Research Article

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COMPARATIVE CLINICAL TRIAL OF BHARANGIMOOLA ARKA AND SALBUTAMOL NEBULIZATION IN TAMAKA SHWASA (ACUTE EXACERBATION OF BRONCHIAL ASTHMA): A CASE SERIES STUDY

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Received on: 20/11/18 Accepted on: 05/01/19

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DOI: 10.7897/2277-4343.100122

ABSTRACT

Tamaka Shwasa (Bronchial asthma) is a disease occurring due to involvement of Vata and Kapha which presents in two forms – Vaigika (Acute exacerbated) or Avaigika (under control). An emergency management is required during acute exacerbation. Pilot study has proved a statistically highly significant difference in symptoms like breathlessness (Z = -4.820, p= 0.000) after treatment with Nebulization of Bharangimoola Arka (5ml administered 8th hourly for 3 times) and also FVC% and FEV1% have improved significantly with a t value equal to -5.857 and -5.090 respectively with $p<0.05$. Hence an effort is put forth to compare Bharangimoola Arka with standard drug salbutamol Nebulization in controlling the acute exacerbation state in six episodes of administration. The main aim of the study was to compare the efficacy of Bharangimoola Arka Nebulization with standard drug Salbutamol in reducing the symptoms of Vegavasta (Acute exacerbated) of Tamaka Shwasa (Acute exacerbation of Bronchial Asthma). It was an open label, single center, prospective, double arm clinical study conducted in 100 patients of acute exacerbation of Bronchial Asthma. The patients falling under the inclusion criteria were taken for the study and pre and post spirometry was done to evaluate the broncho dilation effect. The patients were hospitalized for 2 days, and nebulization was done 8th hourly with a fixed dose of 5 ml of Bharangimoola Arka and 2.5 ml of Salbutamol sulphate in two groups. Before and after each episode of nebulization, Peak Expiratory Flow Test was done. This study provides evidence for the significant effect of 5 ml of Bharangimoola Arka in reducing the symptoms like Breathlessness, Wheeze and Cough in Acute exacerbation of Bronchial asthma which is on par with the standard drug Salbutamol Sulphate - 2.5ml when administered six doses 8th hourly without inducing tremors.

Keywords: Arka, Ayurveda, Bharangimoola, Bronchial asthma, Salbutamol, *Clerodendrum serratum* (Linn.), Nebulization, Tamaka Shwasa.

INTRODUCTION

Tamaka Shwasa can manifest either in Vaigika or Avaigika state due to predominance of Kapha –Vata Doshas.[1] The name of the disease is due to the feeling of entering into darkness during the state of attack, when condition reaches to an acute state. As per the statistics, the prevalence of the same has increased in past two decades due to pollution, rapid environment changes, adaptation of newer dietetic preparation and tremendous psychological stress.[2] It is estimated that around 15-20 million people are asthmatics and it was seen as one of the leading causes of morbidity and mortality in rural India.[3]

In present day the management of acute stage is done by Nebulization, which involves a process administration of suspension of fine vaporized liquid droplets in air (aerosol).[4] This study is carried out with the same aspire to establish the efficacy of herbal preparation in acute exacerbation of Bronchial Asthma based on the pilot study.

In pilot study Patients with acute exacerbation were given with 5ml Bharangimoola Arka in the form of Nebulization 8th hourly for 2 days. Pre and post Spirometry and peak expiratory flow rates were measured. The Bharangimoola Arka Nebulization has shown significant effect on symptoms like breathlessness and wheeze, & moderate effect on symptoms like cough, chest tightness and speech. The administration of Bharangimoola Arka is proven to be safe as it didn't show any side effects for any patients during the study.[5]

This study was carried out to compare the efficacy of Bharangimoola Arka with salbutamol as nebulization in acute exacerbation of Bronchial Asthma.

