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Original Research Article

Bronchodilator activity of *Ocimum sanctum Linn*. (tulsi) in mild and moderate asthmatic patients in comparison with salbutamol: a single-blind cross-over study

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ABSTRACT

Background: Bronchial asthma is one of the commonest chronic inflammatory diseases. The drugs available to treat bronchial asthma such as, beta-2 agonists, though very effective are associated with adverse effects. Therefore, the *Ocimum sanctum (Tulsi)* which was shown to have antiasthmatic activity in Ayurveda, is evaluated in this study.
Objectives: To evaluate the bronchodilator activity of *Ocimum sanctum Linn*. in mild and moderate asthma and compare its efficacy with the standard bronchodilator drug, Salbutamol.
Methods: This is a single-blind cross-over study. Capsules of *Ocimum sanctum Linn.* (200 mg, twice daily) and Salbutamol sulphate (2 mg, twice daily) were administered in 41 patients. Each drug was administered for a period of one week with a washout period of one week between the two drug schedules. FEV_1 and PEFR were recorded in these patients to assess the bronchodilator activity before the drug administration, on 4^{th} and on 7^{th} day of administration of *Ocimum sanctum* and the parameters obtained were compared with that of the standard drug, Salbutamol.
Results: *Ocimum sanctum* 200mg twice daily produced significant improvement in both FEV_1 and PEFR values, on 4th and 7^{th} day and also produced improvement in symptoms of asthma. On comparing the results with that of Salbutamol 2mg twice daily, the bronchodilator activity of *Ocimum sanctum* was found to be less efficacious, where Salbutamol produced very highly significant improvement in FEV_1 and PEFR values on both 4^{th} and 7^{th} day.
Conclusions: Our results suggest that *Ocimum sanctum Linn.* possesses significant bronchodilator activity in mild and moderate bronchial asthma.

Keywords: Bronchodilation, FEV_1, Ocimum sanctum, PEFR, Salbutamol

INTRODUCTION

Bronchial asthma is one of the longest recognized diseases. It has become a public health problem only in the last 30 years and it is now recognized as a common cause of disability, of great economic cost, and of preventable deaths.[1] The prognosis of asthma remains good with as many as 60%-80% of patients being able to lead normal lives without much disruption. However, 10%-20% of patients continue to have severe attacks throughout their lives.[2]

Bronchial asthma is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. Asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods.[3]

Asthma currently affects 300 million people worldwide. Female sex, advancing age, usual residence in urban area, lower socio-economic status, history of atopy, and all forms of tobacco smoking were associated with significantly higher odds of having asthma.[4] In childhood, the incidence is higher in boys than in girls but reverses in the age group 15-50 years and reverses again in the older group when the incidence among men increases.[5]

Airway narrowing is the basic pathophysiologic abnormality that determines the functional and symptomatic status of an asthmatic patient.[6] Asthma is characterized by periodic paroxysms of dyspnea, usually at rest as well on exertion, interspersed with intervals of complete or nearly complete remission, the onset of an attack of asthma is heralded by an unproductive cough and wheeze, followed by the sensations of suffocation and tightness in the chest. Paroxysms occur more commonly in night. Nocturnal breathlessness is a common symptom. Physical signs include, tachypnea, hyperresonance on percussion, inspiratory and expiratory rhonchi and wheezes, decreased breath sounds, and prolonged expiration.[5] The clinical evaluation of asthma patients requires comprehensive history, a thorough physical examination, and Pulmonary Function Tests (PFTs).[3,7]

The pharmacotherapy of asthma employs drugs aimed at reducing airway inflammation (antiinflammmatory agents) and at decreasing bronchospasm (bronchodilators). Six classes of therapeutic agents are presently indicated for asthma treatment which include Bronchodilators (β adrenergic agonists, Methylxanthines, Anticholinergics), Leukotriene antagonists, Mast cell stabilizers, Corticosteroids and Inhibitors of immunoglobulin E, Omalizumab. Salbutamol (Albuterol) is a highly selective β_2 agonist. This is a most effective drug in relaxing airway smooth muscle and reversing bronchoconstriction and preferred treatment for rapid symptomatic relief of dyspnea associated with asthmatic bronchoconstriction. The major adverse effects occur as a result of excessive activation of β-receptors. Tremors, feelings of restlessness, apprehension, anxiety, tachycardia, hypoxemia, increase in concentrations of glucose, lactate and free fatty acids and decrease in K^+ concentration when given parenterally.[8]

