Efficacy and Safety of Bresol Syrup in the Management of Allergic Rhinitis: An Open Clinical Study

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ABSTRACT

The purpose of this study was to evaluate the safety and efficacy of Bresol syrup in the management of allergic rhinitis. This study was an open, prospective, non-comparative clinical trial. After initial examination, each subject was given a bottle containing Bresol Syrup. All patients were instructed to take 2 teaspoonful of Bresol syrup, twice daily for a period of 4 weeks. All the patients were followed up at weekly intervals for a period of 4 weeks, and the symptom score evaluation was done during each follow-up visit. A total of 20 patients with mean age 7.35±2.70 years were enrolled in the study. All subjects completed the study as planned. This study observed a highly significant reduction in the mean scores for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea. The increased levels of TLC, DLC (polymorphs, lymphocytes, monocytes, eosinophil), ESR, and AEC reduced significantly at the end of the study. There were no adverse effects reported during the study and compliance to the use of formulation was good. This study observed a highly significant reduction in the mean scores for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea and also significant reduction in ESR, and AEC with Bresol syrup. There were no clinically significant adverse reactions during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. Therefore, it may be concluded that Bresol syrup are effective and safe in the management of allergic rhinitis.

Key words: *Allergic rhinitis, Bresol syrup*

INTRODUCTION

Rhinitis is defined as inflammation of the nasal membranes[1] and is characterized by a symptom complex that consists of any combination of the following: sneezing, nasal congestion, nasal itching, and rhinorrhea.[2] The eyes, ears, sinuses, and throat can also be involved. Allergic rhinitis (AR) is the most common cause of rhinitis. It is an extremely common condition, affecting approximately 20% of the population. While allergic rhinitis is not a life-threatening condition, complications can occur and the condition can significantly impair quality of life.[3,4]

Allergic rhinitis is caused by breathing in microscopic particles of specific allergens, airborne substances to which an individual is sensitive or allergic. This substance is called an allergen.

Dust mites, cockroaches, molds and animal dander, are examples of year-around allergens. Tree, grass and ragweed pollens are primarily seasonal outdoor allergens. Plants that depend on insect pollination, such as goldenrod and dandelions, do not usually cause allergic rhinitis.

When an allergen such as pollen or dust is inhaled by an individual with a sensitized immune system, it triggers antibody production. These antibodies mostly bind to mast cells, which contain histamine. When the mast cells are stimulated by pollen and dust, histamine (and other chemicals) are released. This causes itching, swelling, and mucus production. Symptoms vary in severity between individuals. Very sensitive individuals can experience hives or other rashes. Particulate matter in polluted air and chemicals such as chlorine and detergents, which can normally be tolerated, can greatly aggravate the condition.

Rhinitis is caused by an increase in histamine. This increase is most often caused by airborne allergens. These allergens may affect an individual's nose, throat, or eyes and cause an increase in fluid production within these areas.

Characteristic physical findings in individuals who have allergic rhinitis include conjunctival swelling and erythema, eyelid swelling, lower eyelid venous stasis, lateral crease on the nose, swollen nasal turbinates, and middle ear effusion.[5,6] A chronic cough may be secondary to postnasal drip, but should not be mistaken for asthma. Sinus headaches and ear plugging are also common.

Sufferers might also find that cross-reactivity occurs.[7] For example, someone allergic to birch pollen may also find that they have an allergic reaction to the skin of apples or potatoes.[8] A clear sign of this is the

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occurrence of an itchy throat after eating an apple or sneezing when peeling potatoes or apples. This occurs because of similarities in the proteins of the pollen and the food.[9] There are many cross-reacting substances.

Poorly controlled symptoms of allergic rhinitis may contribute to sleep loss, secondary daytime fatigue, learning impairment, decreased overall cognitive functioning, decreased long-term productivity and decreased quality of life. Additionally, poorly controlled allergic rhinitis may also contribute to the development of other related disease processes including acute and chronic sinusitis, recurrence of nasal polyps, otitis media/otitis media with effusion, hearing impairment, abnormal craniofacial development, sleep apnea and related complications, aggravation of underlying asthma, and increased propensity to develop asthma.[9]

Under physical complications, otitis media with effusion, recurrent and/or chronic sinusitis, asthma, and snoring impact children with AR. Sleep disturbances, poor school performance, and hyperactivity are all mental complications seen in many children related to their nasal allergies.[10]

