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Research Article

Clinical Study and Assessment of Efficacy of Polyherbal Combination (KNDBHU) in COVID 19 Patients

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ABSTRACT

Even three years after the COVID-19 pandemic initially appeared in December of the year 2019, it is still raging over the globe. There have been numerous attempts to use well-known medications in new ways to treat COVID-19 infection. Many nations, including India, implemented a series of lock downs in an effort to limit the pandemic. Sanitation practices, social seclusion, routine mask wearing, testing, and quarantining of suspected carriers were among the recommended methods for limiting the illness. Numerous treatment strategies have also been used to prevent and treat the illness, but no formal studies using well-known Ayurvedic formulations or any polyherbal combinations have been conducted. A clinical study was planned to test the noble polyherbal combination containing *Withania somnifera, Tinospora cordifolia, Moringa oleifera, Adhatoda vasica, Piper longum, Glycyrrhiza glabra, Ocimum sanctum* and *Curcuma longa*. The study checked the rate of symptom remission in individuals receiving the polyherbal combination in addition to standard of care (SoC) to that in patients with mild and moderate symptoms of COVID-19 infections receiving SoC alone. A prospective randomized interventional clinical study was planned comparing outcomes in 2 cohorts with mild to moderate COVID-19 as under. Cohort-1 was trialled with conventional treatment as per government advisory. Cohort-2 was trialled with polyherbal combination and with conventional treatment as per government advisory. With the current add-on Polyherbal regimen, an early clinical improvement in breathlessness was seen along with early ageusia and cough reduction when compared with conventional treatment. The polyherbal combination (KNDBHU) enhanced recovery in COVID-19 Patients. Given the lack of hospital beds in India, the median length of hospital stays was shortened; this development is significant.

Keywords: Covid19; Add on polyherbal combinationregimen for Corona virus; Early Clinical Improvement; Shortened hospital stays

INTRODUCTION

Even three years after the COVID-19 pandemic initially appeared in December of the year 2019, it is still raging over the globe. There have been numerous attempts to use well-known medications in new ways to treat COVID-19 infection. Despite the early hoopla, it has since been discovered that hydroxychloroquine is ineffective against SARS-CoV-2. Clinical investigations of hydroxychloroquine (HCQ) for recovery and post-exposure prophylaxis (PeP) did not yield encouraging results.[1,2] For treating patients infected with the SARS-CoV-2 virus, no one antiviral medication has been shown to be particularly effective. Patients with mild to severe COVID-19 infections have participated in clinical studies for well-known antiviral medications like Remdesivir. The findings, however, were inconclusive, indicating that Remdesivir may not be the most effective treatment for COVID-19.[3–5] There is a need for intervention from alternative medical systems because there is no known cure. For mild to moderate cases, the typical recovery time is two to three weeks. Even though patients are rigorously sequestered after being identified, there is a 14–30day window during which they could potentially transfer the infection. Unfortunately, because the incubation and illness progression phases are difficult to discern in asymptomatic individuals, this has greatly increased the

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likelihood of viral dispersion. In light of the current dire state of medical problems throughout the world, 3 weeks is a considerable amount of time. Additionally, greater community transmission from this silent viral spread would greatly raise the likelihood that the already overburdened medical infrastructure and services would collapse.

Many nations, including India, implemented a series of lock downs in an effort to limit the pandemic. Sanitation practices, social seclusion, routine mask wearing, testing, and quarantining of suspected carriers were among the recommended methods for limiting the illness.[6] Numerous treatment strategies have also been used to prevent and treat the illness, but no formal studies using well-known polyherbal combination have been conducted. In reality, the Indian government's ministry of health did not include Ayurvedic remedies in its advice on how to treat COVID 19 clinically.[7] Key study fields had been chosen by the Indian Council of Medical Research (ICMR) to produce vital information for preventative and control activities.[8] The Ministry of AYUSH (Ayurveda, Yoga, Unani, Siddha & Homeopathy) has developed suggestions for the disease's symptomatic treatment and prevention (through strengthening immunity).[9]

Results from epidemiological research carried out by the Ministry of Health & Family Welfare, Government of India (GoI), are consistent with those discovered elsewhere.[10] According to the Centres for Disease Control and prevention (CDC), 81% of COVID patients who were hospitalised had significant symptoms.[11] It has been established that the new coronavirus mostly affects the upper and lower respiratory tracts.[12] A range of herbs are suggested by the Ayurvedic medical system for the treatment of illnesses of the respiratory tract; therefore, a clinical study was planned to test the noble polyherbal combination containing *Withania somnifera, Tinospora cordifolia, Moringa oleifera, Adhatoda vasica, Piper longum, Glycyrrhiza glabra, Ocimum sanctum* and *Curcuma longa*. The study was planned to check the rate of symptom remission in individuals receiving the polyherbal combination in addition to standard of care (SoC) to that in patients with mild and moderate symptoms of COVID-19 infections receiving SoC alone.