Ocimum sanctum L. is an erect, hairy perennial shrub popularly known as sacred basil or holy basil, which is grown in temples, courtyards, for religious and medicinal purposes besides being cultivated for essential oil production. Indigenous to India and parts of north and eastern Africa, Hainan Island and Taiwan, China.[9,10] The plant has many uses in ayurveda including asthma and cough.[11] The main components are tannins (4.6%) and essential oil (up to 2%). Essential oil has methyl eugenol (72.5%), eugenol (up to 62%), thymol, ursolic acid (3.221mg/g), ascorbic acid, carotene, β-caryophyllene (5.5%), E-cinnamyl acetate (3.4%), carvacrol and sisquiterpene alcohols as major constituents and terpene compounds, linoleic acid methylchavicol, linalool and 1, 8-cineole as minor constituents.[9,10,12-14]

Clinical study

This study is conducted in normal subjects as well as asthmatic patients either by provoking bronchoconstriction with agents such as histamine, carbachol, methacholine, pollens, cold air and exercise induced etc. and by directly administering bronchodilator agents in asthmatic patients. The different lung volumes are measured before and after administering of drugs.[15]

Since the drugs available for the treatment of asthma so far though very effective, are also associated with adverse effects. *Ocimum sanctum* was shown to be effective in bronchial asthma in Ayurveda. Therefore, the present study is done to evaluate the antiasthmatic activity of *Ocimum sanctum Linn*. and to compare its efficacy with the standard bronchodilator drug, Salbutamol, in mild and moderate asthmatic patients.

METHODS

Materials

The following instruments and drugs were used in this clinical study:

Instruments

1. Mini spirometer SP-1A (Schiller, Switzerland)
2. Wright's mini peak flow meter (Airmed, London)

Drugs

1. *Ocimum sanctum* (OS) capsules
2. Salbutamol sulphate (SS) capsules

Preparation of Ocimum sanctum capsules

Fresh leaves of OS were collected and were authenticated by the botanist. They were washed, shade dried and made in to fine powder. Empty hard gelatin capsules which could contain 200mg of the drug were procured from the College of Nursing, KIMS, Hubli. 700 (as calculated for 50 patients on the basis of twice daily dose for seven days) such empty capsules were filled with 200 mg dried leaf powder of OS, in the Department of Pharmaceutics, KLE's College of Pharmacy, Hubli.

Preparation of salbutamol capsules

Another 700 hard gelatin capsules were selected and Salbutamol sulphate powder (Crystal Pharma, Hubli), 2 mg, was filled in each of these. The remaining 198mg of each Salbutamol filled capsule was made up by adding the excipient, lactose.

Both OS and Salbutamol sulphate capsules were similar to each other in appearance.

Preliminary studies

To arrive at the dosage of *OS* to be used in this clinical study, 6 patients were selected. In two patients 100 mg of *OS* powder was administered orally twice daily, in two patients 200 mg of *OS* capsules twice daily, and in last two pa*tients*, 200 mg capsules of OS, thrice daily were administered. There was equal improvement in FEV_1 and PEFR values with both 200 mg twice daily group and 200 mg thrice daily group, whereas, 100 mg twice daily group showed less improvement than the other two groups. There were no side effects in any of three groups. Based on these results, 200 mg twice daily dose was decided to be evaluated in the clinical study.

Dose selection

The dose selection of *OS* was based on the results of acute toxicity studies conducted in animals by Bhargava and Singh; in this study, LD_{50} of *OS* leaves' extract in mice was reported to be 4508±80mg/kg orally, as reported in Medicinal plants of India and the results of clinical trials conducted by S K Das, in which the dose of approximately 416 mg was administered in patients with viral encephalitis.[16,17] Based on these results, extrapolation of the dose was done and was found to be approximately 3 mg/kg body weight in humans.

