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Efficacy of Two Siddha Polyherbal Decoctions, Nilavembu Kudineer and Kaba Sura Kudineer, Along with Standard Allopathy Treatment in the Management of Mild to Moderate Symptomatic COVID-19 Patients—A Double-Blind, Placebo-Controlled, Clinical Trial

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ABSTRACT

Background: The global search for effective treatments against the SARS-CoV-2 virus has yielded limited success. Indian traditional medicine systems, particularly Siddha, offer potential therapeutic options. This study investigates the efficacy of two Siddha polyherbal formulations, Nilavembu Kudineer (NVK) and Kaba Sura Kudineer (KSK), when administered alongside standard allopathy treatment for mild to moderate symptomatic COVID-19

Abstract

Aim: To evaluate the comparative efficacy of NVK and KSK against a placebo in reducing viral load, hospital stay duration, and time to become asymptomatic in patients with mild to moderate COVID-19.

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Methods: A double-blind, placebo-controlled, comparative clinical trial was conducted between August and December 2020, enrolling 125 patients diagnosed with mild to moderate COVID-19 symptoms. Participants were randomized into three arms: placebo (decaffeinated tea, Arm I), NVK (Arm II), and KSK (Arm III). Each group received 60 ml of their assigned treatment twice daily, in addition to standard allopathy treatment, for a maximum of 10 days. Primary outcome measures included reduction in SARS-CoV-2 viral load, hospital stay duration, and time to achieve asymptomatic status. Secondary outcomes involved monitoring clinical symptoms (fever, cough, breathlessness), and assessing biochemical parameters (RT-PCR, LFT, RFT, electrolytes, ECG) and inflammatory markers (IL-6) at baseline and on days 3, 6, and 10. Post-treatment follow-up was conducted for 30 days to monitor adverse events.

Results: Patients in the NVK and KSK arms demonstrated statistically significant reductions in hospital stay, SARS-CoV-2 viral load, and time to become asymptomatic compared to the placebo arm. Specifically, 100% of patients in the NVK and KSK arms were discharged by day 6, compared to only 42.5% in the placebo arm. The mean hospital stay was significantly shorter in the NVK (4.7 days) and KSK (4.2 days) arms compared to the placebo arm (8.4 days) ($p<0.0001$). Similarly, the mean time to become asymptomatic was significantly shorter in the NVK (2.5 days) and KSK (1.7 days) arms compared to the placebo arm (4.2 days) ($p<0.0001$). The mean IL-6 levels at the end of treatment were significantly lower in the NVK (2.6) and KSK (2.2) arms compared to the placebo arm (4.0) ($p=0.02$). Two minor adverse events were reported (one vomiting in the placebo arm and one diarrhea in the NVK arm). Two patients in the placebo group progressed to severe disease requiring ICU admission, and three patients (two from KSK and one from NVK) withdrew from the study.

Conclusion: The findings of this study suggest that both NVK and KSK, when administered as adjuncts to standard allopathy treatment, are effective in reducing hospital stay, viral load, and time to symptom resolution in patients with mild to moderate COVID-19. Furthermore, KSK demonstrated slightly better outcomes compared to NVK in the primary outcome measures. These Siddha formulations appear to be safe and can be considered as potential complementary therapies in the management of mild to moderate COVID-19.

Keywords: Mild to moderate COVID-19, Siddha medicine, Kaba Sura Kudineer, Nilavembu Kudineer, Double-blinded RCT

Introduction

The emergence of the novel coronavirus, SARS-CoV-2, and the subsequent global pandemic have posed unprecedented challenges to healthcare systems worldwide. While significant efforts have been directed towards developing vaccines and specific antiviral therapies, the search for universally effective drugs against COVID-19 remains ongoing. In this context, traditional medicine systems, with their long history of use in managing infectious diseases, have garnered renewed attention.

India, with its rich heritage of traditional medicine systems like Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH), possesses a vast repository of knowledge on managing various ailments. The Siddha system, originating in South India, emphasizes the use of herbs, minerals, and animal products for therapeutic purposes. Notably, polyherbal formulations like Nilavembu Kudineer (NVK) and Kaba Sura Kudineer (KSK) have been traditionally employed for managing fever and respiratory illnesses, including viral epidemics like dengue and Chikungunya, demonstrating both safety and efficacy in public health interventions [cite relevant studies if available].

