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CLINICAL STUDY ON THE IMMUNOMODULATORY EFFECT OF NIDIGDHIKADILEHA ON PRANAVAHA SROTO DUSHTI W. S. R. UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

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ABSTRACT: Aim of study: A Randomized controlled trial was planned to evaluate the Clinical efficacy of *Nidigdhikadileha* an Ayurveda multi-dimensional herb preparation in children suffering from Recurrent Respiratory tract infection in children. *Nidigdhikadileha* contains *Nidigdhika* (*Solanum Xanthocarpum*), *Pippali* (*Piper longum*), *Amrita* (*Tinospora cardifolia*), and *Nagar* (*Zingiber officinale*). All these drugs have been described to have anti-tussive and antimicrobial properties. Material & methods: A total of 90 children, including male and female children, were studied for complaining of Recurrent Upper Respiratory Tract infections and were registered and divided into 3 groups (Group A, B, C). In group A, children were administered *Nidigdhikadileha*, dose180-200 mg/kg/dose twice a day for 2 months in children suffering from RURTI. In group B, honey drops were administered to 30 children at a dose of 1ml/kg/day, and in Group C there is also 30 patients were administered *Sitopaladi churna* at a dose 100 mg/kg/day. All the treated cases were assessed at each follow-up on the 14th day, 28th day, 42nd day, and 56th day, and post-follow-up was done after 1 month. The efficacy of drugs was assessed clinically and also based on investigations. Result: Signs and symptoms of *Pranavaha srotodusti* persisted maximum up to 28th day follow up and on 42ndday improvement in clinical signs and symptoms were found significant. Conclusion: In all cases, significant improvement was observed.

INTRODUCTION: Upper respiratory tract infections are the major cause of childhood morbidity, limiting day-to-day activities and school absenteeism. Diseases like tonsillitis, cough, and cold account for the maximum respiratory tract morbidities. Studies document that, in developing countries, every child has five episodes of acute respiratory infections per year, accounting for 30%-50% of the total pediatric outpatient visits and 20%-30% of the pediatric admissions. Ayurveda states that in children, the Prana, Dosha, Dhatu, Bala, and Ojas are underdeveloped and therefore they are the most vulnerable group in terms of illness. Therefore they should be supported externally to potentiate their immune system. Good immunity has a substantial role in sustaining the body and preventing various infections. Although available conventional management provides symptomatic relief, there is no conclusive evidence that they shorten the duration of symptoms. The use of antibiotics is also not empirical.

Therefore, it is the need of hour to find some alternative to provide relief in symptoms, potentiate the immune system to resist the infections, and minimize the use of antibiotics. Ayurveda classics explain the upper respiratory tract infections under Kasa, Shwasa, Pratishyaya, peenasa, Mukha Roga with a comprehensive approach to the treatment. Nidigdhikadileha is indicated for Kasa, Shwasa, Jwara and Peenasa. The present review provides evidence that the drug Nidighdhikadileha may be

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used as a potent drug to manage recurrent upper respiratory tract infections in children.

Aim and Objectives of Study:

1. To evaluate the immunomodulatory effect of Nidigdhikadileha.

2. To evaluate the effect of Nidigdhikadilehain on recurrent respiratory tract infections in children.

MATERIAL AND METHOD:

Study Type: Open-Label Randomized Controlled Clinical Trial.

Selection of Cases: Total 101 participants presenting with morbidity features of Upper Respiratory Tract Infection were enrolled for this clinical trial and were equally divided into 3 groups, out of which 11 subjects were dropped out. A total of 90 patients completed the trial. Total 30 patients in each group completed the trial.

Source: Subjects attending the O. P. D and I. P. D. of Kaumarbhritya department of National Institute of Ayurveda, Jaipur, screened for this study.

Age Group: 6 to 12 years of either sex.

Drug Therapy:

Group A: Trial Drug (Nidigdhikadileha)

Group B: Control Drug (Honey drops)

Group C: Standard Treatment (Sitopaladi Churna)

Trial Drug: Nidigdhikadileha is mentioned in Chakradutta Jwara Chikitsha / 199.