Screening of patients

The screening of the patients for asthma was done in out-patient department of Medicine, KIMS, Hubli. The screening was done by obtaining a detailed history and performing general physical examination, respiratory system examination and PFTs. The grading of severity of asthma was done according to NAEPP classification system.[18] The selection of patients was based on the following inclusion and exclusion criteria.

Inclusion criteria

Patients aged between 18 and 50 years, with a history of bronchial asthma of minimum 2 years, with mild and moderate asthma whose lung function tests mainly, FEV_1 values more than 80% and not less than 60% of their predicted values adjusted for age, sex, and height, and who demonstrated at least 12-15% improvement in FEV_1 above baseline measured 15 minutes following 100-400 µg of Salbutamol inhalation were included.[19]

Exclusion criteria

Patients below 18 years and above 50 years of age, those suffering from respiratory diseases other than asthma, cardiovascular, hepatic, renal, neurological diseases or acute lung infections, and those with history of smoking or alcohol consumption.

A total of 50 patients were thus selected for the clinical study based on all above criteria.

Design of the study

This was a 'single-blind cross-over' clinical study, conducted for a period of 3 weeks in each patient; both drugs (OS and SS) were administered for one week each, with a washout interval of one week between two drug regimens. The study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from each patient prior to the study.

Routine investigations of blood (Hb%, TC, DC, ESR, AEC), urine (albumin, sugar, microscopy), and stools (ova, cyst) and chest X-Ray, PA view before the drug administration. Patients were advised not to take any medicine for 24 hours prior to the study. On the day of beginning of study, before administration of either drug (D_0), pulse rate, blood pressure, respiratory rate, height, and weight of patients were recorded and respiratory system was examined. FEV_1 was measured using a portable mini spirometer (SP-1A Schiller, Switzerland). Three readings were taken with a minimum of two minutes interval in between each recording. The best of three readings was taken in to consideration. The results were expressed in Litres (L). PEFR was measured using Wright's mini peak flow meter (Airmed, London). Three readings were taken at an interval of two minutes between each reading. The best of three readings was taken. The results were expressed in Litres/minute (L/min).

Each patient was then randomly assigned one of the following two treatment schedules:

a) 14 Salbutamol sulphate (SS) capsules
b) 14 *Ocimum sanctum* (*OS)* capsules

Patients were advised to take the prescribed drugs twice daily and to be on their normal diet. Patients were also advised to take Salbutamol inhalation if there were any acute exacerbations of asthma or to visit the nearest hospital, if it was still not controlled. They were told to come for follow-up examination on 4^{th} day and 7^{th} day and to take the drug one and half hours before coming for examination on these days.

On 4^{th} day (D_4) and 7th day (D_7), the vital parameters (respiratory rate, pulse, BP) were measured and PFTs were carried out and recorded. The patient compliance was noted by counting the remaining capsules. Patients

were questioned about the improvement in symptoms of asthma and any side effects of the drug like nausea, vomiting, headache, palpitation, tremors, etc. or any other effect the patient experienced during the course of the drug therapy. After 7th day, patients were allowed a washout period of seven days during which no drug was administered. The patients were advised to take Salbutamol inhalation if there were any acute exacerbations of asthma or to visit to the nearest hospital. After washout period, patients were subjected to the next drug regimen 'B' or 'A' as the case may be and the same protocol was repeated.

After the completion of the trial, the patients were asked about the preference of the drug and the reasons for preferring the drug.

Statistical analysis

The results of this study were expressed as Mean (Standard Deviation) [Mean (SD)] of various parameters of patients who completed the study. Results were analyzed by Student's paired and unpaired 't' test. Significance was established when probability value (P value) was less than 0.05. P values were denoted as *P <0.05 as significant and **P <0.01 as highly significant and ***P<0.001 as very highly significant.

RESULTS

The present clinical study was carried out in association with the Department of Medicine, Karnataka Institute of Medical Sciences (KIMS), Hubli, Karnataka.

