

Research Article

A study of the relative bronchodilator responsiveness in smoker asthmatics

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ABSTRACT

Background: Anticholinergic agents established bronchodilator agents which are in use for treatment of asthma but with slow onset and late peak of action. In contrast adrenergic agents are potent bronchodilator with fast action. Beside bronchodilatation they also improve mucociliary transport and reduce release of inflammatory mediators.

Methods: After baseline spirometry at zero hour, sequential doses of salbutamol i.e. 100 micrograms were given every hour to achieve the fullest expression of a neuronal mechanism which was reflected as a plateau on dose response curve, after which the other agent, inhaled ipratropium of dose 80 micrograms was administered. This sequence was reversed on the next visit of the patient with the maximum limit of inhaled salbutamol to be 400 micrograms.

Results: More number of smoker asthmatics showed eosinophil counts less than 350/cu.mm than the non-smokers. Only salbutamol showed no significant difference in smokers, while on addition of ipratropium, there was a significant change. But in the non smokers, salbutamol alone showed a marked improvement.

Conclusions: For smoker asthmatics combination therapy is more useful than either agent used alone as both the sympathetic or parasympathetic tone is acting simultaneously.

Keywords: Bronchodilators, Asthma, Smokers, Salbutamol, Ipratropium

INTRODUCTION

Asthma has attracted a great deal of attention over the centuries because its clinical manifestation of breathlessness and wheezing present themselves in a dramatic manner. The incidence, prevalence and severity of asthma are increasing throughout the world. The prevalence of asthma is estimated to be around 1.2 to 6.3% in adults in most countries and in India it is reported to be around 2.38%.¹⁻⁶

In the present scenario we are facing a worldwide epidemic of asthma, which is probably attributed to a number of factors associated with changes in

environment and lifestyle. Cigarette smoking is overwhelmingly the most important etiological agent in the development of COPD.⁷ Various investigators have reported that cigarette smoking is associated with increased airway responsiveness in asymptomatic as well as in symptomatic smokers.⁸⁻¹¹

Anticholinergic agents are in use for treatment of asthma in India for many centuries. But their use was associated with many systemic side effects. Hence their use is supplanted by development of sympathomimetic agents. With development of synthetic quaternary anticholinergics, there is renaissance in the use of these agents. At present they are well established

bronchodilator agents. These agents mainly have slow onset and late peak of action.¹²

In contrast adrenergic agents are potent bronchodilator with fast action. Beside bronchodilatation they also improve mucociliary transport and reduce release of inflammatory mediators.¹³

Their different sites of action to relieve airway obstruction in asthma and COPD indicate that their combined use will result in additive or synergistic response; so many studies were conducted in this regard. In some studies beta-2 adrenergic agonists have been found to be best to reach the maximum achievable bronchodilatation.^{14,15} However, in some studies patients showed additional broncho-dilatation when anticholinergic agent was given after the adrenergic agent. Among them this response was more significant in elderly and in patient with emphysema.^{16,17}

The present study was aimed at assessing the predominant autonomic control and maximum bronchodilatation in asthmatics who smoke and to compare the bronchodilator response to ipratropium and salbutamol.

METHODS

96 patients of bronchial asthma attending TB & Respiratory Medicine outpatient and inpatient wards of Mamata Medical College and General Hospital, Khammam, India. Patients with acute severe asthma, recent respiratory tract infection in preceding six weeks, those with chest X-ray showing any demonstrable bulla, parenchymal scars, cavity, mass or any opacity or any other significant medical/surgical disease like narrow angle glaucoma, prostatic diseases, bladder outlet obstruction, pregnant female patients and patients having congenital or organic heart disease were excluded from the study.

A detailed clinical history including age, height, weight, BMI, occupation, educational status, symptoms with special reference to cough, shortness of breath wheezing, history of allergic manifestations in the form of allergic rhinitis, eczema and urticaria and any other history of allergic factors were carefully noted. Any history of severe exacerbations of asthma in the past two years, the number of admission or number of emergency visit that were made was recorded. Family history of asthma and allergic manifestations was also taken.

Blood for routine analysis like complete blood picture, hemoglobin, leucocyte counts both total and differential, erythrocyte sedimentation rate, blood glucose, urea were performed. Urine was collected for microscopic examination, sugar and albumin estimation and stool for ova and cyst examination. Chest X ray (PA view) was done for all patients.

The two mechanisms controlling airway caliber (i.e. sympathetic and parasympathetic) were tested by using

the beta 2 adrenergic drug salbutamol, and anticholinergic drug ipratropium bromide.