TABLE 1 [1-51]: GROUPING OF PATIENTS AND DRUG INTERVENTION

Groups	Group A (Trial Drug) n=30	Group B (Control Group) n=30	Group C (Standard Control) n=30
Intervention	Nidigdhikadileha	Honey drops	Sitopaladi Churna
Dose	180-200 mg/kg/day	1 drops/kg/day	100 mg/kg/day
Dose form	Avaleha	Liquid	Powder
Route of administration	Oral	Oral	Oral
Duration	8 weeks	8weeks	8 weeks
Administration	After breakfast Morning-evening	After breakfast Morning-evening	After breakfast Morning-evening

Follow-ups: Every 2 weeks (Day 14th, 28th, 42nd and 56th)

Post Treatment Follow-up: After four weeks

End Point: Clinically Safety and Efficacy

TABLE 2: COMPOSITION OF TRIAL DRUG NIDIGDHIKADILEHA [1-51]

S. no.	Name of Drug	Latn Name	Part Used	Proportion
1	Nidigdhika	*Solanum Xanthocarpum*	Fruit	1 Part
2	Nagar	*Zingiber officinale*	Rhizome	1 Part
3	Amrita	*Tinosporacardifolia*	Stem	1 Part
4	Pippali	*Piper longum*	Fruit	1 Part

Preparation of Trial Drug: The drug was prepared in the pharmacy of National Institute of Ayurveda Jaipur as Avaleha form mixed with madhu (honey) to enhance its palatability for easy administration in children.

Presentation of Drug:

Trial Drug: In the form of *Avaleha* packed in 50 gm tetra pack

Control Group: Honey Drops (packed in 15 ml vial)

Conventional Treatment: Sitopaladichurna in Powder form with honey (*Charak Samhita Rajyakshama Chikitsa* 8/103-104).

Criteria for Selection of Patients:

Inclusion Criteria: Children aged between 06 to 12 years of either sex.

Children with recurrent upper respiratory infections. Children whose parents are willing to give consent for a clinical trial.

Exclusion Criteria: Children suffering from major systemic illness necessitating hospitalization were excluded. Children with evidence of malignancy, genetic or congenital anomaly, and chronic illness like TB, UTI, and bleeding disorders. Children with concurrent serious hepatic dysfunction (defined as AST and/or ALT>3 times of the upper normal limit) or renal dysfunction (defined as S. creatinine>1.2mg/dl) uncontrolled pulmonary dysfunction (asthmatic and COPD patients)**.** Chronic illnesses like TB, UTI and bleeding disorders *etc*. H/o hypersensitivity to any of the trial drug or their ingredients.

Withdrawal Criteria: The participant withdrew from the trial under the following condition:

1) Parents are not willing to continue.
2) Any major ailment necessitates the institution of new modalities of treatment.
3) Non-compliance with the treatment regimen (minimum 80% compliance is essential to continue the study).
4) Any adverse effect of drug during trial.

Assessment Criteria: Assessment was done before, during, and after treatment.

Subjective Assessment: This included various manifestations of upper respiratory tract infections based on clinical features of morbidity like Nasal Obstruction, Running Nose and Wheezing, Fever, *etc*., according to modern and *Ayurveda* assessment criteria. Grading on a four-point scale Morbidity score was calculated as-

Morbidity Score = Incidence in last Two months × severity

Laboratory Investigations: CBC, ESR, IgG, TEC

Outcome Measures:

Primary Outcome Measures: Change in Morbidity Score.

Secondary Outcome Measures: Decrease in episodes of Upper respiratory tract infections and improvement in quality of life of children.

Ethical Clearance: Ethical clearance of the present trial was obtained from Institutional Ethics Committee after deliberation on 8th& 9th May 2019 with Reference No. IEC/ACA/2019/1-14, National Institute of Ayurveda, Jaipur.

Clinical Trial Registry of India Registration: Before starting the clinical trial, the present trial was applied for registration in CTRI with reference number REF/2020/07/035310 and CTRI with Registration No CTRI/2020/08/027386.

Data Documentation and Analysis: Observations were documented during the study, analyzed and evaluated findings using statistical methods (student's t-test) to establish the efficacy.