The study was conducted between November 2007 and October 2008, in the OPD/IPD of Department of Medicine, at KIMS, Hubli, Karnataka. A total of 50 patients were selected for the study; out of which 41 patients attended the study completely which included 11 males, 30 females; 9 patients failed to attend the follow-up at various levels of the study and they were dropped out of the study. *Their* Mean (SD) *age was* 40.41±9.3 years. Out of 41 patients screened, 12 patients had mild asthma and 29 patients had moderate asthma.

Table 1 show the FEV_1 and PEFR values before (D_0), on 4th day and 7th day of administration of *Ocimum sanctum (OS)*. Table 2 show the FEV_1 and PEFR values before, and on 4th and 7th day of administration of Salbutamol Sulphate (SS) capsules.

Table 3 shows the comparison of the improvement of FEV_1 and PEFR following *Ocimum sanctum* capsules. As shown in Table 3, there is significant difference in the FEV_1 and PEFR values on day 4 and highly significant difference on day 7, following *Ocimum sanctum* administration.

Table 4 shows the comparison of the improvement of FEV_1 and PEFR following Salbutamol sulphate capsules. As shown in Table 4, the difference in the FEV_1 and PEFR values on day 4 are highly significant and very highly significant on day 7, following Salbutamol sulphate administration.

Table 1: FEV_1 and PEFR values before (D_0), on 4th day and 7th day of administration of *Ocimum sanctum*.

Sl. No	FEV_1 (Litres)			PEFR (Litres/min)		
	D_0	D_4	D_7	D_0	D_4	D_7
1	2.1	2.3	2.4	250	270	280
2	1.4	1.5	1.6	190	210	230
3	2	2	2	260	260	260
4	2.1	2.3	2.3	250	270	280
5	1.5	1.5	1.5	190	190	190
6	2.4	2.5	2.6	290	310	330
7	1.9	2.1	2.2	240	260	270
8	2.2	1.8	1.7	250	200	200
9	1.9	2	2.1	240	250	260
10	1.7	1.9	1.9	230	250	250
11	2.5	2.7	2.7	310	330	350
12	1.7	1.7	1.7	250	250	250
13	1.9	2.1	2.2	260	280	300
14	2.4	2.6	2.6	360	380	390
15	1.9	2.1	2.2	240	260	270
16	2.6	2.8	2.8	370	390	390
17	1.3	1.5	1.5	170	190	190
18	1.7	1.8	1.9	230	250	260
19	1.9	2.1	2.1	250	260	270
20	2.1	1.7	1.6	260	220	210
21	1.4	1.4	1.5	190	200	200
22	2.5	2.6	2.7	350	370	380
23	2.5	2.7	2.7	310	330	330
24	2.5	2.1	2	340	290	270
25	2.2	2.3	2.4	270	290	300
26	1.8	1.9	2	240	260	270
27	1.5	1.6	1.7	210	230	250
28	1.4	1.5	1.6	190	210	220
29	2.3	2.3	2.3	330	330	330
30	1.8	2	2.1	250	270	280
31	3.1	3.3	3.4	400	420	430
32	2.3	1.9	1.8	330	290	260
33	2.5	2.7	2.8	340	360	380
34	2.2	2.3	2.4	260	280	290
35	2.2	2.2	2.2	250	270	270
36	2	2.2	2.2	260	280	280
37	1.3	1.5	1.5	180	190	180
38	1.4	1.5	1.5	200	220	210
39	2.6	2.8	2.9	370	400	400
40	1.6	1.8	1.8	220	240	250
41	2.4	1.9	1.9	370	320	310

When the results of 4th and 7th days following *Ocimum sanctum* and salbutamol are compared, the latter showed highly significant improvement over *Ocimum sanctum.*

Table 2: FEV_1 and PEFR values before, and on 4th and 7th day of administration of Salbutamol Sulphate (SS) capsules.