MATERIALS AND METHODS

This study design was cleared from institutional ethics committee SDM/IEC/104/2016-2017and registered with CTRI No. 2016/10/012476. Written consent was procured from the subjects with acute presentation. Patients were recruited from In – Patient Department of general medicine of Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan through purposive sampling. The self-structured proforma consisting of clinical symptoms of Tamaka Shwasa and Acute Exacerbation in Bronchial Asthma as per criteria mentioned in GINA-Global Initiation for Asthma were administered to the patients to include into the study.[6]Subjects who are fulfilling inclusion criteria were allocated to Group A – administered with Bharangimoola Arka and Group B – Salbutamol Sulphate.

Assessment criteria

Clinical features of patients were assessed before and after six episodes of Nebulization. Grading for the signs and symptoms is as follows
0– No symptoms
1 – Mild – while walking, can lie down
2 – Moderate- while at rest, prefers sitting
3 – Severe –while at rest, sits upright

Spirometry parameters were observed before and after the 1st dose and 6th Dose of nebulization. Peak Expiratory Flow Rate (PEFR) were observed before and after all the dose of nebulization

Inclusion & Exclusion criteria

Patients of both gender aged between 16 – 60 years with mild to moderate acute exacerbation, who are conscious and well oriented were included for the study. The patients with severe exacerbation, emphysema, chronic airway limitation, with history of tuberculosis and cardiac involvement, other complicated respiratory diseases having any organic lesion such as tumor or any anatomical defect in airway, cyanosis and uncontrolled hypertension, diabetes mellitus and suffering with other systemic illness were not included for the study.

Method of Drug Preparation

Required quantity of water was added to the root of Bharangi for soaking and kept overnight. Next day it was poured into the Arka Yantra (distillation apparatus) and boiled after adding remaining water. The vapors generated was condensed and collected in a receiver, which was stored in amber color bottle.

Intervention

The patient falling under the inclusion criteria are taken for the study and pre and post spirometry was done to evaluate the effect of bronco dilation. The patients were hospitalized for 2 days, nebulization was done 8th hourly with a fixed dose of 5 ml of Bharangimoola Arka and 2.5ml/5mg of salbutamol sulphate. Before and after each episodes of nebulization, Peak Expiratory Flow Test was done. In between if the patients got the attack then same medicine was repeated.
After the treatment if notable effect is not elicited then co-current medication will be advised as per expert opinion

Group A	**Group B**
Sample Size : 50 patients	Sample Size: 50 patients
Drug: Bharangimoola Arka	Drug: Salbutamol sulphate
Dose: 5 ml.	Dose: 2.5ml/5mg.
Duration of treatment: 2 days hospitalization.	Duration of treatment: 2 days hospitalization.

Table 1: Effect of Bharangimoola Arka and Salbutamol on Symptoms of Tamaka Shwasa

Symptoms	GROUP	Mean Rank	Sum of Ranks	Mann- Whitney U & Wilcoxon W	Z	Asymp. Sig. (2-tailed)	Significance
Breathlessness BT	Bharangimoola Arka	60.10	3005.00	770.0 2045	-3.513	.000	HS
	Salbutamol	40.90	2045.00				
Breathlessness AT	Bharangimoola Arka	50.50	2525.00	1250 2525	.000	1.000	NS
	Salbutamol	50.50	2525.00				
Wheeze BT	Bharangimoola Arka	63.60	3180.00	595 1870	-4.819	.000	HS
	Salbutamol	37.40	1870.00				
Wheeze AT	Bharangimoola Arka	54.00	2700.00	1075 2350	-1.951	.051	S
	Salbutamol	47.00	2350.00				
Talks in BT	Bharangimoola Arka	55.09	2754.50	1020.500 2295.500	-1.686	0.92	NS
	Salbutamol	45.91	2295.50				
Talks in AT	Bharangimoola Arka	53.00	2650.00	1125 2400	-2.283	.022	S
	Salbutamol	48.00	2400.00				
Cough BT	Bharangimoola Arka	59.69	2984.50	790.500 2065.500	-3.433	.001	HS
	Salbutamol	41.31	2065.50				
Cough AT	Bharangimoola Arka	54.54	2727.00	1048 2323	-2.191	0.028	HS
	Salbutamol	46.46	2323.00				
Sputum production BT	Bharangimoola Arka	60.04	3002.00	773 2048	-3.433	.001	HS
	Salbutamol	40.96	2048.00				
Sputum production AT	Bharangimoola Arka	56.01	2800.50	974.500 2249.500	-3.258	.001	HS
	Salbutamol	44.99	2249.50				
Chest tightness BT	Bharangimoola Arka	62.01	3100.50	674.500 1949.500	-4.158	.000	HS
	Salbutamol	38.99	1949.50				
Chest tightness AT	Bharangimoola Arka	56.98	2849.00	926 2201	-2.506	.012	S
	Salbutamol	44.02	2201.00				