After baseline spirometry at zero hour, sequential doses of salbutamol i.e. 100 micrograms were given every hour to achieve the fullest expression of a neuronal mechanism which was reflected as a plateau on dose response curve. Once the plateau was reached, or side effects appeared or the maximum dose of 600 micrograms was given, the other agent, inhaled ipratropium of dose 80 micrograms was administered, to see whether additional bronchodilatation occurred or not. This sequence, in which the two drugs were administered, was reversed on the next visit of the patient with the maximum limit of inhaled salbutamol to be 400 micrograms.

Vital signs like pulse rate, blood pressure and signs and symptoms of overdose were closely monitored. Side effects such as coarse tremors, palpitations, heart rate >25% of base line, blurring of vision, confusion of excitement were looked for.

Both the drugs were administered as aerosolized solutions via metered dose inhalers with spacer, which delivered fixed amount of drug per activation (puff).

All the participants were asked to withhold their bronchodilator agents 24 hours prior to study. Steroid dose was not omitted and patients on maintenance steroids were included in the study. All the participants were asked to withhold smoking prior to study and no smoking was allowed on the day of study.

The statistical methods used were unpaired t test for inter group comparison and paired t test for intragroup comparisons, Chi square test for smoking and non-smoking comparisons. The data was expressed as mean±SD for continuous variables.

RESULTS

Out of the 96 patients in the study, 48 each were smokers and non-smokers. Most of the patients in both the categories belonged to the 20-29 age group. The mean age in smokers was 30.25±6.31 years and in non-smokers was 27.88±5.84 years. There was no significant difference in the age group among smokers and non smokers. Most of the patients were men while 14 of them were females of whom 6 were smokers. Among the smokers, 11-15 years was the most common duration of illness while it was 6-10 years among the smokers, though there were a significant number of them in the 11-15 year duration also. The history of illness was similar in both the categories, though the familial history was higher among the non-smokers as compared to the smokers (Table 1).

28 (58.3%) patients among the smoker asthmatics showed eosinophil counts less than 350/cu.mm. While only 18 (37.5%) patients among the non-smokers showed eosinophil counts more than 350/cu.mm³ (Table 2).

Table 1: Demographic and clinical details of the smokers and the non smokers.

Details	Non Smokers	Smokers
Smoking-habits (n=96)	48	48
Age		
20-29	26	30
30-39	16	16
40-49	6	2
Sex		
Men	40	42
Women	8	6
Duration of illness		
1-5 years	4	4
6-10 years	6	22
11-15 years	18	13
16-20 years	2	9
>20 years	10	0
History of allergy		
Present	26 (54%)	20 (41.6%)
Absent	22 (46%)	28 (58.4%)
Familial history of asthma		
Present	30 (62.5%)	22 (45.8%)
Absent	18 (37.5%)	26 (44.2%)
No of ER visits in past 2 years		
0	28 (58.3%)	12 (25%)
1	12 (25%)	14 (29.2%)
2	8 (16.7%)	14 (29.2%)
≥3	0 (0%)	8 (16.7%)

Table 2: Absolute eosinophil count among the smokers and non-smokers.

Count/ Cu MM	Non smokers		Smokers	
	With H/O allergy	With Out H/O allergy	With H/O allergy	Without H/O allergy
<350	6 (12.5%)	12 (25%)	10 (20.8%)	18 (37.5%)
350-440	4 (8.3%)	4 (8.3%)	2 (4.2%)	6 (12.5%)
440-600	8 (16.7%)	6 (12.5%)	6 (12.5%)	4 (8.3%)
> 600	8 (16.7%)	0 (0%)	2 (4.2%)	0 (0%)
Total	26 (54.2%)	22 (45.8%)	20 (41.7%)	28 (58.3%)

Improvement in FEV₁ and FVC after giving salbutamol as first drug showed no significant difference among smokers. However, significant improvement was seen in the smokers group as compared to non smokers after giving ipratropium as second drug (p<0.001) at 15, 30 and 60 min. While in FEV₁/FVC, improvement in ratio was significantly more in non smoker group as compared to smokers after giving salbutamol as first drug (p<0.001). But after giving ipratropium as second drug improvement was found to be more in smoker group as compared to nonsmokers at 15, 30 and 60 min (p<0.001). Similar result was seen in the case of PEFr (Table 3).

Table 3: Comparison of improvement among asthmatics on first visit.