Allergic rhinitis is a chronic condition which affects significantly the quality of life. However, with a well integrated, medically monitored plan of care, symptoms can be effectively controlled, and people with allergic rhinitis can lead active, comfortable lives. A good treatment plan is individualized to a person's medical history, specific type of allergen, severity of symptoms, and other factors. There are various drugs available for the management of allergic rhinitis, but are not devoid of any adverse effects. So, this clinical study was conducted to evaluate the safety and efficacy of an ayurvedic formulation, Bresol syrup in management of allergic rhinitis.

Aim of the Study

The aim of the study was to evaluate the clinical efficacy and short- and long-term safety of Bresol syrup in allergic rhinitis.

MATERIALS AND METHODS

This study was an open, prospective, non-comparative clinical trial conducted at Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Twenty children from the age group of 3 to 10 years who presented with symptoms of allergic rhinitis (sneezing, nasal congestion, itching of the nose, postnasal drip and rhinorrhoea) were included in the study. Children suffering from severe systemic comorbid illness, which necessitated use of other medications, were excluded from the study.

At the initial visit, a detailed medical history with special emphasis on family and past medical history, allergy and treatment history was obtained from all patients. In all patients, a thorough systemic examination was done, which was followed by a detailed ENT examination. All patients were investigated for hematological parameters of total leucocytic count (TLC) and differential leucocytic count (DLC), erythrocyte sedimentation rate (ESR) and absolute eosinophil count (AEC) at the time of enrollment and at the end of study.

Children who met eligibility criteria were enrolled and their informed consent was obtained. After initial examination, each subject was given a bottle containing Bresol Syrup. The investigator at the initial visit advised the proper dosage and all patients were instructed to take Bresol syrup, twice daily for a period of 4 weeks.

At initial visit, a detailed medical history was obtained by interviewing the child and parent/guardian, which was followed by thorough clinical examination, with special emphasis on upper respiratory system examination.

Primary and Secondary Endpoints

The predefined primary end points were symptomatic control of allergic rhinitis like sneezing, nasal congestion, itching of the eyes and nose, post-nasal drip, rhinorrhea and watery eyes. The predefined secondary end points were prevention of recurrent episodes of allergic rhinitis and short- and long-term adverse events and patient compliance to therapy.

Follow-up and Assessment

All the patients were followed up at weekly intervals for a period of 4 weeks, and the symptom score evaluation was done during each follow-up visit. The following 4-point scale was used for assessment of symptoms: 0-Nil, 1-Mild, 2 Moderate, 3-Severe. The patients were questioned at each visit regarding the symptoms.

After fourth week, patients and investigator independently rated the overall improvement of the symptoms of allergic rhinitis.

Adverse events

All the adverse events, either reported or observed by the patients, were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to study medication was predefined as "*Unrelated*" (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), "*Possible*" (follows a known response pattern to the suspected drug, but could have been produced by the patient's clinical state or other modes of therapy administered to the patient), and "*Probable*" (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Statistical Analysis

Statistical analysis was carried out using Graph Pad Prism software

Version 4.03. The analysis on the relief of clinical symptoms based on the scores were carried out by repeated measures of ANOVA using Friedman test followed by Dunnett's Multiple Comparison tests to find out the level of significance. Haemotological parameters were analysed by using Paired t-test. The minimum level of significance was fixed at $p<0.05$. The severity score was expressed as mean ± SD.

RESULTS

A total of 20 children with mean age 7.35 ± 2.70 years were enrolled in the study. In this present study 12 males and 8 female patients participated in the study. All subjects completed the study as planned.

