Efficacy of Two Siddha Poly herbal 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

Anurag Srivastava
Government Institute of Medical Sciences
Manickavasagam Rengaraju (nismanick@gmail.com)
Central Council for Research in Siddha https://orcid.org/0000-0001-8570-0193
Saurabh Srivastava
Government Institute of Medical Sciences
Vimal Narayanan
Central Council for Research in Siddha
Vivek Gupta
Government Institute of Medical Sciences
Rashmi Upadhayay
Government Institute of Medical Sciences
Jitender Kumar
Center for Bioinformatics and Computational Biology
Sathiya Rajeshwaran Parameswaran
Central Council for Research in Siddha
Kanakavalli Kadarkarai
Central Council for Research in Siddha
Aarthi Velmurugan
Central Council for Research in Siddha

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Abstract

Background & Aim: Globally, the ongoing pursuit in exploring an effective drug to combat severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus has not met with significant success till date. Indian traditional medicines, especially poly herbal formulations like Nilavembu Kudineer (NVK) and Kaba Sura Kudineer (KSK) of the Siddha system of medicine have been used as public health interventions for controlling viral epidemics like dengue and Chikungunya. These traditional therapies have been found safe, effective, and widely accepted. The current study evaluates the comparative efficacy of NVK and KSK as opposed to the placebo, in the management of mild to moderate COVID-19 disease.

Methods: The study was a double blind, placebo controlled comparative clinical trial, with the primary objective of determining the efficacy of KSK and NVK. Patients (n=125) diagnosed with mild to moderate COVID-19 symptoms were enrolled in the study over a period of 4 months (Aug 2020 – Dec 2020). Participants were randomised into 3 arms; placebo-decaffeinated tea in Arm 1; NVK in Arm II and KSK in Arm III. Each arm received 60 ml of the respective treatment twice a day, post morning and evening meals, along with standard Allopathy treatment for a maximum of 10 days. The main outcome measures of the study were the reduction in SARS-CoV-2 viral load, hospital stay, and time taken by the patients to become asymptomatic from symptomatic. Efficacy assessments included clinical symptoms (fever, cough and breathlessness) each day and real-time reverse transcription-polymerase chain reaction (RT-PCR),liver function test (LFT), renal function test (RFT) and electrolytes and electrocardiogram (ECG) at baseline (Day 0), Day 3, 6 and 10. Post treatment, participants were followed up for 30 days via phone for adverse effects if any. Effects of drugs on inflammatory markers (IL6,) at the end of treatment were also recorded. Adverse events (AE) were monitored throughout the study.

Results: The results revealed that when compared to patients in placebo arm, those in NVK and KSK arms showed a statistically significant reduction in hospital stay time, reduction in viral load of SARS-CoV-2, and the time taken to become symptomatic from asymptomatic. Out of 125 COVID-19 patients recruited, 120 completed the study; two from the placebo group developed severe symptoms and were shifted to intensive care unit (ICU) and three patients from arms II and III withdrew from the study. The mean age of females (n=60) and males (n=60) enrolled was between 40.2 and 44.3 years respectively. Results were more promising for all the patients in NVK and KSK arms as all enrolled participants (100%) under this group got discharged by day 6 as compared to only 42.5% (n=17) from placebo groupon that day. The hospital stay time for patients in Arm I, was significantly longer (Mean [SD]=8.4 [2.0] days) as compared to the Arm II and III (Mean [SD]=4.7 [1.5] and 4.2 [1.5] days respectively (Kruskal Wallis test, p=0.0001).Patients in the three groups took a significantly different number of days to become asymptomatic. While Arm II and III patients took mean 2.5 and 1.7 days respectively, Arm I, patients took a mean of 4.2 days (Kruskal Wallis test, p=0.0001). In all, two adverse events were recorded, one for vomiting and one for diarrhoea lasting a day in Arm I & Arm II respectively. Mean value of interleukin-6 (IL6) was significantly different in comparison to the placebo-decaffeinated tea arm (NVK=2.6 and KSK=2.2, Placebo=4.0, p=0.02).The other blood biochemical parameters like C-Reactive Protein (CRP),

Lactate Dehydrogenase (LDH), Ferritin and D-Dimer that were analysed at the baseline and at the time of discharge from hospital, were not significantly different in the three arms.