HS – highly significant b) NS – not significant c) BT – before treatment d) AT – after treatment e) SD – standard deviation f) SE – standard error

OBSERVATIONS AND RESULTS

In this study 43.3% of patients were in the age group of 16-26 years. The sample included 33.3% labor workers, 26.7% students, 23.3% housewives, and 10% and 6.7% are professionals and business men respectively.

Statistically significant result was observed in following symptoms of breathlessness (Z = -3.513, *p*= 0.000), cough (Z = -3.433, *p*= 0.002), sputum production (Z = -2.191, *p*= 0.001) and chest tightness (Z = -4.158, *p*= 0.000) in the group and difficulty in speech (Z = -2.283, *p*= 0.022) in Group B. (Table 1)

Repeated measures ANOVA determined that mean PEFR has increased significantly after treatment. Post hoc tests using the Bonferroni correction 0.008 revealed that treatment elicited an increase in PEFR from 1st dose BT to 6th dose AT was statistically highly significant. On comparing the effect of treatment in between treatments it was found that treatment was statistically significant after each episode of nebulization. (Table 2, 3)

Statistically highly significant improvement was observed in all the parameters of Spirometry (Pulmonary Function Test). FVC% and. FEV_1% improvement was recorded which is significant in both the groups. (Table 4)

Table 2: Effect of Bharangimoola Arka and Salbutamol on PEFR with repeated measure ANOVA

(I) factor1pefr	(J) factor1pefr	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
1st dose	2nd dose	-70.500*	5.796	.000	-82.000	-59.000
	3rd dose	-132.150*	6.068	.000	-144.190	-120.110
	4th dose	-196.150*	7.186	.000	-210.409	-181.891
	5th dose	-264.650*	7.159	.000	-278.854	-250.446
	6th dose	-305.050*	6.473	.000	-317.894	-292.206
2nd dose	1st dose	70.500*	5.796	.000	59.000	82.000
	3rd dose	-61.650*	4.966	.000	-71.504	-51.796
	4th dose	-125.650*	6.007	.000	-137.570	-113.730
	5th dose	-194.150*	7.462	.000	-208.957	-179.343
	6th dose	-234.550*	6.958	.000	-248.356	-220.744
3rd dose	1st dose	132.150*	6.068	.000	120.110	144.190
	2nd dose	61.650*	4.966	.000	51.796	71.504
	4th dose	-64.000*	2.902	.000	-69.759	-58.241
	5th dose	-132.500*	4.216	.000	-140.866	-124.134
	6th dose	-172.900*	4.115	.000	-181.066	-164.734
4nd dose	1st dose	196.150*	7.186	.000	181.891	210.409
	2nd dose	125.650*	6.007	.000	113.730	137.570
	3rd dose	64.000*	2.902	.000	58.241	69.759
	5th dose	-68.500*	4.353	.000	-77.137	-59.863
	6th dose	-108.900*	5.013	.000	-118.847	-98.953
5th dose	1st dose	264.650*	7.159	.000	250.446	278.854
	2nd dose	194.150*	7.462	.000	179.343	208.957
	3rd dose	132.500*	4.216	.000	124.134	140.866
	4th dose	68.500*	4.353	.000	59.863	77.137
	6th dose	-40.400*	2.699	.000	-45.755	-35.045
6th dose	1st dose	305.050*	6.473	.000	292.206	317.894
	2nd dose	234.550*	6.958	.000	220.744	248.356
	3rd dose	172.900*	4.115	.000	164.734	181.066
	4th dose	108.900*	5.013	.000	98.953	118.847
	5th dose	40.400*	2.699	.000	35.045	45.755