Sl. No.	FEV_1 (Litres)			PEFR (Litres/min)		
	D_0	D_4	D_7	D_0	D_4	D_7
1	2.2	2.5	2.6	250	280	290
2	1.4	1.6	1.7	190	220	240
3	1.9	2.2	2.3	260	280	300
4	2.1	2.4	2.5	250	280	300
5	1.5	1.8	1.8	190	220	240
6	2.5	2.7	2.7	290	290	290
7	2	2	2	270	300	310
8	2.1	1.8	1.7	250	200	220
9	1.8	2.1	2.2	240	280	300
10	1.8	2.1	2.2	230	260	280
11	2.6	2.6	2.6	310	310	310
12	1.7	2	2	250	270	290
13	1.9	2.2	2.4	260	300	310
14	2.4	2.4	2.4	350	350	350
15	2	2.3	2.4	240	270	290
16	2.6	2.8	2.9	370	410	420
17	1.4	1.6	1.8	170	210	220
18	1.8	2.1	2	220	240	270
19	1.9	2.1	2.2	250	290	290
20	2.4	1.8	1.7	260	200	190
21	1.4	1.7	1.9	190	240	270
22	2.5	2.5	2.5	350	350	350
23	2.6	2.8	2.9	310	340	350
24	2.6	2.1	2	350	290	270
25	2.2	2.5	2.7	280	320	350
26	1.9	2.2	2.4	240	260	300
27	1.6	1.9	1.9	230	260	280
28	1.5	1.8	2	200	230	270
29	2.2	2.4	2.4	320	340	360
30	1.9	2.2	2.3	270	300	310
31	3.3	3.6	3.7	420	450	470
32	2.3	1.8	1.8	330	270	250
33	2.4	2.7	2.8	320	350	380
34	2.4	2.7	2.9	250	300	320
35	2.1	2.3	2.4	240	280	290
36	1.9	2.2	2.3	250	280	300
37	1.4	1.7	1.8	200	220	240
38	1.4	1.7	1.8	190	250	260
39	2.6	2.9	3	370	400	440
40	1.7	1.9	2	230	260	270
41	2.4	1.9	1.9	370	320	300

DISCUSSION

FEV_1 and PEFR were chosen for studying the antiasthmatic effects of OS and Salbutamol because these parameters are reliable, widely accepted, and they correlate with the progression of disease, use of health care, and severity of asthma. They are also easy to monitor and can be measured with portable instruments which are easily available.[19]

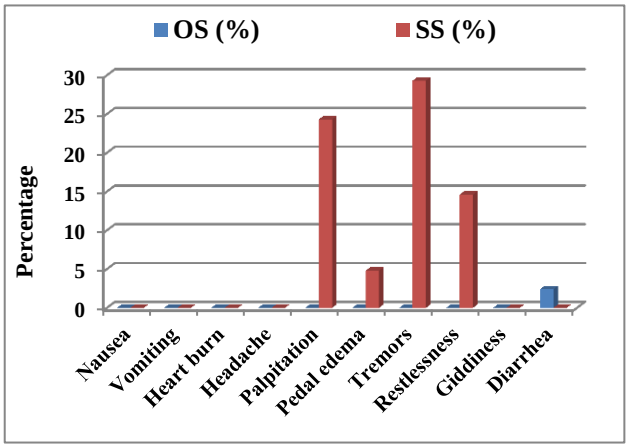

Figure 1: The percentage of adverse effects following *Ocimum sanctum* and salbutamol administration.

The significant antiasthmatic activity of OS may be due to a) its smooth muscle relaxant property which is attributed to elevation of cAMP in bronchial smooth muscle cells and due to blocking of replication of smooth muscle cells.[20] Its smooth muscle relaxant property has also been shown on intestinal smooth muscle, when it was administered parenterally and orally, b) its property of modulating humoral responses at various levels in the immune system such as antibody production (IgE production in case of asthma), release of mediators of hypersensitivity reactions (such as histamine, PGs, LTs) and tissue response to these mediators, c) or its anti-stress properties, as reported by Bhargava and Singh, that *OS* prevented stress induced ulcers in rats.[21-23] Based on these studies and antistress properties of OS may be helpful in its efficacy in asthma. Activity of OS may be probably due to eugenol in the volatile oil. It may be predicted that hydroxy group on 4th position of phenyl ring is responsible for bronchial smooth muscle relaxation. Presence of methoxy and propylene group on the phenyl ring may confer a maximum β-activity and selectivity. The presence of ursolic acid in the volatile oil may be responsible for anti-inflammatory activity, which may be due to inhibition of COX.[24]