Conclusion: NVK and KSK arms showed a statistically significant reduction in hospital stay time, reduction in viral load of SARS-CoV-2 and time taken for patients to become asymptomatic from symptomatic, when compared to the placebo (decaffeinated tea).The primary outcome measures of KSK arm were significantly better than that in the NVK arm.

Introduction

Globally, there has been an ongoing pursuit in exploring an effective treatment to combat severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) virus. However, this quest across various treatment verticals have led to a despair amongst the scientific community.[1] In India, the role of traditional treatments especially Siddha medicines in the management of various diseases is well known that has proven effective, safe and widely accepted across all ages. During the Chikungunya and Dengue epidemic in the year 2015 in Tamilnadu, India, the administration of Nilavembu Kudineer (NVK)played a major role in controlling the morbidity.[6]Siddha medicine has contributed in lowering the disease burden during public health emergencies. These medicines could be repurposed for the management of COVID-19. However, there is limited evidence for the integrative treatment approach (standard of care, Allopathy treatment along with Siddha medication) in the management of COVID-19.

COVID-19 is a respiratory tract infection caused by a newly emergent corona virus, SARS-CoV-2, that was first reported in Wuhan, China, in December 2019. At present, we have limited evidence from randomized clinical trials to support pharmacological treatments from conventional medicine for COVID-19.[2]

According to Siddha Medical Literature, the symptoms and signs of COVID-19 including cold, cough and fever are analogous with Kaba Suram.[3,4]Standard Siddha medicines for tackling these conditions are Kabasurakudineer (KSK) and Nilavembu Kudineer (NVK).NVK was one of the essential medicines used as anti-viral Siddha drugs, especially in the treatment of Chikungunya and Dengue during the past outbreaks.[5] Recent *in-vitro* studies have revealed that ethanolic extract of NVK has anti-viral properties against Chikungunya and Dengue.[6]Toxicity studies utilizing NVK as per Organisation for Economic Co-operation and Development (OECD) guidelines found it to be safe for consumption. Apart from this, antipyretic, anti-microbial, anti-inflammatory and immuno stimulant activities of NVK have also been proven by phyto-chemical screening study.[8] Recent clinical studies have revealed the prophylactic and antiviral activities of NVK in viral fevers. [9,10] These indicate the growth inhibition of viral pathogens, and ability to effectively inhibit spill-over and transmissibility of the viruses. Therefore, in the current study, NVK was selected as one of the drugs against COVID-19.

KSK is a classical Siddha formulation comprising of 15 herbs and each herb possesses antiviral activity.[11,12]It has been found that a few phyto components in KSK decoction such as Cucurbitacin B(-112.09), Cardiofoliolide (-111.5), Apigenin (-98.84) and Pyrethrin (-92.98) bind to virus and inhibits its

replication hence could be effective in the management COVID-19. In-silico studies of KSK ingredients have shown to be potent against SARS-CoV-2 spike proteins.[13]Determination of organo leptic characters, preliminary phyto-chemical analysis, physico- chemical analysis, thin layer chromatography (TLC) photo documentation and high performance thin layer chromatography(HPTLC) fingerprint studies on KSK are reported.[14]A study has shown that KSK has antipyretic, anti-inflammatory and anti-bacterial properties and found to be safe in toxicity test.[15]KSK has also been shown as an immuno-modulator and having thrombolytic activity.[16] A retrospective observational study to measure the effect of integrated therapy KSK with Vitamin C and Zinc on COVID-19 patients has proven that there is reduction of length of hospital stay.[17]

In the absence of systematic evaluation of integrated therapy (with standard of care, Allopathy and KSK or NVK from Siddha system of medicine in COVID-19 management, this was proposed as a comparative study.

Materials And Methods

The study was conducted at the Government Institute of Medical Sciences (GIMS), Greater Noida. Uttar Pradesh, India. Patients were enrolled from 22 August 2020 to 31 December 2020. The Ethics Committees of the participating site and Siddha Clinical Research Unit, New Delhi, Safdarjung Hospital approved the protocol. Prior to participation in the study, each patient was informed about the nature and purpose of the study and written informed consent was obtained. All research procedures were strictly adhered to, based on AYUSH GCP and Indian Council for Medical Research (ICMR)Guidelines. The trial was registered in the Clinical Trial Registry of India (CTRI) and the registration Number is CTRI/2020/08/027286 .[19] The Detailed Protocol of the Study was already Published[19].