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Table 3: Effect of Bharangimoola Arka and Salbutamol on PEFR of Tamaka Shwasa

	GROUP	N	Mean
PEFR 1st dose BT in l/sec	Bharangimoola Arka	50	1.3436E2
	Salbutamol	50	1.5234E2
PEFR 1st dose AT in l/sec	Bharangimoola Arka	50	2.1788E2
	Salbutamol	50	2.3372E2
PEFR 2nd dose BT in l/sec	Bharangimoola Arka	50	2.0478E2
	Salbutamol	50	2.2292E2
PEFR 2nd dose AT in l/sec	Bharangimoola Arka	50	2.7736E2
	Salbutamol	50	2.9804E2
PEFR 3rd dose BT in l/sec	Bharangimoola Arka	50	2.6820E2
	Salbutamol	50	2.8280E2
PEFR 3rd dose AT in l/sec	Bharangimoola Arka	50	3.3780E2
	Salbutamol	50	3.5560E2
PEFR_4D_BT_SEC	Bharangimoola Arka	50	3.3140E2
	Salbutamol	50	3.4760E2
PEFR_4D_AT_SEC	Bharangimoola Arka	50	4.0660E2
	Salbutamol	50	4.2040E2
PEFR_5D_BT_SEC	Bharangimoola Arka	50	4.0112E2
	Salbutamol	50	4.1488E2
PEFR_5D_aT_SEC	Bharangimoola Arka	50	4.5978E2
	Salbutamol	50	4.7692E2
PEFR_6D_BT_SEC	Bharangimoola Arka	50	4.3920E2
	Salbutamol	50	4.5760E2
PEFR_6D_AT_SEC	Bharangimoola Arka	50	4.9500E2
	Salbutamol	50	5.1720E2

Table 4. Effect of therapy on Spirometry parameters in *Tamaka Shwasa* Patients

Group A	Parameters	Mean BT	Mean AT	Mean difference	SD	SE	't' value	p' value	Remark
	FVC %	1.64	2.03	-0.39	0.361	0.066	-5.857	.000	HS
	FEV1 %	1.41	1.67	-0.26	0.278	0.051	-5.090	.000	HS
Group B	**FVC %**	1.53	2.25	-0.28	0.368	0.056	-5.456	.000	HS
	FEV1 %	1.83	2.03	-1.20	0.272	0.045	-5.111	.000	HS

HS – highly significant b) NS – not significant c) BT – before treatment d) AT – after treatment e) SD – standard deviation f) SE – standard error g) FVC- forced vital capacity h) FEV1- forced expiratory volume in 1 second

DISCUSSION

If Tamaka Shwasa is not managed timely or if the patient indulges in unwholesome regimens during the disease being exacerbated become fatal like the deadly snake-venom. The manifestation of the same can be either in Vega or Avega Avastha**,** the study has been taken with the aim of evaluating the efficacy of Bharangimoola Arka Nebulization in reducing the symptoms of acute exacerbation in six episodes of the administration and comparison of its efficacy with the standard drug salbutamol sulphate.

Nebulization therapy in acute stage of asthma is more beneficial due to larger surface area which increases the rate of absorption, there by delivery of proteins derivative in lung tissue will become more active. However on regular usage of nebulization patient feels tiredness with loss of appetite and tremors. Also The side effects related to plasma concentrations of theophylline are minor complications like nausea, vomiting, and headache; it can lead to cardiac arrhythmias and seizures due to adenosine A1-receptor antagonism.[7]

Bharangimoola Arka Nebulization with the dose of 5ml of was administered 8 hourly for 6 times. On the basis of observations in pilot study the interval period between the dose was fixed to 8 hours considering the time of medication for Tamaka Shwasa as Muhur Muhu (Repeated administration of Medicine).The symptom breathlessness, tightness of chest, wheeze and cough was reduced significantly (p value =.000. (P value .002) (Table 1, 2& 3) respectively after nebulization. This facilitates the movement of *Prana vayu* (Type of Vata) by liquefying the tenacious sputum in the *Srotas* (channels).