		Non-smoker		Smoker		P value
		Mean (litres)	observed Mean % improvement	Mean (litres)	observed Mean % improvement	
FEV ₁	At baseline	2.07±0.21		1.81±0.18		
	with salbutamol	3.43±0.23	67.04±12.98	3.0±0.16	66.64±13.6	>0.05.
	After pratriopium					
	At 15 min	3.42±0.23	-0.27±1.34	3.11±0.16	3.6±2.16	<0.001
	At 30 min	3.44±0.22	0.11±1.50	3.18±0.18	6.1±2.22	<0.001
	At 60 min	3.43±0.21	0.13±2.14	3.27±0.17	9.22±2.08	<0.001
FVC	At baseline	3.61±0.43		3.14±0.33		
	with salbutamol	4.71±0.21	31.98±14.05	4.30±0.21	38.17±12.93	>0.05
	After pratriopium					
	At 15 min	4.69±0.22	-0.44±0.67	4.35±0.21	1.29±2.9	<0.001
	At 30 min	4.68±0.21	-0.7±1.13	4.36±0.22	1.46±0.78	<0.001
	At 60 min	4.69±0.22	-0.56±1.4	4.41±0.22	2.5±1.54	<0.001
FEV ₁ /FVC	At baseline	57.53±4.74		57.85±4.0		
	with salbutamol	73.37±4.23	28.24±11.60	69.83±4.77	21.10±9.72	<0.001.
	After pratriopium	73.39±4.51				
	At 15 min	73.86±4.53	0.01±1.31	71.79±4.92	2.86±3.20	<0.001
	At 30 min	73.66±4.23	0.67±1.6	73.62±4.84	5.40±2.60	<0.001
	At 60 min	319.04±27.77	0.39±1.77	75.36±4.73	8.01±2.94	<0.001
PEFR	At baseline			304.5±14.36		
	with salbutamol	514±21.30	62.08±13.55	479.29±12.72	57.66±6.98	>0.05
	After pratriopiu					
	At 15 min	513.75±21.17	-0.04±0.86	479.75±12.82	0.09±.62	>0.05
	At 30 min	513.33±22.45	-0.13±0.87	489.12±12.17	2.06±1.0	<0.001
	At 60 min	512.75±21.66	-0.24±0.67	505.75±14.59	5.52±1.39	<0.001

FEV: Forced expiratory volume, FVC: Forced vital capacity, PEFr: Peak expiratory flow rate.

Table 4: Comparison of improvement among asthmatics on second visit.

		Non-smoker		Smoker		P value
		Mean observed (litres)	Mean % improvement	Mean observed (litres)	Mean % improvement	
FEV ₁	At baseline	2.07±0.18		1.84±0.14		
	with ipratropium	2.48±0.15	20.06±7.06	2.60±0.15	41.95±4.57	<0.001
	After salbutamol					
	At 15 min	2.71±0.17	9.86±2.66	2.79±0.16	7.39±2.53	<0.001
	At 30 min	2.81±0.19	13.92±5.31	2.95±0.13	13.55±3.94	>0.05
	At 60 min	3.04±0.11	23.16±5.07	3.09±0.10	19.09±4.9	<0.001
FVC	At baseline	3.59±0.35		3.12±0.20		
	with ipratropium	4.08±0.28	14.49±10.83	3.96±0.26	27.01±8.19	<0.001
	After salbutamol					
	At 15 min	4.18±0.20	2.69±4.53	4.01±0.25	1.47±1.10	>0.05
	At 30 min	4.31±0.21	5.83±4.71	4.08±0.25	3.20±1.30	<0.001
	At 60 min	4.41±0.21	8.47±5.12	4.15±0.24	5.06±1.90	<0.001
FEV ₁ /FVC	At baseline	58.03±6.12		58.81±2.52		
	with ipratropium	60.87±4.99	5.5±9.3	65.90±4.14	12.13±6.92	<0.001
	After salbutamo					
	At 15 min	65.14±4.90	7.24±6.81	69.79±4.57	5.86±2.94	>0.05
	At 30 min	65.44±4.32	7.92±8.22	72.43±3.83	10.05±3.93	>0.05
	At 60 min	68.97±2.88	13.83±7.91	73.96±4.97	12.41±6.61	>0.05
PEFR	At baseline			305.71±12.08		
	with ipratropium	393.25±17.32	23.70±6.35	414.83±13.42	35.78±4.10	<0.001.
	After salbutamol					
	At 15 min	420.37±17.90	6.91±1.27	426.54±14.4	2.82±0.91	<0.001
	At 30 min	442.33±18.22	12.50±1.71	449.17±14.4	8.28±1.27	<0.001
	At 60 min	467.08±18.02	18.81±1.60	477.75±11.58	15.20±1.92	<0.001

In FEV₁ and FVC improvement was significant among smokers after giving ipratropium as first drug as compared to non-smokers (p<0.001). But improvement was significant in non-smoker asthmatics after giving salbutamol as second drug at 15 and 60 min (p<0.001) though no significant improvement was seen at 30 min in FEV₁. In FEV₁/FVC, improvement was significant after giving ipratropium in smokers as compared to non-smokers (p<0.001). However, more improvement was found after giving salbutamol as second drug in non-smokers at 15, 30 and 60 min though it was not statistically significant. Smokers showed significant improvement after giving ipratropium as first drug in PEFR as compared to non-smokers (p<0.001). However, non-smokers showed significantly more improvement in PEFR after giving salbutamol as second drug at 15, 30 and 60 min (p<0.001) as compared to non-smokers (Table 4).