METHODOLOGY

Preclinical Study

Acute toxicity

Six female Wistar rats for the treatment group and five female Wistar rats for the control group were employed in the acute toxicity study using the fixed-dose methodology. There was a single dosage of the drug containing 2,000 mg/kg of Polyherbal formulation given orally. No fatalities or significant toxic effects were observed at the end of the experiment, and it was found that the polyherbal formulation's lethal dose 50% (LD50) was more than 2,000 mg/kg. Both a macroscopic and microscopic examination of the vital organs failed to detect any toxicity indicators.

Sub-chronic toxicity

The polyherbal preparation was administered orally to female rats for 91 days in 5 dose changes during the sub-chronic toxicity research: 250 mg/kg, 500 mg/kg, 1000 mg/kg, 2000 mg/kg, and 4000 mg/kg, respectively. The daily dose for a human is the same at the lowest level of 250 mg/kg. Regarding physical symptoms, gaining weight, diet, haematological measures, biochemical data, and macroscopic and microscopic inspection of organs no significant negative effects were observed at any of the doses based on intake. These findings showed that, when taken as advised, oral administration of polyherbal formulation is both short- and long-term safe.[13]

Clinical Study

Study design and Participants

A prospective randomized interventional clinical study was planned comparing outcomes in 2 cohorts with mild to moderate COVID-19 as under:

Cohort-1: Trialled with conventional treatment as per government advisory.

Cohort-2: Trialled with polyherbal combination containing *Withania somnifera, Tinospora cordifolia, Moringa oleifera, Adhatoda vasica, Piper longum, Glycyrrhiza glabra, Ocimum sanctum* and *Curcuma longa* along with conventional treatment as per government advisory.

Trial was conducted at the Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India.

1. **Inclusion criteria were**

   (a) Laboratory-confirmed mild to moderate symptomatic cases of COVID-19 above 18 years irrespective of sex was included.
   (b) Patients able to take medicines orally.
   (c) Patients willing to provide signed informed consent.

2. **Exclusion criteria were**

   (a) ALT/AST > 5 times the upper limit of normal.
   (b) Stage 4 severe chronic kidney diseases requiring dialysis (i.e. eGFR< 30).
   (c) Pregnant women or Lactating mother.
   (d) Anticipated transfer to another hospital which is not a study site within 72 hours.
   (e) Patients with serious underlying diseases, including but not limited to heart disease (including history of angina pectoris or coronary heart disease or myocardial infarction, atrio ventricular block), lung, kidney, liver malfunction and mental disease that cannot be treated together.

(f) Suspected or confirmed history of alcohol consumption and drug abuse.
(g) Participated in other drug trials in the past month.
(h) The researchers judged that patients were not suitable for the study.

Physicians who were not involved in the trial randomly divided the patients into the treatment and control groups from the daily admission list. Patients in both groups got standard care in accordance with ICMR recommendations (Table 1). The treating physicians made the decision on the SoC and oxygen supplementation.

Table 1: Standard of Care as ICMR Guidelines

Standard of Care	Drug name	
Group 1 - Anti-pyretic / Analgesic	Paracetamol Extended release	As required
Group 2 - Antacid / anti-emetic	Pentaprazole + Domeperidone	1 Once Daily
Group 3 - Disease modifier	Hydroxychloroquine	400 mg Day 1 200 mg for 5 days
Group 4 - Steroids	Dexamethasone	as per schedule
	Methyprednisolone	as per schedule
Group 5 - Antibiotics	Azithromycin	500 mg Once Daily
	Ceftriaxone	Intravenous
	Doxycycline	Intravenous
Group 6 - Anticoagulants	Clexane	Subcute
	Heparin Unfractionated	Subcute
Group 7 - Anti Viral drugs	Remdesivir	Intravenous
Group 8 - Immunomodulators	Tocilizumab	Intravenous
	Colchicine	as per schedule

In the treatment group (polyherbal combination) which consisted of two tablets, was administered to the therapy group. These tablets were produced in facilities with a GMP certification. In Table 2 the herbs of the polyherbal combination is provided in detail. Each patient was given two tablets eight hourly after meals. According to approved criteria, treatment lasted for 15 days.

