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RESEARCH ARTICLE

TO STUDY THE EFFECT OF KANTAKARYAVALEHYA ON EOSINOPHIL CATIONIC PROTEIN (ECP) LEVELS IN CHILDHOOD ASTHMA.

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Abstract

Background: Childhood asthma is one among the most common causes for hospital visits in India. It has its impact on the socio-economic and psychological factors of the sufferers. School absenteeism in children due to childhood asthma is not uncommon. Ayurveda line of treatment can be of immense help in preventing and providing succor to patients. This study was intended to assess the efficacy of Kantakaryavalehya clinically and on ECP levels in Childhood asthma.

Objectives: This research study had two objectives

1. To assess the efficacy of Kantakaryavalehya on Childhood asthma clinically
2. To assess the efficacy of Kantakaryavalehya on Eosinophil Cationic Protein levels in Childhood asthma.

Methods: 20 childhood asthmatics were selected for the study. They were administered with the trial drug Kantakaryavalehya for 90 days with assessment at interval of every 30 days. Blood was drawn before and after the study period to evaluate the serum ECP levels. GINA guidelines 2016 was followed for clinical assessment of Asthma.

Results: In both clinical and objective evaluations, results were encouraging. Clinical assessment of level of asthma control was found statistically marginally significant (p=0.059), improvement in terms of PEF rate was highly significant (p=0.03). Assessment of ECP levels in serum and comparison before and after treatment showed marginally statistically significant results (p=0.07). Though the effect of Kantakaryavalehya on ECP levels was marginally significant, it was strikingly evident in terms of clinical improvement and with respect to PEFR.

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Conclusion: Kantakaryavalehya may be used as a drug of choice in the management of Childhood asthma.

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Introduction:-

Childhood asthma, a common respiratory disorder is one such condition which requires repeated visits to a doctor. Asthma is a crippling disease that imposes not only physical suffering but also social and economic strain on the individual. Among school going children, the prevalence is found to be 4-20% which is much higher in comparison to the prevalence of adults which is 10-12%. It is more prevalent in urban areas than in rural areas. Childhood Asthma is responsible for school absenteeism, restricted activities, social, economic and psychological impact on the family(1, 2).

Asthma is a disease complex to mean a symptom, an exacerbation of underlying diseases of the airway. It is a reversible obstructive airway disease coupled with bronchial hyper responsiveness and airway inflammation. Asthma is a chronic inflammatory disorder of the airways which causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early in the morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with the treatment. The inflammation also causes an associated increase in the existing bronchial hyper responsiveness to a variety of stimuli.

The assessment of asthma is based mainly on surrogate measures of airway inflammation using spirometer and related techniques. Direct measurement of airway inflammation using biological markers could potentially redefine asthma management and this explains current research interest in eosinophil granule proteins in asthma. In recent years, clinical research has suggested an emerging clinical usefulness of eosinophil granule proteins in the assessment and management of asthma, of which eosinophil cationic protein (ECP) has been most widely characterised and researched(3).

Eosinophil Cationic Protein is one of the basic proteins contained in the matrix of secondary eosinophil granules. It is a protein of 133 amino acids. It belongs to Ribonuclease family and is also called as Ribonuclease-3(4). Eosinophil also produces other proteins like Major basic protein-1 and 2, Eosinophil peroxidase, Eosinophil derived neurotoxin and Charcot-Leyden crystal protein(5) to ECP exhibits a modest ribonucleolytic activity, and a marked cytotoxicity against parasites, bacteria, single stranded RNA viruses and mammalian cells, and can also cause airway hyper responsiveness. Cationic proteins cause airway hyper responsiveness by a complex mechanism that involves generation of bradykinin, tachykinin peptides, altered airway permeability and reduction of epithelial derived relaxing factor, strongly implicating a key role for cationic proteins and eosinophil is severe forms of asthma(6). 5% of all asthmatic patients are resistant to treatment with conventional therapy. As a continuation of the previous study done by the Principal Investigator on the effect of Kantakaryavalehya in Childhood Asthma, this research study was taken up to study the effect of Kantakaryavalehya on Eosinophil Cationic Protein level in Childhood Asthma.

Objectives Of The Study

1. To assess the effect of Kantakaryavalehya in Childhood Asthma clinically.
2. To study the effect of Kantakaryavalehya on Eosinophil Cationic Protein levels in Childhood Asthma.

