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Original Research Article

Efficacy of relative bronchodilatation of salbutamol and ipratropium in smokers and non-smokers with asthma

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ABSTRACT

Background: Asthma is an age old disease with breathlessness and wheezing as a part of its clinical manifestations. Adrenergic drugs are also used as bronchodilators as they have a fast action. They are also useful in improving the mucilary transport and in the reduction in the release of inflammatory mediators.
Materials and Methods: Sympathetic and parasympathetic mechanisms for airway calibre control were tested on 80 patients above the age of 18 years with bronchial asthma using salbutamol (beta 2 androgenic drug) and ipratropium bromide (anticholinergic drug).
Results: The base line values in our study, of the smokers and non-smokers on Day 1, where Salbutamol was given as the primary drug with Ipratropium as the second drug showed a significant difference in the FEV1, FVC and PEFR values, while there was no significant difference in the FEV1/FVC ratio. After giving salbutamol to the maximum effect, in comparison to the base line, there was a considerable improvement in all the values in both the smokers and non-smokers. But on giving Ipratropium, there was no further substantial improvement in the values in the non-smokers, but a significant improvement was seen among the smokers. On day two, there was a significant improvement in the FEV1, FVC, FEV1/FVC and PEFR values compared to the base line values, and on giving salbutamol, there was a substantial increase in the expiration volume in both smokers and non-smokers.
Conclusions: In case of smoker asthmatics, a combination therapy of Salbutamol and Ipratropium is more useful.

1. Introduction

Asthma is an age old disease with breathlessness and wheezing as a part of its clinical manifestations. It is one of the diseases that is known to affect all the age groups.[1] Asthma is prevalent throughout the world and its occurrence is rapidly increasing. Around 1.2 to 6.3% of the adults in many countries are said to be asthmatics and in India, the occurrence is 2.38%.[2–6]

Asthma is generally said to be a disease that begins in childhood and becomes predominant by the time the patient is 40 years of age.[7] However, those who have an onset of the disease in adulthood have a lower lung function as compared to those with onset in childhood, although at this time the duration is much longer than the former.[8]

One of the most common causes of mortality, which can be prevented is smoking. It is one of the most common causes of chronic obstructive pulmonary disease (COPD). Quitting smoking has been established to reduce the risk of diseases such as lung cancer, strokes, cardiovascular diseases etc.[9,10]

There have been a few studies which have shown a negative association between smoking and pulmonary airways and respiratory allergy.[11–14] Intermittent asthma is often found among the smokers and some of these patients continue to smoke without worsening the symptoms. However, the patients who have been long time smokers show a decreased lung capacity.[15–17]

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A patient with a family history of atopy and smoking habit further increases his chances of developing respiratory allergic symptoms such as allergic rhinitis and bronchial asthma.[18]

The most common mode of treatment for asthma is inhaled corticosteroids. Patients with moderate and severe asthma respond to corticosteroids effectively and show improvement in the asthma symptoms and lung functions.[19,20] In India, for a very long time anticholinergic drugs are used for the treatment of asthma, but it has a few side effects. Therefore, with advancement in development of drugs, now, a quaternary generation of anticholinergic drugs are being used for effective treatment. Adrenergic drugs are also used as bronchodilators as they have a fast action. They are also useful in improving the mucilary transport and in the reduction in the release of inflammatory mediators.[21]

There are few studies demonstrating the effects of smoking on patients with asthma and the responsiveness to bronchodilators. Hence this study was taken up to throw more light on the effect of Salbutamol and Ipratropium alone and in conjunction with each other among the smoker and non-smoker asthmatics.

2. Materials and Methods

This study was undertaken by the Department of Pulmonology at Narayana Medical College during the period of 18 months from March 2018 to October 2019. 80 patients above the age of 18 years with bronchial asthma, out of which 40 were smokers and 40 were non-smokers were included into our study.

Patients with severe acute asthma, a recent respiratory illness requiring antibiotics, a positive chest X-ray for parenchymal scars, mass, cavity or any opacity, other diseases like prostatic diseases, narrow angle glaucoma, obstruction of bladder outlet were excluded from the study.