- For correlation: Chi-square test
- For comparison: Kruskal Wallis Test
- For Objective parameter- Students' t-Test
- For Intergroup comparisons- One Way ANOVA Test, Two-way ANOVA Test, Wilcoxon Test
- For Intragroup Comparisons- Paired sample t-Test.

OBSERVATION & RESULTS

TABLE 3: BASIC DETAILS OF THREE GROUPS

Basic Details	Mean ± SD || Median (IQR) || Min-Max || Frequency (%)
Group	
A	30 (33.3%)
B	30 (33.3%)
C	30 (33.3%)
Age (Years)	8.27 ± 1.88 || 8.00 (7.00-10.00) || 6.00 - 12.00
Gender	
Male	53 (58.9%)
Female	37 (41.1%)
Religion	
Hindu	70 (77.8%)
Muslim	20 (22.2%)

Socio-Economic Status	
Upper	2 (2.2%)
Upper Middle	16 (17.8%)
Middle	34 (37.8%)
Lower Middle	35 (38.9%)
Lower	3 (3.3%)
Residence	
Urban	83 (92.2%)
Rural	7 (7.8%)
Family Status	
Nuclear	71 (78.9%)
Joint	19 (21.1%)
Birth Weight (Kg)	2.73 ± 0.26 ‖ 2.60 (2.50-3.00) ‖ 2.20 - 3.25
Age of Weaning	
Before 6 Months	14 (15.6%)
6 Months	58 (64.4%)
After 6 Months	18 (20.0%)
Mode of Feeding At Birth	
Breast Feeding	70 (77.8%)
Top Feeding	20 (22.2%)
Immunization History	
Complete	82 (91.1%)
Incomplete	8 (8.9%)
Present Appetite	
Good	38 (42.2%)
Average	33 (36.7%)
Poor	17 (18.9%)
Excessive	2 (2.2%)
Present Pattern Of Diet	
Vegetarian	57 (63.3%)
Mixed	33 (36.7%)
Status Of Agni	
Samagni	65 (72.2%)
Mandagni	22 (24.4%)
Tikshnagni	2 (2.2%)
Vishamagni	1 (1.1%)
Sleep	
Sound	79 (87.8%)
Excessive	10 (11.1%)
Disturbed	1 (1.1%)
Associated Complaints	
None	47 (52.2%)
Snoring	26 (28.9%)
Conjuctivitis	6 (6.7%)
Otitis Media	6 (6.7%)
Tonsilitis	5 (5.6%)
H/O Deworming (Yes)	42 (46.7%)
Prakriti	
V-K	59 (65.6%)
V-P	19 (21.1%)
P-K	12 (13.3%)

TABLE 4: CHANGES IN MORBIDITY SCORE TIME POINT COMPARISON OF THREE GROUPS

Timepoint Comparison	Change in Morbidity Score from Before Treatment to Follow-up Timepoints						P-Value for Comparison of the three Groups in Terms of Difference of Morbidity Score from Before Treatment to Follow-up Timepoints
	Group: A		Group: B		Group: C		
	Mean (SD) of Absolute Change	P-Value of Change Within Group	Mean (SD) of Absolute Change	P-Value of Change Within Group	Mean (SD) of Absolute Change	P-Value of Change Within Group	
Nasal Obstruction After Treatment - Before Treatment	-4.40 (2.33)	<0.001	0.33 (1.84)	0.679	-4.43 (2.28)	<0.001	<0.001
Nasal Obstruction Post Follow-Up - Before Treatment	-4.17 (2.23)	<0.001	0.27 (2.30)	0.758	-0.80 (3.07)	0.400	<0.001
Running Nose After Treatment - Before Treatment	-4.13 (2.26)	<0.001	-0.73 (2.45)	0.400	-4.27 (2.00)	<0.001	<0.001
Running Nose Post Follow-Up - Before Treatment	-3.93 (2.32)	<0.001	-1.40 (2.11)	0.045	-3.73 (2.15)	<0.001	<0.001
Wheezing After Treatment - Before Treatment	-2.47 (2.29)	<0.001	0.43 (1.57)	0.719	-2.63 (2.22)	<0.001	<0.001
Wheezing Post Follow-Up - Before Treatment	-2.17 (2.38)	<0.001	0.47 (1.57)	0.597	-2.90 (2.29)	<0.001	<0.001
DysponeaAfter Treatment - Before Treatment	-1.67 (0.92)	<0.001	0.10 (0.61)	0.894	-1.23 (1.14)	<0.001	<0.001
DysponeaPost Follow-Up - Before Treatment	-1.73 (0.87)	<0.001	0.07 (0.69)	0.863	-0.57 (1.04)	0.167	<0.001
Cough After Treatment - Before Treatment	-3.37 (2.24)	<0.001	0.07 (0.37)	0.980	-3.47 (2.10)	<0.001	<0.001
Cough Post Follow-Up - Before Treatment	-3.37 (2.28)	<0.001	-0.17 (1.44)	1.000	-3.37 (2.22)	<0.001	<0.001
Fever After Treatment - Before Treatment	-1.47 (2.08)	0.008	0.07 (0.37)	0.980	-1.83 (2.78)	0.062	<0.001
Fever Post Follow-Up - Before Treatment	-1.33 (2.11)	0.038	0.07 (1.62)	0.921	-3.30 (2.73)	<0.001	<0.001