Materials And Methods:-

Source And Method Of Collection Of The Data

20 patients of either sex of the age group 5 to 15 years were randomly selected from the OPD of JSS Ayurveda Medical College Hospital, Lalithadripura road, Mysuru-570028 and special camps were conducted in this regard in the hospital and at JSS School, Suttur, Nanjangud Taluk, Mysuru district.

Sampling:

This was a single group study of 20 Childhood Asthmatics to study the effect of Kantakaryavalehya clinically and on their Serum ECP levels.

Intervention

The drug Kantakaryavalehya is mentioned under Kasa rogadohikara of Bhaishajya Ratnavali, a classical text in Ayurveda literature, which deals with formulations for treatment to various diseases. It is composed of drugs like Kantakari, Chavya, Pippali, Maricha, Musta, Chitraka, Bharangi, Shunti, Guduchi, Rasna, Shati, Karkatashruni, Dhanvayaasaka and Vamshalochana which are Kapha-vata hara predominantly, Kasahara, Shwasahara, Shothahara, Deepana, Pachana(7).Kantakaryavalehya was used in the form of Syrup keeping in mind the age group of subjects, where a palatable, effective and minimal dose preparation is preferred.

The ingredients of the multidrug combination Kantakaryavalehya and their mode of action are as follows –

Kantakari –

Both glycol alkaloid and fatty acid fractions of the plant's extracts cause liberation of histamine from chopped lung tissue. The beneficial effect of the drug on bronchial asthma may be attributed to the depletion of histamine from bronchial and lung tissue. Numerous research works have proven its anti-tussive, anti-asthmatic, expectorant and histamine depleting effects(8).

Chavya –

It contains alkaloids Piperine and Piplartine. Active principles show muscle relaxant properties(8).

Pippali –

Piperine is the major alkaloid. It is antipyretic, hypotensive, analeptic, CNS stimulant. It has been reported to exert significant protection against CCl₄ induced hepatotoxicity in mice. It improves drug availability in experimental animals, and is used for enhancing the efficacy of administered medicaments. Milk extract of fruit effectively reduced passive cutaneous anaphylaxis in rats. It protected guinea-pigs against antigen-induced bronchospasm.

Research activities have revealed its Respiratory stimulant, anti-inflammatory properties. Significant effect in controlling the frequency and severity of asthmatic attack was also observed(8).

Maricha –

Stimulant, carminative, diuretic, anticholerin, sialogogue, bechic, antiasthmatic. Fruit extracts and essential oils are inhibitory to various bacteria, it is anti-fungal and also increases permeability in intestines(8).

Musta –

Its active ingredients Cyperol and Cyperene have shown significant anti-bacterial activity against a number of organisms and especially Staphylococcus aureus. Alcoholic extracts are antagonistic to stimulant effect of histamine, bradykinin and serotonin on smooth muscles(8).

Chitraka –

Root yielded Naphthoquinone derivatives and Plumbagin – the most important active principle and exhibited specific antimicrobial activity(8).

Bharangi –

It is antiasthmatic, antihistaminic, antispasmodic, antitussive, carminative, febrifuge. Found to be effective in pleuritis(8).

Shunti –

It is Anti-inflammatory, expectorant, circulatory stimulant and increases bioavailability of other drugs. Its anti-inflammatory activity is comparable to that of Prednisolone. Alcoholic extract showed some significant activity against E. coli, Proteus vulgaris, Staphylococcus aureus, Streptococcus viridans.

Gingerol and Shogaol found in both fresh and dried rhizomes suppress gastric secretion and reduce vomiting. They have also shown cardio-tonic activities(8).

Guduchi –

Anti-pyretic, anti-inflammatory, smooth muscle relaxant, histamine antagonist, anti-allergic property on histamine induced bronchospasm. Alcoholic extract shows activity against E.coli(8).

Rasna –

Flavonoids in rhizomes have potent anti-fungal and antibacterial activity against both Gram positive and Gram negative bacteria. They are also active against Leukotrienes(8).

Shati –

In clinical studies, EtOH extracts showed encouraging results in TPE and anti-inflammatory properties. The oil of rhizome inhibits the growth of several fungi and antimalarial activity in in-vitro studies(8).