A total of 65 participants were screened in accordance with the inclusion criteria; 55 patients were enrolled in the study. On Day 3, four patients complaining problem in swallowing tablets were taken out of the study. Patients who successfully finished the study were then examined. Out of 51 patients, 26 received an additional polyherbal combination and 25 received simply Standard Care. (Figure 1)

Table 2: Detailed information of Polyherbal Combination KND BHU tablet

Polyherbal Herbal Combination (KNDBHU)		Part used	Each Tablet contains 250 mg extract	
Sanskrit Name	**Latin Name**			
Ashwagandha	*Withania somnifera*	Root	Aqueous	31.25 mg
Guduchi	*Tinospora cordifolia*	Stem	Aqueous	31.25 mg
Shigru	*Moringa oleifera*	Stem	Aqueous	31.25 mg
Vasa	*Adhatoda vasica*	Whole Plant	Aqueous	31.25 mg
Pippali	*Piper longum*	Fruits	Aqueous	31.25 mg
Madhuyashti	*Glycyrrhiza glabra*	Root	Aqueous	31.25 mg
Tulsi	*Ocimum sanctum*	Whole Plant	Aqueous	31.25 mg
Haridra	*Curcuma longa*	Rhizome	Aqueous	31.25 mg

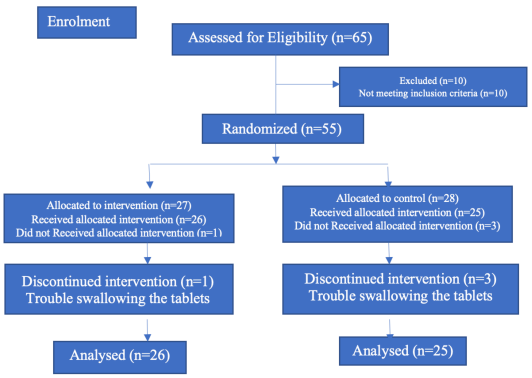

Fig. 1: CONSORT flow diagram

RESULTS

The demographic makeup of the treatment and control groups was comparable. Table 3 displays the biochemical and haematological values at baseline.

The treatment group's median day of admission following the onset of symptoms was the sixth (range: 1–12), whereas the control group's median day was the fifth (range: 1–23). 82.35% of patients had co-morbid conditions like diabetes and hypertension. Other co-morbidities that were noted included hypothyroidism and asthma.

The symptoms that were noted throughout the trial included fever, shortness of breath, cough, ageusia and headache. Table 4 lists the number of patients who had each of these conditions on days 1, 3, 7 and 15 of treatment. Fever was the most prevalent symptom, whereas shortness of breath was reported by least number of patients. On days 1, 3, 7 and 15 in the treatment group, the percentage of

Table 3: Demographic and baseline hematological evaluation

Parameters	Baseline Observations	
	Study Group	Control Group
Mean Age in years	41.6	44.2
Patients with Co-morbidities	24	18
Mean Hemoglobin in gm %	13.5	13.1
Median TLC per cu mm	8700	8000
Median Platelet per cu mm	290000	340000
Median Sr. Creatinine mg %	1.2	1.4
Median CRP mg/L	37.45	29.67
Median Sr. Ferritin ng/ml	368.58	427.52
Median D-dimer ng/ml	413.69	382.61

patients experiencing breathlessness decreased from 46.15% to 15.38% to 7.69% to 3.84%, whereas in the control group, the percentage decreased from 48% to 36% to 26% to 12%.

Ageusia is regarded as a prominent symptom of COVID 19; on days 1, 3, 7 and 15 the percentage of patients experiencing it declined from 69.23% to 65.38 % to 46.15% to 3.84% in the treatment group and from 68% to 64% to 56% to 16% in the control group. There was a similar decline in the proportion of feverish people in both groups. At days 7 and 15, there was a statistically significant decrease in headache, fever and dyspnoea. On days 1, 3, 7 and 15 the percentage of patients having fever declined from 92.30% to 76.92% to 69.23% to 00% in the treatment group and from 88% to 76% to 64% to 4% in the control group. Fever subsided after 7 days in all the patients of treatment group, whereas in control group one patient got fever after 15 days of treatment.

Cough was the second most prominent symptom and on days 1, 3, 7 and 15 it reduced from 76.92% to 69.23% to 38.46% to 7.69% in the treatment group and from 88% to 84% to 64% to 24 % in control group. Headache was complained by the least number of patient and the symptom was reduced by 53.84% to 26.92% to 7.69% to 00% in treatment group whereas in control group symptom reduced from 56% to 36% to 20% to 00% on days 1, 3, 7 and 15 respectively.

