outcomes. The utility of aerosolized and intramuscular atropine in preventing the deterioration in pulmonary functions has shown conflicting results.[17,30,39] However, it should be noted that none of these studies specifically targeted patients with pre-existing airway obstruction. Stolz *et al.*[32] specifically attempted to evaluate the effectiveness of a 200 µg of inhaled β_2 agonists in patients with COPD undergoing bronchoscopy and observed that this intervention did not improve safety or prevent decline in FEV_1 following FOB. Most literature investigating the effect of pre-FOB bronchodilators in asthma has demonstrated favorable results in terms of reduction in the change in lung volumes, the incidence of wheezing, and oxygen desaturation,[29,40,41] primarily by reversing the bronchoconstriction.[29]

We used a dose of 400 µg inhaled salbutamol in our patients, without any demonstrable adverse effects. Hattotuwa *et al.*[42] used inhaled salbutamol in a much higher dose of 2.5 mg in patients with moderate and severe COPD and demonstrated superior procedure safety. Paradoxically, they also reported a 2.0% incidence of adverse events requiring hospital treatment; causation of these events with salbutamol dose was; however, not conclusively demonstrated.

The total dose of topical lignocaine used was similar in both groups of the current study and that which has been used in most previous studies.[32,30,39] Lignocaine has been implicated as a cause of deterioration of pulmonary function during bronchoscopy,[36-38] hence, minimizing the topical usage of lignocaine may prevent FEV_1 decline although this factor was not tested in our study.

This study has some obvious limitations. The pre-FOB spirometric reversibility status was not known for the majority of patients; hence, the diagnosis of existing obstructive airway disease could not be made or ruled out. Second, the sample size was not adequately powered to provide statistically-clearer differences between spirometric values of both groups before and after FOB. Third, since all patients had to be discharged within 2–3 h following the procedure, spirometry was repeated only once after FOB. Finally, a subgroup of patients was already receiving inhaled medications on a regular basis, hence, salbutamol represented additional treatment on top of a combination therapy of long-acting β_2 agonist, anticholinergics, and/or inhaled steroids. While no additional benefit could be demonstrated in either case, this may have influenced our results. In spite of these limitations, this age and sex matched, randomized double-blinded trial provides useful insights regarding the effect of pre-FOB inhaled salbutamol on post-procedure symptoms and pulmonary functions.

Our study concludes that FOB in patients with pre-existing airway obstruction is associated with aggravation of cough and dyspnea, with a concomitant decline in FEV_1 and FVC. The administration of pre-FOB inhaled Salbutamol does not have any significant beneficial effect on procedure- related outcomes.

Conflicts of interest
There are no conflicts of interest.

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