This study was cleared by the Institutional Ethical Committee. The nature of the study was explained thoroughly to the patients and the relatives and informed consent was taken from all the patients. Those who refused to give the informed consent were excluded from the study.

Detailed demographic data such as age, sex, height, weight, body mass index, educational status, occupation etc. were noted. Their smoking status were also noted. All the patients were subjected to a thorough medical examination. Respiratory disorders such as rhinitis, cough, shortness of breath, any allergic manifestations, eczema were taken into consideration. Exacerbations of asthma especially in the previous two years, earlier admission in hospital were noted. Family history of the patients with regards to asthma was also noted.

Blood was collected from the medial cubital vein for regular analysis such as complete blood picture, erythrocyte sedimentation rate, liver profile, lipid profile, random blood sugar were done. Complete urine analysis and sugar and albumin estimation was done with urine and stool was also collected for ova and cyst analysis. All the patients were subjected to chest X-ray.

Sympathetic and parasympathetic mechanisms for airway calibre control was also tested using salbutamol (beta 2 androgenic drug) and ipratropium bromide (anticholinergic drug).

At Zero hour, base line spirometry was done and every hour 100 μg sequential doses of salbutamol was given in order to attain the fullest expression of the neuronal mechanism (2 puffs). On the dose response curve, this was reflected as a plateau. Once this was reached or if there were any side effects or a maximum of 600 μg was attained, 80 μg of ipratropium was inhaled for further bronchodilatation and spirometry was done after 15 mins, 30 mins and 60 mins. In the next visit, this order of the administration of the drug was reversed till 400 μg of salbutamol, which was the maximum dose. These were introduced as aerosols via inhalers with fixed amount of drug delivery during the puff.

If the participants were on bronchodilators, during the duration of the study, they were asked to withhold those 24 hours prior to the start of the study. However, the steroid doses were continued. Smoking was not allowed during the study period.

In each visit, during the dosage, the vital signs were monitored closely. Any side effects, tremors, increase of heart rate by 25%, palpitations, blurring of vision were checked.

Statistical analysis was done using Microsoft excel and paired and unpaired t test.

3. Results

Most of the participants were men with 71/80 (88.75%) patients and 9 (11.25%) were women (Figure 1).

Most of the study participants (n=32) were between 31-40 years of age (40%), while 26 were between 21-30 years of age (32.5%). 16 (20%) were between 41-50 years and very few i.e., 4 patients (5%) were above the age of 50 years (Figure 2)

Among the smokers, the duration of the illness was predominantly between 6-10 years as seen in 25 (62.5%) of the patients, followed by 11 – 15 years in 11 (27.5%) of the cases, while among the non-smokers the most predominant duration was 11-15 years in 21 (52.5%) of the cases. A duration of 16-20 years and >20 years were seen in 8(20%) and 7 (17.5%) respectively. Among the Smokers, 21 (52.5%) of the patients had no history of asthma in the family but among the non-smokers, 27 (67.5%) had someone within the close family members with asthma. In 22 (55%) of the smokers, there was no history of allergy, while 18 (45%) of them had a allergy in the past. Among the non-smokers, 25 (62%) of the patients had a history of allergy, while 15 (37.5%) had no history of allergy. 16 (40%) of the smokers had visited the Emergency Room at least 2