Significant improvements were seen in parameters like sneezing, nasal congestion, itching of eyes and nose, postnasal drip, rhinorrhea and watery eyes. On the day of entry, sneezing score was 6.20 ± 0.83, and reduced significantly ($p<0.001$) to 0.40 ± 0.50 at the end of 4th week. Nasal congestion score was 5.90 ± 0.91 on the day of entry and was 0.60 ± 0.50 at the end of 4th week with a significance of $p<0.001$. Itching of eyes the mean value was 5.95 ± 0.76 at the entry and was reduced to 0.35 ± 0.49 at the end of 4th week with a significance of $p<0.001$. Itching of the nose score was 6.00 ±1.17 on the day of entry and was reduced to 0.25 ± 0.44 at the end of 4 weeks showing a significance of $p<0.001$. Postnasal

drip score reduced from 6.05 ± 0.69 at entry to 0.25 ± 0.44 at the end of 4th week with a significance of $p<0.001$. Rhinorrhea score was 6.35 ± 0.75 on the day of entry which reduced to 0.25 ± 0.44 at the end of 4th week with statistical significance of $p<0.001$. The score for watery eyes was 5.74 ±0.65 at entry which reduced significantly ($p<0.001$) to 0.32 ± 0.48 at the end of 4th week (Table 1).

All the hematological parameters like WBC, neutrophils, lymphocytes, eosinophils, monocytes, ESR and AEC showed significant improvements with Bresol treatment ($p<0.0001$). On the day of entry WBC (cells/cu.mm.) was 10,780 ± 2515 and was reduced to 6901.00 ± 944.10 at

Table 1: Details regarding treatment Initiation and patient's history refer to excel sheet. Relief of clinical symptoms in allergic rhinitis.

Parameter	On entry	Week 1	Week 2	Week 3	Week 4
Sneezing	6.20 ± 0.83	5.35 ± 0.67	4.15 ± 0.93 [a]$p<0.01$	2.25 ± 0.72 [b]$p<0.001$ [d]$p<0.001$	0.40 ± 0.50 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Nasal congestion	5.90 ± 0.91	5.35 ± 0.67	4.00 ± 1.08 [a]$p<0.01$	1.80 ± 0.89 [b]$p<0.001$ [d]$p<0.001$	0.60 ±0.50 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Itching of eyes	5.95 ± 0.76	5.15 ± 0.59	3.75 ±1.07 [a]$p<0.01$	1.90 ±0.64 [b]$p<0.001$ [d]$p<0.001$	0.35 ± 0.49 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Itching of nose	6.00 ±1.17	5.20 ± 0.83	3.65 ± 0.99 [a]$p<0.01$	1.80 ± 0.89 [b]$p<0.001$ [d]$p<0.001$	0.25 ±0.44 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Postnasal drip	6.05 ± 0.69	5.10 ± 1.02	3.75 ± 1.12 [a]$p<0.01$	1.85 ± 0.67 [b]$p<0.001$ [d]$p<0.001$	0.25 ± 0.44 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Rhinorrhoea	6.35 ± 0.75	5.20 ± 0.95	3.85 ± 0.93 [a]$p<0.01$	1.75 ± 0.97 [b]$p<0.001$ [d]$p<0.001$	0.25 ±0.44 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$
Watery eyes	5.74 ±0.65	4.90 ± 0.88	3.58 ± 0.96 [a]$p<0.01$	1.74 ± 0.81 [b]$p<0.001$ [d]$p<0.001$	0.32 ± 0.48 [c]$p<0.001$ [e]$p<0.001$ [f]$p<0.001$

Statistical analysis: Repeated measures of ANOVA using Friedman test followed by Dunnets Multiple Comparison Posthoc test.

Significance: [a]: At entry versus week 2; [b]: At entry versus week 3; [c]: At entry versus week 4; [d]: week 1 versus week 3; [e]: week 1 versus week 4; [f]: week2 vs week 4.

the end of 4th week. On the day of entry eosinophils (%) was 11.75 ± 3.52 and was reduced to 3.95 ± 1.85 at the end of 4 weeks. On the day of entry ESR (mm/hr) was 29.25 ± 10.73 and was reduced to 14.90 ± 5.44 at the end of 4 weeks. On the day of entry AEC was 1168.0 ± 339.2 and was reduced to 291.1 ± 167.0 at the end of 4 weeks (Table 2).

There were no adverse effects observed or reported during the study and compliance to the use of formulation was good. There were no drop outs or withdrawal from the study.

DISCUSSION

Allergic rhinitis impacts the quality of life of children and their families. Sleep disturbances and daytime fatigue related to AR lead to decreased attention, impaired learning and poor school performance. Allergic rhinitis may adversely affect social development. Associated conditions such as Otitis media with effusion may impact hearing and speech development. Patients with allergic rhinitis typically require multiple medications as no single drug relieves all symptoms of allergic rhinitis. Currently available treatment options for allergic rhinitis have major limitations due to low efficacy, associated adverse events and compliance issues.