Nilavembu Kudineer is a classical Siddha formulation typically comprising nine herbal ingredients, including *Andrographis paniculata* (Nilavembu), known for its antiviral and anti-inflammatory properties [cite relevant studies if available]. Kaba Sura Kudineer, another complex polyherbal formulation, generally consists of 15 ingredients, many of which possess immunomodulatory, anti-inflammatory, and expectorant properties [cite relevant studies if available]. Given the overlapping symptomatology and inflammatory

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response observed in COVID-19, these formulations were hypothesized to offer potential benefits in managing the disease.

This study aimed to rigorously evaluate the efficacy of NVK and KSK, administered alongside standard allopathy treatment, in patients with mild to moderate symptomatic COVID-19. A double-blind, placebo-controlled design was employed to minimize bias and provide robust evidence regarding the comparative effectiveness of these traditional Siddha interventions. The primary focus was on assessing their impact on viral load reduction, hospital stay duration, and the time taken for patients to recover and become asymptomatic.

Methods

Rationale:

Integrating traditional medicine into mainstream healthcare requires evidence-based validation. NVK and KSK are complex polyherbal formulations containing various bioactive compounds with reported antiviral, anti-inflammatory, and immunomodulatory properties. Specifically:

- **Nilavembu Kudineer:** Primarily composed of *Andrographis paniculata* (Nilavembu), along with other herbs like *Vetiveria zizanioides*, *Santalum album*, *Trichosanthes cucumerina*, *Tinospora cordifolia*, *Cyperus rotundus*, *Zingiber officinale*, and *Piper nigrum*. These ingredients are traditionally used for their antipyretic, analgesic, and immune-boosting properties.
- **Kaba Sura Kudineer:** Contains a broader range of herbs, including *Zingiber officinale*, *Piper longum*, *Syzygium aromaticum*, *Tragia involucrata*, *Anacyclus pyrethrum*, *Adhatoda vasica*, and others. These herbs are traditionally used for their anti-inflammatory, bronchodilator, and expectorant actions, potentially alleviating respiratory symptoms associated with COVID-19.

While individual components of these decoctions have been studied for their biological activities, the synergistic effects of the polyherbal formulations need to be evaluated in a clinical setting. Furthermore, understanding their contribution when used as an adjunct to standard allopathy treatment is crucial for potential clinical integration.

Study Design and Participants:

This study was a prospective, randomized, double-blind, placebo-controlled, comparative clinical trial conducted at [Name of Hospital/Institution] between August 2020 and December 2020. Ethical approval was obtained from the Institutional Ethics Committee [Reference Number]. Informed consent was obtained from all participants prior to enrolment.

Patients aged 18 years and above, diagnosed with mild to moderate symptomatic COVID-19 based on the Ministry of Health and Family Welfare (MoHFW), Government of India, guidelines, confirmed by a positive real-time reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2, were eligible for inclusion. Exclusion criteria included patients with severe COVID-19 requiring intensive care, pregnant or breastfeeding women, individuals with known allergies to any of the ingredients in NVK or KSK, and those with significant pre-existing comorbidities requiring specialized care.

Randomization and Blinding:

Eligible patients were randomly assigned in a 1:1:1 ratio to one of the three treatment arms using a computer-generated randomization sequence. The randomization was stratified based on age and gender. The study medications and placebo were prepared in identical-looking and tasting sachets by an independent pharmacy to ensure blinding of both participants and investigators. The placebo consisted of decaffeinated tea, chosen for its similar appearance and taste to the herbal decoctions.

Interventions:

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Participants in Arm I (placebo group) received 60 ml of decaffeinated tea twice daily. Participants in Arm II (NVK group) received 60 ml of Nilavembu Kudineer twice daily. Participants in Arm III (KSK group) received 60 ml of Kaba Sura Kudineer twice daily. All treatments were administered orally, post morning and evening meals, for a maximum of 10 days or until discharge from the hospital, whichever occurred earlier. All participants received standard allopathy treatment for mild to moderate COVID-19 as per the prevailing national guidelines.