DISCUSSION

Due to the irritating effect of tobacco smoke, as well as the association of cigarette smoke with respiratory illness, patients with asthma would seem to be a group that would avoid smoking entirely. However, this is not entirely true.

Prevalence of smoking with asthma has been reported to be quite high.¹⁸ Smoking too had been linked as an etiological factor in causation of asthma in some studies but not in others.^{19,20} However, the corticosteroid resistance in smoker asthmatics has been well studied in recent few years.²¹ But studies regarding the relative bronchodilator response of airways to adrenergic versus anticholinergic agents in smoker asthmatics are lacking.

In the present study baseline value of FEV₁, FVC and PEFR were found to be significantly lower in smoker asthmatics as compared to the non-smoker asthmatics (p<0.001). However, no significant difference is found in level of FEV₁/FVC ratio among smoker and non-smoker asthmatics. The Copenhagen city heart study which includes longitudinal measurement of FEV₁ over 15 year period found that the average decline in FEV₁ in asthmatic smokers is more than non-smokers.²² Apostol G et al found that the decline in FEV₁ was 8.5% in non smokers without asthma, 10.1% in nonsmokers with asthma and 11.1% in smokers without asthma.²³ Similar case was found INA study by James et al.²⁴

In the present study, non-smoker asthmatics showed significant improvement in all the four parameters vis. FEV₁, FVC, FEV₁/FVC ratio and PEFR after giving supramaximal dose of salbutamol. However, no significant improvement was noted at 15, 30 and 60 min

after giving ipratropium as second drugs in non-smoker asthmatics. But on second visit, we found significant response in the FEV₁, FVC, FEV₁/FVC ratio and PEFR from the baseline after giving the ipratropium as the first drug in supramaximal doses (p<0.001). There was also significant response in all these parameters after giving salbutamol as the second drug (p<0.001). Though both the drugs were showing significant improvement as the first drug but it was significantly more in salbutamol group (p<0.001).

Our findings are consistent with the study conducted by Jindal et al and Wempe et al.^{14,25} In contrast, in a study by Brophy et al, salbutamol and ipratropium in combination were used in acute severe asthma, and it was concluded that the addition of ipratropium reduced hospital admission and increased FEV₁, by 75% when compared with groups receiving beta-2 stimulants alone.²⁶

Our study showed that smoker asthmatics showed significant response in FEV₁, FVC, FEV₁/FVC ratio and PEFR after giving salbutamol as the first drug (p<0.001). Significant response was also noted in FEV₁, FVC and FEV₁/FVC ratio after giving ipratropium as second drug at 15, 30 and 60 min (p<0.001). However, there was no significant response seen at 15 min in PEFR but significant at 30 and 60 min (p<0.001). On the second visit, in smoker asthmatics, response was significant after giving ipratropium as first drug. Response in FEV₁, FVC, FEV₁/FVC ratio and PEFR improvement was significant after giving ipratropium as first drug (p<0.001). Significant improvement was also noted in FEV₁, FVC, FEV₁/FVC ratio and PEFR after giving salbutamol as the second drug (p<0.001).

These results show that either the adrenergic tone is decreasing or there is increase in cholinergic tone in smoker asthmatics or both the phenomenon are occurring which was in concordance to similar studies by Gross et al and Laustiola et al.^{16,27}

Emergency visits as a result of exacerbations were also found to be higher in number of studies.^{28,29} In this study significant emergency admission rates were found in smoker asthmatics as compared to non-smoker asthmatics. They were found to be in greater need for rescue medication, thus causing more frequent emergency room visits.

Our study shows that for smoker asthmatics combination therapy is more useful than either agent used alone as both the sympathetic or parasympathetic tone is acting simultaneously.

CONCLUSION

The baseline pulmonary function test was found to be lower in smoker asthmatics as compared to non-smoker asthmatics and the adrenergic tone is predominant as they showed maximal response with the salbutamol alone and

Ipratropium is not needed as a second drug to achieve maximal bronchodilatation. But the reverse is not true as the ipratropium is not sufficient to achieve maximal bronchodilatation as salbutamol is able to cause further bronchodilatation when added as second drug. While in smokers both adrenergic and cholinergic tone is acting simultaneously as it is possible to attain further bronchial dilatation with ipratropium when the salbutamol is used as first drug. Reverse is also true.

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