Six patients showed no improvement in their symptoms and lung function tests. The reason may be, decreased compliance in taking drugs by some of these patients or due to acute exacerbations during the therapy in some patients in which OS is not effective. But the exact reason is yet to be elucidated.

Nineteen patients complained of cough before the administration of OS of which nine patients showed improvement. This effect can be explained by its antitussive property, which could be due to presence of active ingradients of which saponins and ursolic acid are important.[25,26] This property also has been described in Indian materia medica by A.K. Nadkarni.

Table 3: Comparison of the improvement of FEV1 and PEFR on 4th and 7th day following administration of Ocimum sanctum capsules.

	FEV_1			PEFR		
	D_0	D_4	D_7	D_0	D_4	D_7
Mean (SD)	1.993 (0.445)	2.085 (0.449)	2.122 (0.464)	267.07 (60.51)	276.34 (60.11)	280.98 (62.44)
SEM	0.069	0.07	0.073	9.45	9.39	9.75
P-value	-	0.0202 (Significant)	0.0088 (Highly significant)	-	0.01 (Significant)	0.0056 (Highly significant)

Table 4: Comparison of the improvement of FEV1 and PEFR on 4th and 7th day following administration of Salbutamol sulphate capsules.

	FEV_1			PEFR		
	D_0	D_4	D_7	D_0	D_4	D_7
Mean (SD)	2.056 (0.439)	2.198 (0.413)	2.28 (0.441)	268.54 (59.86)	287.07 (55.46)	300.97 (56.87)
SEM	0.069	0.064	0.069	9.35	8.66	8.88
P-value		0.0016 (Highly significant)	0.0001 (Very highly significant)		0.0004 (Very highly significant)	0.0001 (Very highly significant)

The highly significant bronchodilator activity of Salbutamol is due to various mechanisms such as, it activates β_2 receptors on human bronchial smooth muscle and causes the activation of G_s adenylyl cyclase-cAMP pathway, which in turn activates Protein Kinase A. This causes the phosphorylation of cellular proteins resulting in the reduction of airway smooth muscle tone. Salbutamol also increases the conductance of large Ca^{2+}sensitive K^+ channels in airway smooth muscle, leading to membrane hyperpolarization and relaxation, and it inhibits the function of numerous inflammatory cells including mast cells, basophils, eosinophils, and neutrophils. These all mechanisms ultimately result in smooth muscle relaxation of the bronchial airways.[8]

The adverse effects such as, palpitations or tachycardia are due stimulation of cardiac β_1 receptors.[8] Patient compliance of >90% was observed with both drugs which may be due to the hope of getting a better drug for their treatment with least side effects. So, on comparing the results on 4th and 7th day of therapy with *Ocimum sanctum* and salbutamol, it is evident that both drugs increased FEV_1 and PEFR values significantly on 7th day as compared to the 4th day of therapy. When compared to SS, the activity of OS was less significant in the percentage increase on both 4th and 7th day and in producing bronchodilation and in relieving symptoms of asthma. The increase in FEV_1 values on 7th day of *Ocimum sanctum* (OS) therapy was approximately equivalent to that of Salbutamol Sulphate (SS) therapy on 4th day.

CONCLUSION

The present clinical study shows that OS (Tulsi) dried leaves' powder contains the essential oil which contains constituents such as eugenol, methyleugenol, saponins and ursolic acid which may be responsible for the bronchodilator activity. Thus, OS (Tulsi) possesses antiasthmatic activity in mild and moderate asthma. Though it produced significant activity in mild and moderate asthma, the activity was less than that of Salbutamol, the standard drug, which was used for comparison in this study.

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