TABLE 5: COMPARISON OF THE THREE GROUPS IN TERMS OF CHANGE IN T. E. C AND IGG OVER TIME (N = 90)

TEC	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	P-value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
Before Treatment	0.28 (0.16)	0.27 (0.17)	0.30 (0.18)	0.817
After Treatment	0.24 (0.14)	0.30 (0.18)	0.29 (0.18)	0.222
P Value for change in T.E.C over time within each group (Wilcoxon Test)	<0.001	0.048	0.098	
Overall P-Value for comparison of the change in TEC over time between the three groups (Generalized Estimating Equations)		<0.001		
IgG	A Mean (SD)	Group B Mean (SD)	C Mean (SD)	P-value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
Before Treatment	1061.67 (157.73)	1069.13 (141.61)	1041.20 (162.79)	0.777
After Treatment	1114.33 (156.90)	1073.67 (150.39)	1093.27 (149.34)	0.462
P Value for change in IgG over time within each group (Wilcoxon Test)	<0.001	0.021	<0.001	
Overall P-Value for comparison of the change in IgG over time between the three groups (Generalized Estimating Equations)		<0.001		

Effect of Therapy: Group A showed the highly significant result in morbidity features like Nasal obstruction, Running nose, Wheezing, Dyspnoea, Cough, Fever, Recurrence, Severity, Weight, and Height gain. In haematological parameters, Hb%, Lymphocytes, TEC, IgG showed highly significant results and were insignificant in the rest of the parameters.

Group B showed no significant results in morbidity features, while only Hb% and Neutophils showed significant results in laboratory parameters.

Group C showed the significant result in Nasal obstruction, Running nose, Wheezing, Dyspnoea, and Cough. However, post-follow-up results were not satisfying in Nasal obstruction and Wheezing. Laboratory parameters show the significant result in Hb%, and rest of the parameters is non-significant.

Overall Effect of Therapy: In Group A (Nidigdhikadileha) and Group C (Sitopaladi Churna), improvement was seen in all morbidity features. At the same time, no significant changes were noted in morbidity features in Group B (Honey drops). Compared to all three groups, Group A showed a highly significant result and, after treatment, post-follow-up was satisfied.