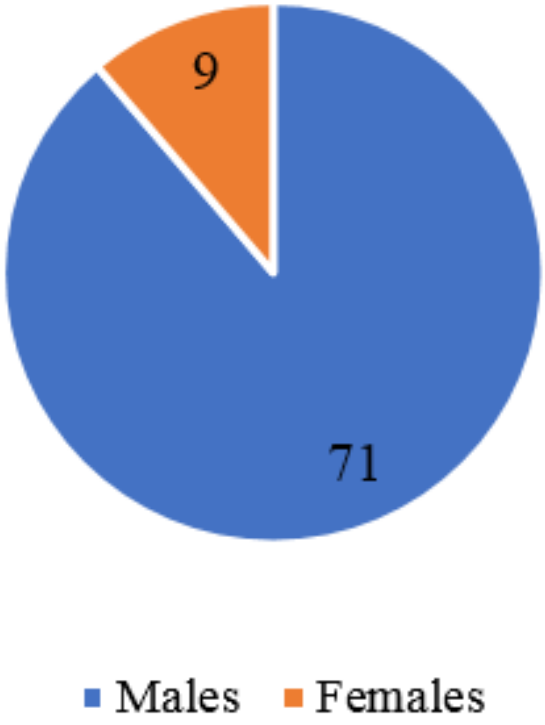

Fig. 1:

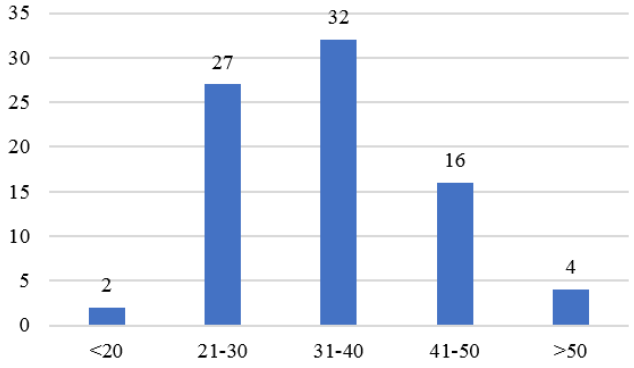

Fig. 2: Age wise distribution of patients

times in the past, 10 (25%) once and 7 (17.5%), the present time was the first time. However, 2 (5%) of the patients had been admitted into the ER more than 3 times in the past. Among the non-smokers, none of them visited the ER more than 3 times, while for 15 (37.5%) the present time was the first time. 11 (27.5%) of them visited twice earlier and 10 (25%) visited once before (Table 1).

Allergy such as urticaria or rhinitis was seen in 28 (70%) of the patients who smoked and 12 patients (30%) had no allergy, while among the non-smokers, 21 (52.5%) of the patients had allergy and 19 (47.5%) of them had no allergy. The eosinophil count among the patients with allergy was above 600 cumm in 2 (7.1%) of the cases, while 9 (32.1%) had a count between 440 – 600 cumm. A majority of 12 (42.9%) of them had eosinophil count of 350-440 cumm. Among the smokers with no allergy, most of them (7(58.3%)) had a count of < 350 cumm, while 3 (25%) had 350-440cumm and 2 (16.7%) had between 440-600 cumm. Among the non-smokers, 1 (4.8%) patient had an eosinophil count of >600cumm, while most of them 11 (52.3%) has <350. Among the non-smokers with no allergy, 8 patients (42.1%) each had an eosinophil count of 350-440 and <440 cumm (Table 2)

ON day 1 after the administration of salbutamol as the primary drug, the forced expiratory volume (FEV1) saw a significant increase compared to the baseline in both smokers and non-smokers. However, consecutively, on the administration of the second drug, i.e. Ipratropium, there was no significant increase in the FEV1 levels in the non-smokers, but the smokers saw a significant increase after 15, 30 and 60 mins. A similar case was seen in the Forced vital capacity, where there was no significant rise in the volume among the non-smokers after the administration od Ipratropium, while among the smokers it was significant in 15, 30 and 60 mins, but in both the cases, after the administration of the primary drug, there was a significant improvement. In the FEV1/FVC ratio, there was a considerable rise in the value after the salbutamol dose to around 74% in the non-smokers and around 67% among smokers, which was significant. But after the administration of Ipratropium, the non-smokers did not see an improvement while there was a significant improvement among the smokers. Similar was the case in the Peak Expiratory flow rate among the smokers and the non-smokers (Table 3)

On day 2, there was a significant rise in the mean maximal response of the patients for FEV1, FVC, FEV1/FEV and PEFR after the administration of Ipratropium in both the smokers and the non-smokers groups. After the administration of salbutamol, in both the groups, there was a steady improvement in all the pulmonary functions i.e., FEV1, FVC, FEV1/FVC, PEFR after 15 mins, 30 mins and 60 mins by spirometry (Table 4).