Karkatashrunji –

Expectorant, anti-asthmatic. The oil extracted from galls is found to be anti-spasmodic, anti-bacterial and anti-helminthic(8).

Vamshalochana –

Is extracted from nodal joints of stems of species of Bambusa arundinacea.

Diagnostic Criteria

All cases were assessed, diagnosed and evaluated based on GINA guidelines 2016.

SYMPTOMS		YES	NO
1	Typical symptoms	Wheezing	
		Shortness of breath	
		Chest tightness	
		Cough	
2	Variability of the above said symptoms		
3	Symptoms often occur or are worse at night		
4	Symptoms triggered by	Exercise	
		Laughter	
		Allergens	
		Cold air	
5	Symptoms often occur with or worsen with viral infection		

Inclusion Criteria

1. Patients in the age group of 5 to 15 years
2. Atopics
3. Intermittent, Mild persistent and Moderate persistent Asthma (diagnosed based on GINA guidelines 2016)

TYPE	SYMPTOMS	NIGHT TIME SYMPTOMS
Intermittent	<1time a week Asymptomatic and normal PEFr between attack	≤2 times a month
Mild persistent	>1 time a week but <1 time a day	>2 times a month
Moderate persistent	Daily use of β ₂ -agonist Daily attack affect activity	>1 time a week
Severe persistent	Continuous Limited physical activity	Frequent

Exclusion Criteria

1. Patients with cardiovascular, renal and other systemic disorders
2. Patients with other chronic and infective disorders of Respiratory system.
3. Primary complex
4. Foreign body aspiration
5. Acute severe asthma
6. Severe persistent asthma

Investigations Performed

Serum ECP levels before and after the treatment by ELISA method.

Study Design

Patients fulfilling the diagnostic criteria were selected for the study under a single group, blood samples were drawn for analysis of ECP in their serum and intervention started with Kantakaryavalehya for 3 months. Every 30 days patients were assessed for the symptomatology with respect to level of asthma control and PEFR values noted. After the duration, blood samples were again drawn and analysed for ECP levels in serum and analysed statistically.

Study Period:

3 month

Assessment Criteria

Level of Asthma control was assessed based on GINA guidelines 2016

	In the past 4 weeks, has the patient had	YES	NO	Well Controlled (NONE)	Partly controlled (1-2 of these)	Uncontrolled (3-4 of these)
1	Day time symptoms more than twice/week?					
2	Any night awakening due to asthma?					
3	Reliever needed more than twice/week?					
4	Any activity limitation due to asthma?					

PEFR values were also recorded during every visit.

Results:-**Table 1:-**Representing Response To The Treatment – Level Of Asthma Control

TYPE OF ASTHMA	Follow up			Total	Chi	P
	1	2	3			
PARTLY CONTROLLED	7	2	1	10	8.570	0.059
UNCONTROLLED	2	1	1	4		
WELL CONTROLLED	11	17	18	46		
Total	20	20	20	60		

As per the GINA guidelines of asthma management, response to treatment was monitored based on the level of control.

Level of Asthma control during 1st visit (after 30 days) – Among 20 cases studied, 2 cases (10%) were uncontrolled, 7 cases (35%) were partially controlled and 11 cases (55%) were well controlled.

Level of Asthma control during 2nd visit (after 60 days) – Among 20 cases studied, 1 case (5%) was uncontrolled, 2 cases (10%) were partially controlled and 17 cases (85%) were well controlled.

Level of Asthma control during 3rd visit (after 90 days) – Among 20 cases studied, 1 case (5%) was uncontrolled, 1 case (5%) was partially controlled and 18 cases (90%) were well controlled.

Thus based on the clinical evaluation among the cases during the subsequent visits, it can be said there is a good clinical improved observed. But statistically with 'p' value 0.059 only marginally significant results were obtained.

Table 2:-Representing Response To Treatment In Terms Of PEFR

PEF	Mean	Std. Deviation	F	P
0	196.67	40.117	3.134	0.030
1	220.33	33.173		
2	235.81	63.119		
3	239.67	55.133		

The mean Peak Expiratory (PEF) Rate of 20 cases before the treatment was 196.67, during the first visit on 30th day the mean PEF was 220.33, during second visit on 60th day the mean was 235.81 and on 90th day during the third visit the mean PEF value was 239.67.