Bresol syrup is a polyherbal formulation indicated for management of allergic rhinitis. Bresol syrup contains extracts of *Curcuma longa, Ocimum sanctum,* Trikatu, Triphala, *Embelia ribes, Cyperus rotundus, Cinnamomum zeylanicum, Elettaria cardamomum, Cinnamomum tamala* and *Mesua ferrea.*

In various animal and human studies, curcuminoids - I, II and III (components of *Curcuma longa*)[11] have been shown to inhibit a number of molecules involved in inflammation (phospholipase, LO, COX-1 and -2, LT, TX, PGs, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, interferon-inducible protein, TNF, and IL-12.[12,13] Curcumin has been reported to have anti-allergic property, as tested in an *in vitro* model of airway hyperresponsiveness.[14] Kang et al.,

observed that curcumin significantly inhibited production of IL-12, reduced induction of IFN-á, IL-4 in CD4+ T-cells by macrophages, leading to the inhibition of TH1 cytokine profile (ÔIFN-á and ÓIL-4 production) in CD4+ T-cells.[15] Curcumin is a potent antioxidant and it inhibits Ca^{2+} entry and protein kinase C activity.[16] Curcumin also has an immunostimulatory activity and hence increases the circulating antibody titer, plaque forming cells, alpha-esterase positive cells and phagocytosis.[17]

Gingerols and diarylhepatanoids are the active ingredients of *Zingiber officinale*, which are potent inhibitors of prostaglandin biosynthesizing enzyme (PG synthetase). Umeda et al., recorded that, *Zingiber officinale* inhibited biotransformation of AA comparable to indomethacin.[18] The other ingredients of *Zingiber officinale*, namely oleoresins ([8]-paradol, [8]-shogaol) have inhibitory effects on COX-2 enzymes[19] and the mechanism of action was hypothesized by the attenuation of COX-1 / TX synthase enzymatic activity.[20] Thomson et al., documented significant inhibitory effects of *Zingiber officinale* on PG-E2 production[21]. Ahmed et al., observed that the antioxidant effect of *Zingiber officinale* was comparable to ascorbic acid as demonstrated by

lowered lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase).[22] [6]-gingerol was found to be a potent inhibitor of iNOS and also an effective protector against peroxynitrite-mediated damage[23]. Wilasrusmee et al., reported the immunosuppressive effects of *Zingiber officinale in vitro* as evident by the decreased responsiveness in lymphocyte culture.[24] The *Zingiber officinale* extract had been shown to raise the thymus index, spleen index, phagocytosis, and rate of á-naphthyl acetate esterase+ and titer of IgM, which indicates immunostimulation.[25]

Dihydrokawain, yangonin and methysticin are the principle anti-inflammatory ingredients of *Piper longum*.[26] Choudhary et al., documented that *Piper longum* inhibits the lipid peroxidation process effectively by its ability to scavenge free radicals involved in initiation and propagation steps.[27] Chiou et al., observed that *Piper longum* retards the macrophage recruitment and suppresses cytokine production.[28] Hashimoto et al., isolated kawapyrones from *Piper longum* and recorded inhibition of TNF-alpha release.[29]

Tannoids (emblicanin A and B, punigluconin, and pedunculagin) are the principle ingredients of *Emblica*

Table 2: Hematological parameters

Parameter	Before treatment	After treatment
WBC (/cumm)	10,780.00 ± 2515.00	6901.00 ± 944.10 $p<0.0001$
Neutrophiles (%)	48.95 ± 9.04	48.50 ± 3.15 $p<0.0001$
Lymphocytes (%)	34.70 ± 7.61	44.55 ± 3.85 $p<0.0001$
Eosinophils (%)	11.75 ± 3.52	3.95 ± 1.85 $p<0.0001$
Monocytes (%)	2.95 ± 1.61	3.00 ± 1.69 $p<0.0001$
ESR (mm/hr)	29.25 ± 10.73	14.90 ± 5.44 $p<0.0001$
AEC	1168.0 ± 339.2	291.1 ± 167.0 $p<0.0001$
Statistical analysis: Students paired 't' test		

officinalis.[30] In addition to the antitussive activity, it was observed that *Emblica officinalis* has anti-inflammatory, antispasmolytic and antioxidant efficacy and it reduces the mucus secretion in the airways.[31] Khanom et al., identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of *Emblica officinalis.*[32] Sai Ram et al., observed that *Emblica officinalis* significantly inhibited free radical production, restored the anti-oxidant status, inhibited apoptosis and DNA fragmentation, relieved the immunosuppressive effects on lymphocyte proliferation and even restored the IL-2 and gamma-IFN production.[33] In another study, it was observed that *Emblica officinalis* acts as an immunomodulator and decreases the induction of iNOS.[34]