On days 5 of the treatment, 4 patients complained of hiccups, which was self-limiting. Three patients in the study group reported salty taste (Lavanasyata) and polydipsia (Talushoosha) on days 3 and 5, respectively.

Patients with COVID pharyngitis in the study group had a median hospital stay of 5 days, compared to 7 days in the control group. In the study group, individuals with COVID pneumonia spent an average of 7 days in the hospital, compared to 8 days in the control group.

Few patients had their chest digital roentgenograms (X-rays) compared. By day 5, the patchy opacities on the follow-up chest X-ray in the study group were decreased without the use of antiviral medications. Although statistical analysis was not done, the observed alterations were clinically significant.

One participant in the trial arm was symptom-free from days 3 to 7, but on day 7 developed symptoms. The patient continued to receive the same add-on regimen until day 15, when he stopped exhibiting symptoms. One patient in the control group who later required intensive care had a protracted stay of 23 days due to enhanced untoward symptoms.

Even though, the study group had a higher percentage of co-morbidities, only one out of 26 patients in that group needed Remdesivir whereas, three out of 25 in the control group.

Table 4: Severity of Symptoms

Symptoms	Severity of Symptoms							
	Pattern of reduction in severity of symptoms from Day 1 to Day 15 of treatment							
	Study Group				Control Group			
	Number (%) of patients with symptoms as observed on							
	Day 1	Day 3	Day 7	Day 15	Day 1	Day 3	Day 7	Day 15
Fever	92.3	76.92	69.23	0	88	76	64	4
Shortness of breath	46.15	15.38	7.69	3.84	48	36	28	12
Cough	76.92	69.23	38.46	7.69	88	84	64	24
Ageusia	69.23	65.38	46.15	3.84	68	64	56	16
Headache	53.84	26.92	7.69	0	56	36	20	0

DISCUSSION

The goal of this study was to examine a polyherbal combination's potential using evidence rather than just personal experience. After lengthy discussions among the medical professionals within this institute this study was planned. Patients with COVID 19 had low-grade fever, dry cough, ache in their muscle, and malaise. Sore throat and headache were noted in several patients. At presentation, there were no symptom of acute pneumonia other than cough and shortness of breath. Ageusia along with anosmia was primarily seen. According to European research, 88% of patients with mild to moderate COVID 19 infection reported gustatory impairment.[14,15] It was discovered that a dry cough frequently accompanied respiratory problems. Bilateral multifocal alveolar opacities were visible on the chest X-ray. Radiological improvement was observed on fifth day of the treatment. Few individuals showed elevated levels of d-dimer while the majority of patients had elevated levels of C-reactive protein.[16] Scientific studies on all the herbs suggested that they had immunomodulatory, analgesic, antipyretic, anti-platelet aggregation, and antiviral properties. The patients' hospital stay was cut short due to the add-on arm's considerable improvement in ageusia and dyspnea. Due to a lack of beds with oxygen, an early hospital

discharge was crucial. Only 3.2 hospital beds were available per 10,000 people in India, while only 2 hospital beds were available per 10,000 people in Maharashtra.[17] India's metropolitan areas have a higher concentration of beds than its rural areas.[18] The shorter hospital stay might directly correlate with more beds being available to accommodate more patients in need. Although much effort has been put into trying to discover factors linked with increased morbidity or death, consensus is yet anticipated. COVID 19 has exhibited a varying natural course throughout the world. Given these uncertainties, calculating statistical significance in such small population is challenging.

Important positives and negatives of this research are described below:

Strengths

Cost effective: The present add-on polyherbal combination regimen has low risk and is highly cost effective as it reduced hospital stay.

Adverse effects

No adverse effects were observed in study group.

Limitations

A systematically randomized large sample study would be better with tighter controls. However, the public response to the pandemic makes it difficult to strictly adhere to trial protocols. Comparison of haematological & biochemical parameters will be desirable, once the global standards are evolved for COVID 19. A comparative radiological imaging is also recommended for future studies.

CONCLUSION

With the current add-on polyherbal combination regimen, an early clinical improvement in breathlessness was seen along with early ageusia and cough reduction when compared with conventional treatment. Given the lack of hospital beds in India, the median length of hospital stays was shortened; this development is significant. The possibility of Ayurvedic therapy in treating COVID 19 is what can be learned from this study.

Ethical Approval

Study was approved by Institutional Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University with IEC Letter Number Dean/2020/EC/1981dated 02-06-2020.

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Conflict of Interest

The authors are declared that there is no conflict of interest.

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