In this disease Vata moves in the reverse order and pervades the channels afflicting the neck and head, and stimulates Kapha to cause signs and symptoms due to obstruction. Hence the therapies will be beneficial which induce downward movement of Vata just like the snow melts on account of the hot rays of the sun, the stable Kapha in the body gets dissolved on account of the heat generated by oleation and fomentation therapies. That liquefied Kapha should be eliminated by administering emesis therapy[10]. And also the residual Dosha which are still remaining in channels can be eliminated by the administering medicated fumes.[8]

Significant improvement in initial mean score of PEFR, FVC & FEV1 was observed from 1st dose to the 6th doses in both the group. It suggests significant reduction in airway obstruction.

The phyto chemical of Bharangimoola Arka (root of *Clerodendrum serratum (Linn.))* on preliminary test have proven to be positive for Carbohydrates, Phenolic, Tannins and Terpenoids.Generally, previous researches on phytochemical among carbohydrates components D-mannitol was found.[9]

The components of Bharangimoola Arka - phenolic compound, Tannins and Terpenoids are found to be anti-inflammatory in Asthma.[10] The Bharangimoola *(Clerodendrum serratum (*Linn*.)*, due to its anti-inflammatory action succeed to restrict the underlying pathology instantly. The anti-inflammatory effects of phenolic compounds are related in previous research are; due to modulation of the expression of pro-inflammatory genes, like NOS, cyclooxygenase, lipooxygenase; acting throughout nuclear factor (NF-κB) signaling; and mitogen-activated protein kinase and activating the Nrf2/Keap1 pathway.[11]

In another way the role play of any particular phenolic antioxidant is directly associated with the capacity of the hydrogen radical donation from the phenolic group and the presence of an unpaired electron in the aromatic ring.

A study is evident that the ethanolic root extract of *Clerodendrum serratum (*Linn*.)* showed significant anti-inflammatory activity in carrageenan-induced oedema in the cotton pellet model in experimental mice, rats and rabbits at concentrations of 50, 100 and 200 mg/kg.[12]

The Ices hydropicenic Acid (IHPA) pent acyclic triterpenoid saponin, first isolated component from roots of *Bharangi*, at the dose of 100mg/kg provides protection of mast cell degeneration (59.62%) in comparison to standard sodium cromoglycate (64.48%).[13] Another components of Bharangimoola Saponin and D mannitol possesses antihistamine and anti-allergic effect respectively, Apigenin-7-glucoside (flavonoid) acts as anti-inflammatory and antimicrobial agent.[14]

CONCLUSION

Hence with the evidence of present clinical trial and other research updates the Bharangimoola Arka is found to have more sustained effect in reduction of Tamaka Shwasa in acute stage in comparison with Salbutamol Sulphate. No adverse effects like tremor, dryness of mouth was not observed among the subjects treated with Bharangimoola Arka.

AKNOWLEDGEMENT

We are thankful for the Rajiv Gandhi University of Health Sciences Karnataka, Bengaluru for funding this research, we also acknowledge the support of Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan, India

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Cite this article as:

Manjunatha Adiga *et al*. Comparative clinical trial of bharangimoola arka and salbutamol nebulization in tamaka shwasa (acute exacerbation of bronchial asthma): A case series study. Int. J. Res. Ayurveda Pharm. 2018;10(1):90-94 http://dx.doi.org/10.7897/2277-4343.100122

Source of support: Rajiv Gandhi University of Health Sciences Karnataka, Bengaluru, India, Conflict of interest: None Declared