It can be observed there is significant improvement in the mean of PEF values and with 'p' value of 0.030 the above finding is also statistically significant. This result is very similar to the qualitative clinical improvement found in cases and also in the quantitative evaluation through the Peak Expiratory Flow Rate.

Table 3:-Representing Response To Treatment In Terms Of Ecp

SERUM ECP	Mean	Std. Deviation	Mean Difference	P
Before treatment	8.89	3.44	1.55	0.07
After Treatment	7.34	1.90		

The mean of Eosinophil Cationic Protein (ECP) level in the blood serum of 20 cases before treatment was found to be 8.89, whereas the mean of ECP level after treatment was 7.34. With 'p' value at 0.07, it can be understood that the improvement in ECP levels is only marginally statistically significant which may be attributed to less number of samples.

Discussion:-

Bronchial Asthma is a disease characterized by increased responsiveness (hyper responsiveness) of the trachea and bronchi to various stimuli. It manifests by widespread narrowing of the airways causing paroxysmal dyspnoea, wheezing and cough.

Airway obstruction in asthma is caused by

1. Oedema and inflammation of mucous membrane lining the airways
2. Excessive secretion of mucous, inflammatory cells and cellular debris
3. Spasm of smooth muscle of bronchi (9)

Eosinophils are actively involved in all inflammatory reactions and release their cytoplasmic granules in response to reactions. Eosinophil proteins like Major basic protein-1 and 2, Eosinophil peroxidase, Eosinophil derived neurotoxin and Charcot-Leyden crystal protein and among them Eosinophil Cationic Protein is one of the many bio markers which are used to assess the severity of Asthma, response to therapy and level of Asthma control. Serum ECP has also been found to be a more sensitive marker for asthma severity than peripheral blood eosinophil counts in acute exacerbations in children.

There is strong evidence that serum ECP is raised in asthmatics, both in children and adults, and is increased in classic asthma, cough-variant asthma and occupational asthma, along with other atopic diseases like allergic rhinitis. ECP is also elevated in conditions that are not associated with eosinophil inflammation or atopy as in rhinovirus infections and bacterial sinusitis. Hence, ECP is not a useful diagnostic marker for asthma for poor specificity as it is poorly associated with exercise induced asthma, atopic eczema and food allergies(10).

There is now enough studies and evidence that ECP can be used to assess severity of asthma. Serum ECP has been shown to correlate with asthma severity, but it is mainly useful in distinguishing between intermittent or mild persistent and severe asthmatics. Serum ECP levels in an asthmatic child increases significantly during acute asthma exacerbation than at the clinical remission. The same was observed in the present study also as cases who were having episodes acute exacerbations had correlatively higher ECP levels than cases without(10). But the ECP level in serum of cases in the present study was inconsistent with the available research papers on the topic. The reason might be that all the studies conducted were in a different geographical outset than the present study conducted. And it was also observed that children with asthma and atopy had higher levels of ECP in their serum than non atopics which is also an observation stated as children with asthma and atopy had higher levels of ECP than with asthma without atopy or without asthma and atopy(3).

Drug selected to treat asthma should aim at different aspects of pathophysiology of asthma and should relieve

1. Oedema and inflammation of mucous membranes of bronchi
2. Excessive mucous secretion
3. Bronchial smooth muscle spasm.

Kantakaryavalehya is a poly herbal formulation with its indication in respiratory disorders may be termed rather as a perfect suitable drug to treat asthma, as it has the capability to relieve all the above said factors thus able to bring about break in the process of pathology by its anti-tussive, bronchodilator, smooth muscle relaxant, anti-histaminic, antibacterial, antifungal, antihelminthic, bio availability enhancer effects.

Conclusion:-

Activated eosinophils release granular proteins such as Eosinophil cationic protein, which can be measured in the serum. Increased levels of ECP seem to be related to the presence and activity of asthma and other atopic disorders. Serum ECP is useful as a useful marker for airway inflammation(11). Kantakaryavalehya is a poly herbal formulation which has considerable clinical improvement in terms of qualitative clinical evaluation based on GINA guidelines as well as quantitative evaluation using Peak Expiratory Flow Rate. But its effect on the serum marker ECP is found to be marginally statistically significant. With all the multi modal approach possible through the formulation Kantakaryavalehya, it can be considered as a formidable drug and drug of choice in the treatment of Childhood Asthma.

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