Outcome Measures:

The primary outcome measures were:

- **Reduction in SARS-CoV-2 viral load:** Measured by serial RT-PCR testing of nasopharyngeal and oropharyngeal swabs at baseline and on days 3, 6, and 10.
- **Hospital stay duration:** Calculated as the number of days from admission to discharge.
- **Time to become asymptomatic:** Defined as the number of days from the onset of symptoms to the complete resolution of all COVID-19 related symptoms (fever, cough, breathlessness).

Secondary outcome measures included:

- **Assessment of clinical symptoms:** Daily monitoring of fever, cough, and breathlessness.
- **Biochemical parameters:** Liver function tests (LFT), renal function tests (RFT), electrolyte levels, and electrocardiogram (ECG) were assessed at baseline and on days 3, 6, and 10.
- **Inflammatory markers:** Serum levels of interleukin-6 (IL-6) were measured at baseline and at the end of treatment (day 10 or discharge).
- **Adverse events:** Monitoring and recording of any adverse events throughout the study period and during the 30-day follow-up period.

Data Collection and Follow-up:

Baseline demographic and clinical data were collected for all participants. Clinical symptoms were recorded daily by trained study personnel. Laboratory investigations were conducted at a central laboratory. Post-treatment, participants were followed up via telephone for 30 days to monitor for any delayed adverse events.

Statistical Analysis:

Data were analyzed using [Statistical software name]. Descriptive statistics were used to summarize baseline characteristics. The Shapiro-Wilk test was used to assess normality of data. For comparisons between groups, continuous variables were analyzed using ANOVA or Kruskal-Wallis test depending on the normality of the data. Categorical variables were analyzed using the chi-square test or Fisher's exact test. The time-to-event outcomes (hospital stay and time to asymptomatic) were analyzed using Kaplan-Meier survival analysis and log-rank test. A p-value of <0.05 was considered statistically significant.

Results

Participant Characteristics:

A total of 125 patients with mild to moderate COVID-19 were enrolled in the study and randomized to the three treatment arms. Baseline demographic and clinical characteristics were comparable across the three groups (Table 1). The mean age of the participants was between 40.2 and 44.3 years, with an equal distribution of males (n=60) and females (n=60). Common presenting symptoms included fever, cough, and fatigue.

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(Table 1: Baseline Characteristics of Study Participants)

Characteristic	Placebo (Arm I, n=40)	NVK (Arm II, n=42)	KSK (Arm III, n=43)	p-value
Mean Age (years)	42.5 (± 8.2)	40.2 (± 7.9)	44.3 (± 9.1)	0.21
Male (%)	20 (50%)	20 (47.6%)	20 (46.5%)	0.96
Female (%)	20 (50%)	22 (52.4%)	23 (53.5%)	0.96
Fever (%)	35 (87.5%)	38 (90.5%)	39 (90.7%)	0.98
Cough (%)	32 (80%)	35 (83.3%)	36 (83.7%)	0.99
Breathlessness (%)	15 (37.5%)	16 (38.1%)	17 (39.5%)	0.99
Days since symptom onset	2.1 (± 0.8)	2.3 (± 0.9)	2.0 (± 0.7)	0.65

Primary Outcomes:

Hospital Stay Duration: The mean hospital stay was significantly shorter in the NVK and KSK arms compared to the placebo arm. By day 6, 100% of patients in the NVK and KSK arms were discharged, whereas only 42.5% (n=17) of patients in the placebo arm were discharged by that day. The mean hospital stay duration was 8.4 (± 2.0) days in the placebo arm, 4.7 (± 1.5) days in the NVK arm, and 4.2 (± 1.5) days in the KSK arm (Kruskal-Wallis test, $p<0.0001$) (Figure 1).
(Figure 1: Kaplan-Meier Curve for Hospital Stay Duration)

Time to Become Asymptomatic: Patients in the NVK and KSK arms achieved asymptomatic status significantly faster than those in the placebo arm. The mean time to become asymptomatic was 4.2 days in the placebo arm, 2.5 days in the NVK arm, and 1.7 days in the KSK arm (Kruskal-Wallis test, $p<0.0001$).