4. Discussion

The morbidity and the mortality due to asthma is more among the people who smoked rather than the people who didn't. The asthma symptoms among the smokers is very severe with urgent requirement of intervention.[22,23]

The visits to the emergency room are more seen among the patients who are asthmatics and smokers.[22] In the present study too, more number of smokers with asthma had prior emergency room visits rather than the patients who did not smoke. For only 17.5% of the smokers, the present visit was the first one, while among the non-smokers, this was the first visit for 37.5% of the patients.

Table 1: Demographic details:

Parameter	Smoker N=40	Percentage	Non smoker N=40	Percentage
Duration of illness				
1-5 years	1	2.5%	1	2.5%
6-10 years	25	62.5%	3	7.5%
11-15 years	11	27.5%	21	52.5%
16-20 years	3	7.5%	8	20%
>20 years	0	0	7	17.5%
History of asthma in family				
Yes	19	47.5%	27	67.5%
No	21	52.5%	13	32.5%
Previous history of allergy				
Yes	18	45%	25	62.5%
No	22	55%	15	37.5%
No of ER visits in the past 2 years				
0	7	17.5%	15	37.5%
1	10	25%	10	25%
2	16	40%	11	27.5%
3	5	12.5%	4	10%
>3	2	5%	0	0

Table 2: Eosinophil count among the smokers and non-smokers with and without allergy

Eosinophil count in cumm	Smokers		Non smokers	
	With Allergy N=28	With No Allergy N= 12	With Allergy N=21	With No Allergy N=19
Above 600	2 (7.1%)	0 (0)	1 (4.8%)	0 (0)
440-600	9 (32.1%)	2 (16.7%)	4 (19.1%)	3 (15.8%)
350-440	12 (42.9%)	3 (25%)	5 (23.8%)	8 (42.1%)
<350	5 (17.9%)	7 (58.3%)	11 (52.3%)	8 (42.1%)

Table 3: Pulmonary functions of the smokers andnon-smokers on day 1

Test		Mean Baseline value	Mean Maximal response after Salbutamol	Mean Response After Ipratropium 15min	30 min	60 min.
FEV_1 (liters)	Non Smokers	2.23 ± 0.68	3.47 ± 1.61*	3.48 ± 0.91	3.47 ± 1.32	3.48 ± 0.88
	Smokers	1.78 ± 0.15	3.03 ± 0.94*	3.10 ± 1.26*	3.17 ± 1.29*	3.26 ± 1.33*
FVC (liters)	Non Smokers	3.58 ± 0.55	4.67 ± 0.41*	4.66 ± 0.77	4.66 ± 0.82	4.68 ± 1.05
	Smokers	3.15 ± 1.84	4.29 ± 3.11*	4.33 ± 4.19*	4.38 ± 4.11*	4.42 ± 3.96*
FEV_1/FVC (%)	Non Smokers	59.61 ± 5.61	74.96 ± 6.19*	74.93 ± 5.03	74.03 ± 3.79	73.99 ± 6.19
	Smokers	55.39 ± 5.11	67.62 ± 4.91*	70.27 ± 4.22*	73.46 ±3.89*	76.18 ± 4.69*
PEFR (liter/sec)	Non Smokers	321.01 ± 24.11	512.89 ± 27.48*	513.01 ± 25.92	512.45 ± 27.26	512.83 ± 25.61
	Smokers	302.55 ± 11.49	47.28 ± 11.43*	478.14 ± 16.87*	485.22 ± 19.44*	502.84 ± 12.93*