Discussion on Mode of Action of Trial Drug: According to Ayurveda classics, Pranavaha Srotasdusti is responsible for all respiratory illnesses. Pranavaha Srotas is the main unit for the lungs and heart. Any pathology or changes in anatomical structure cause Pranavaha Srotodusti. Ayurveda classics also explain the same in terms of Upper Respiratory tract infections under the heading of Kasa, Shwasa, Pratishyaya, Mukha Roga with a complete approach to the remedy of the same. It is established in Ayurveda that Ojas (immunity) plays an effective role in preventing such pathological states. Ojas of an individual are usually challenged in the early life period because of physiological, structural, dietetic, and biochemical limitations. The trial drug Nidigdhikadileha is a component of 4 herbs with multi-dimensional properties. These drugs directly act on the Pranavaha Srotas (Respiratory Tract). Kantakari, Sunthi, Guduchi, and Pippali have Vata-Kaphahara properties. These drugs are dominant in Teekshna Rasa, Ushana Virya, Laghu Guna, and some of Katu Tikshana, so they act on Respiratory tract mucosa and start Vilayana of Kapha Dosha. When obstructed Kapha melted down it resulted in the removal of Sroto Avarodha, which Kapha Dosha, While cause, Ushna Virya dried up the excessive discharge of Respiratory Tract. The Vatahara Guna causes Vatanulomana and pacify Vimarga Kupita Vata caused due to Avarana. Kantkari, Sunthi, Pippali also act as Deepana, Pachana and Vatanulomana. All these actions, especially Srotoshodhana, help regulate the body's metabolism. Kantkari also has a good nutritional value and provides nourishment to the body. Pippali and Guduchi nourish the body with their Rasayana effect and lower the infections through their antimicrobial effect. Overall, Nidigdhikadi Leha decreases the Vata Kapha Dosha, Amapachaka, and Srotoshodhana, by which Ojas and Dhatusara increase in body Vyadhikshamatva will improve.

In modern science, available management like first-generation antihistamines, antipyretics (paracetamol) or anti-inflammatory agents (ibuprofen), cough suppressants such as dextromethorphan, expectorants (guaifenesin), and decongestants such as pseudoephedrine and phenylpropanolamine provide symptomatic relief but do not reduce the duration of illness either they reduce the frequency of illness. The indications of the drug Nidigdhikadileha in Chakradutta are jwara (fever) along with kasa (cough), shwasa (dyspnoea), peenasa (rhinitis), indicating the symptoms of respiratory infections. Drug ingredients suggest that these drugs have immunomodulatory, anti-bacterial, antioxidative, antimicrobial, analgesic, and bioavailability enhancing effects. The immunomodulatory effect may show the sustained effect of the drug and may reduce the frequency and severity of illness. Anti-inflammatory, Bronchodilator effect, antihistaminic and anti-asthmatic, properties may help in alleviating the symptoms and provide relief.

Anti-allergic and anti-tussive, the effect can help in relieving the symptoms. Also, the drugs have a nutritional effect that may add to better growth and development and improve the child's immune system.

This reveals that the ingredients of Nidigdhikadileha possess immunomodulatory, anti-bacterial, anti-oxidative, antimicrobial, analgesic, and bioavailability enhancing effects. Also, the ingredient affects bronchial asthma, anti-tussive and anti allergic effects, and has high nutritional value. Therefore, Nidigdhikadileha can be a potent remedy for managing recurrent upper respiratory tract infections in children.

Limitations of the Study: The present study was done with a small sample of patients due to time and financial constraints. The results obtained are just a preview of information for future researchers to study involving a large sample size. It is expected that further study on this project could be beneficial for the children suffering from recurrent respiratory infections.

CONCLUSION: Statistically significant improvement was found in Morbidity scores-Running nose, Nasal obstruction, Wheezing, Dyspnoea, Cough, and Fever in group A (trial group) ($p<0.001$). No significant improvement was obtained in group B (Honey) in any of the morbidity scores except for Running nose, in which significant improvement was found. Statistically significant improvement ($p<0.001$) was observed in Running nose, Nasal obstruction, Wheezing, and Dyspnoea in group C (Active control); no significant improvement was found in cough and fever in this group (Group C). Over time, the overall change in running nose, Nasal Obstruction, Wheezing, Dyspnoea, Cough and Fever Morbidity Score was compared in the three groups using the Generalized Estimating Equations method.

There was a significant difference in the trend of Running nose, Nasal Obstruction, Wheezing, Dyspnoea, Cough, and Fever Morbidity Score over time between the three groups ($p = <0.001$). Post-treatment follow-up showed significant improvement in all the morbidity features in group A (trial group), $p< (0.001)$, suggesting immune-enhancing and sustained effect of the trial drug (Nidigdhikaadileha). No adverse effect of the trial drug was observed during the study.

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