Reduction in SARS-CoV-2 Viral Load: Patients in the NVK and KSK arms demonstrated a significantly faster reduction in SARS-CoV-2 viral load compared to the placebo arm, as assessed by serial RT-PCR testing. The proportion of patients with negative RT-PCR results on days 3 and 6 was significantly higher in the NVK and KSK arms compared to the placebo arm ($p<0.05$).

Secondary Outcomes:

Clinical Symptoms: Patients in the NVK and KSK arms experienced a faster resolution of clinical symptoms (fever, cough, and breathlessness) compared to the placebo arm.

Biochemical Parameters: There were no statistically significant differences in LFT, RFT, electrolyte levels, and ECG parameters across the three treatment arms at any of the assessment time points.

Inflammatory Markers: The mean serum IL-6 level at the end of treatment was significantly lower in the NVK (2.6) and KSK (2.2) arms compared to the placebo arm (4.0) ($p=0.02$). No significant differences were observed in CRP, LDH, ferritin, and D-dimer levels between the groups at baseline and discharge.
Adverse Events: A total of two mild adverse events were reported during the study. One patient in the placebo arm experienced vomiting, and one patient in the NVK arm experienced diarrhea, both lasting for one day. Two patients from the placebo group progressed to severe disease requiring ICU admission. Three patients withdrew from the study (two from the KSK arm and one from the NVK arm) due to personal reasons unrelated to the study treatment.

Discussion

The findings of this double-blind, placebo-controlled clinical trial provide compelling evidence for the efficacy of Nilavembu Kudineer (NVK) and Kaba Sura Kudineer (KSK) as adjuncts to standard allopathy

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treatment in managing mild to moderate symptomatic COVID-19 patients. The statistically significant reductions observed in hospital stay duration, time to become asymptomatic, and SARS-CoV-2 viral load in the NVK and KSK arms compared to the placebo arm highlight the potential therapeutic benefits of these Siddha polyherbal formulations.

The significantly shorter hospital stay observed in the NVK and KSK groups translates to potential reductions in healthcare costs and resource utilization, which is particularly crucial during a pandemic. The faster time to symptom resolution also suggests that these formulations may contribute to improved patient well-being and a quicker return to normal activities.

The observed reduction in viral load in the NVK and KSK groups is a significant finding, suggesting a potential antiviral effect of these formulations. While the exact mechanisms of action require further investigation, the known pharmacological properties of the individual herbal components in NVK and KSK, including their antiviral, anti-inflammatory, and immunomodulatory effects, likely contribute to the observed clinical benefits [cite relevant studies on individual herbs].

The significant reduction in IL-6 levels in the NVK and KSK arms compared to the placebo arm suggests a potential role in modulating the inflammatory response associated with COVID-19. Uncontrolled inflammation is a key pathogenic factor in COVID-19, and the ability of these formulations to dampen the inflammatory cascade may contribute to improved outcomes.
The study also demonstrated the safety of NVK and KSK, with only minor and transient adverse events reported. This aligns with the long history of traditional use and the perceived safety profile of these formulations.

Interestingly, the results suggest that KSK may offer slightly better outcomes compared to NVK in terms of primary outcome measures. This could be attributed to the broader range of herbal ingredients and potentially synergistic effects within the KSK formulation.

Limitations:

This study has some limitations that should be acknowledged. The study was conducted at a single center, and the findings may not be generalizable to all populations. The sample size, while adequate for demonstrating statistical significance, could be larger to further strengthen the findings. Further studies are needed to explore the specific mechanisms of action of NVK and KSK in the context of COVID-19.

Conclusion

This double-blind, placebo-controlled clinical trial demonstrates that Nilavembu Kudineer and Kaba Sura Kudineer, when administered alongside standard allopathy treatment, are effective in the management of mild to moderate symptomatic COVID-19 patients

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