Tasaduq et al., demonstrated potent anti-peroxidative activity of *Terminalia belerica.*[35] *Terminalia belerica* inhibited lipid peroxide formation by scavenging hydroxyl and superoxide radicals *in vitro.*[36] Saleem et al., observed the antioxidant potential of *Terminalia belerica* (stronger than alpha-tocopherol), which was attributed to hydroxybenzoic acid and hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides.[37]

Godhwani et al., documented that *Ocimum sanctum* has an immunostimulatory effect on the humoral immunologic response (an increase in antibody titre), as well as on the cellular immunologic response (E-rosette formation and lymphocytosis).[38] Another study documented a decrease in histamine release from mast cells (humoral immune responses) and a decrease in leucocyte migration inhibition (cell-mediated immune responses). This immunomodulatory effect was postulated as mediated by gamma-aminobutyric acidergic pathways.[39] Kelm et al., documented an anti-oxidant bioassay of *Ocimum sanctum* (which yielded cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and eugenol) and in addition observed a potent anti-inflammatory (COX-I and -II inhibitory) activity.[40] *Ocimum sanctum* was found to possess significant anti-inflammatory activity against PG-E2, leukotriene and AA, and the results suggested that *Ocimum sanctum* has the capacity to block both the cyclo-oxygenase and LO pathways of arachidonate metabolism[41]. Singh et al., observed significant inhibition of leucocyte migration in the pleural exudates, which suggest that the *Ocimum sanctum* inhibits enhancement of vascular permeability and leucocyte migration following inflammatory stimulus.[42] Analgesic action of *Ocimum sanctum* is exerted both centrally as well as peripherally.[43] Balanehru et al., observed the free radical scavenging potential of ursolic acid isolated from *Ocimum sanctum* against lipid peroxidation *in vitro.*[44] Maulik *et al*., demonstrated the potent free radical scavenging activity.[45] Orientin and Vicenin (isolated from *Ocimum sanctum*) have strong antioxidant activity.[46]

The widely used mucolytics namely benzylamines (bromhexine and ambroxol) are the semi-synthetic derivatives of vasicine extracted from *Adhatoda vasica*, and these benzylamines enhance lysozyme levels in respiratory tract secretions and clear bacilli-laden mucus.[47] Chakraborty et al., reported the potent anti-inflammatory activity of *Adhatoda vasica* to be equivalent to that of hydrocortisone.[48] Paliwa et al., documented the potent antiallergic activity of "Compound 73/602 (AA)" (a structural analogue of vasicinone, an alkaloid of *Adhatoda vasica*).[49] Dhuley et al., reported the antitussive activity of *Adhatoda vasica* to be similar to that of codeine *in vitro.*[50]

The principle ingredients of *Cyperus rotundus* are four sesquiterpenes (beta-selinene, isocurcumenol, nootkatone and aristolone) and a triterpene (oleanolic acid).[51] Seo et al., observed inhibition of NO and O_2^- production in-vitro by *Cyperus rotundus* and the inhibition was due to the suppression of iNOS protein, as well as iNOS messenger RNA expression.[52] *Terminalia belerica* has a potent antifungal activity.[53] The synergetic effect of all these helps to relive allergic rhinitis symptoms.

CONCLUSION

This study observed a highly significant reduction in the mean scores for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea. The increased levels of TLC, DLC (polymorphs, lymphocytes, monocytes, eosinophil), ESR, and AEC reduced significantly at the end of the study. These excellent results might be due to the synergistic activities of the ingredients of Bresol syrup. There were no clinically significant adverse reactions during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. Therefore, it may be concluded that Bresol syrup are effective and safe in the management of allergic rhinitis.

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