*:p<0.001

Table 4: Pulmonary functions of the smokers andnon-smokers on day 2

Test		Mean Baseline value	Mean Maximal response after Ipratropium	Mean Response After Salbutamol		
				15min	30 min	60 min.
FEV_1 (liters)	Non Smokers	2.27 ± 0.24	2.51 ± 0.80*	2.73 ± 0.21*	2.82 ± 0.53*	3.07 ± 0.19*
	Smokers	1.80 ± 0.19	2.76 ± 0.64*	2.94 ± 0.76*	3.01 ± 0.91*	3.15 ± 1.51*
FVC (liters)	Non Smokers	3.46 ± 0.49	4.16 ± 0.23*	4.35 ± 0.53*	4.52 ± 0.56*	4.66 ± 0.17*
	Smokers	3.19 ± 1.96	4.0.29 ± 0.26*	4.36 ± 0.28*	4.39 ± 0.73*	4.44 ± 0.76*
FEV_1/FVC (%)	Non Smokers	61.04 ± 5.78	59.24 ± 9.25*	65.35 ± 5.92*	66.71 ± 8.29*	69.57 ± 11.43*
	Smokers	59.66 ± 4.36	67.38 ± 6.27*	70.72 ± 7.24*	72.56 ± 1.45*	76.83 ± 4. 94*
PEFR (liter/sec)	Non Smokers	323.45 ± 21.72	395.35 ± 19.43*	422.45±9.78*	445.82 ± 12.54*	4.70 ± 5.91*
	Smokers	304.61 ± 16.41	471.64± 17.45*	480.87 ± 16.26*	488.35 ± 14.59*	506.48 ± 16.98*

*:p<0.001

The base line values in our study, of the smokers and non-smokers on Day 1, where Salbutamol was given as the primary drug with Ipratropium as the second drug showed a significant difference in the FEV1, FVC and PEFR values, while there was no significant difference in the FEV1/FVC ratio. After giving salbutamol to the maximum effect, in comparison to the base line, there was a considerable improvement in all the values in both the smokers and non-smokers. But on giving Ipratropium, there was no further substantial improvement in the values in the non-smokers, but a significant improvement was seen among the smokers. In a similar study by Ahmad and Singh, additional improvement was seen in the smokers in comparison to the non-smokers when ipratropium was given as the second drug after giving Salbutamol as the primary drug, corroborating our study.[24] A study by Iramain et al., observed that children treated with Ipratropium along with salbutamol showed marked improvement in severe asthma rather than salbutamol alone.[25] Similar results were found in another similar study by Raju and Rajendranath.[26]

Ina study by Copenhagen city heart, measured the longitudinal aspect of the FEV1 in 15 years. It was found that there was a decline of FEV1 in smokers with asthma rather than those who didn't smoke.[27] Similar decline was observed in a study by Apostol et al, where the decline was 8.5% in FEV1.[28]

On day 2, there was a significant improvement in the FEV1, FVC, FEV1/FVC and PEFR values compared to the base line values, and on giving salbutamol, there was a substantial increase in the expiration volume in both smokers and non-smokers. Similar results were found in another study by Ahmad and singh.[24] This was in similar to reported by Jindal et al, Wimpe et al., and Raju and Ravidranath.[26,29,30] However another study by Brophy et al., reported that on addition of ipratropium, FEV1 was increased by 75% thereby reducing the hospital admission, when compared to the administration od a beta-2 stimulus alone.[31]

A study by O'Driscoll et al., Rebuck et al., and Rossing et al., have reported that the patient who have severe asthma, seem to have a better reaction to addition of ipratropium bromide to salbutamol.[32–34] However, Roeseler et al., reported that a patient with a PEFR of less than 60 L/min were not benefitted with this.[35] A study by Garret et al showed that those patients who had severe asthma did not benefit much with Ipratropium bromide as they benefitted with salbutamol.[36]

5. Conclusion

In case of smoker asthmatics, a combination therapy of Salbutamol and Ipratropium is more useful. Ipratropium alone was not an efficient bronchodilator and needed salbutamol to give the desired effect as a second drug. But when salbutamol is used as the first drug, Ipratropium gives further bronchodilatation resulting in both androgenic and cholinergic tone in smokers.

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8. Conflict of Interest

Authors has no conflict of interest whatsoever.

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