Study Design:

This was a randomized, double-blind, placebo-controlled, clinical trial where mild/moderate patients were randomly assigned to study treatment in a 1:1:1 ratio, to placebo (Arm I) or NVK (Arm II) or KSK (Arm III) groups. Patient allocation to treatment arm was performed using simple stratified randomization method.

Eligibility criteria: Eligible patients were 18-65 years of age with mild to moderate symptoms of COVID-19 and willing to consent. COVID-19 was confirmed by RT-PCR screening following the ICMR guidelines. A total of 155 confirmed COVID-19 patients with mild to moderate symptoms of COVID-19 were screened at the site. 125 patients were enrolled and admitted to hospital and all the guidelines laid by ICMR, Govt. of India, for COVID-19 management were followed. The participants were categorized as mild or moderate COVID-19 following WHO criteria.[21] The patients having oxygen saturation(SpO2) of <94%>90%, Respiratory rate >24 breaths per minute and chest X-Ray showing pneumonia, were classified as moderate COVID-19 patients, whereas patients with SpO2>94% and respiratory rate <24 breaths per minute were classified as mild COVID-19 patients. Patients were excluded from study if they had severe

primary respiratory disease or other pathogenic microbial pneumonia, with uncontrolled Diabetes mellitus (≥350 mg/dL Fasting Sugar), severe Hypertension (HT)(180/120 mmHg), chronic Bronchial Asthma (BA) (≥5 years Based on Clinical History), renal dysfunction (Known Chronic Kidney Disease[CKD] ≥5 years Estimated Glomerular Filtration Rate(eGFR) Stage ≥3), pregnant and lactating mothers. Patients with other systemic malignant diseases such as malignant tumours, mental illnesses, which the researchers considered unsuitable for participation in the study, people who had a history of allergy to Siddha medicine or who were part of other COVID-19 clinical trials were excluded from the study.

Study Treatment:

All the patients in the three arms received standard Allopathy treatment as per ICMR guidelines, which included Doxycycline /Hydroxy chloroquine and Ivermectin/Fabiparavir. Additionally, the patients with moderate disease also received steroids (Methyl prednisolone or Dexamethasone, if required) and low molecular weight Heparin. Participants were randomised to receive 60 ml of placebo in Arm I, 60 ml of NVK in Arm II and60 ml of KSK in Arm III, twice a day post morning and evening meals along with standard Allopathy treatment, for a maximum for 10 days. Post-treatment, patients were followed up for 30 days via phone for safety. The study design is displayed in Figure1.

Procedure to Prepare Poly Herbal Decoction of KSK and NVK:

Both the KSK and NVK decoctions were prepared as per the Siddha Formulary of India Guidelines.[20]In order to obtain NVK or KSK decoctions,5mg coarse powder of NVK or KSK, obtained from Central Pharmacy-Central Council for Research in Siddha(CCRS), Chennai, India was boiled in 240 ml of water and reduced to one-fourth (60ml), followed by filtration. Composition of poly herbal decoction ingredients of both NVK and KSK are detailed in Tables 1a and 1b respectively.

The distribution of participants included in the study (N=125) is summarized in Figure 2.Out of the 125 enrolled patients, 5 patients withdrew (2 from placebo and 3 from treatment groups)and 120 patients completed the study; 40 patients each in Arms 1, 2 and 3. In each arm, the male (n=20) and female (n=20) patients were equally distributed. In each arm,the 40 patients were further divided 3:1 ratio for mild (n=30) and moderate (n=10) cases based on ICMR, Ministry of Health COVID-19 Criteria.

Outcome Measures:

The primary outcome measures were the reduction in SARS-CoV-2 viral load (RT PCR Ct value), time taken by patient to become asymptomatic from symptomatic, and reduction in hospital stay. Patient was discharged from hospital if they were RT PCR negative. Immunity markers (IL-6) and other biological and haematological markers (CRP, LDH, D-Dimer and Ferritin) at baseline and on the day the patient got discharged were also analysed.

Efficacy Evaluations:

Clinical assessment for symptoms like fever (≤36.6°C or -axilla, ≤37.2 °C oral or ≤37.8°C rectal or tympanic, cough), breathlessness (respiratory rate ≤24/minute on room air, Oxygen saturation (SpO2) >94% on room air, cough -mild or absent on a patient reported scale (cough symptoms score ≤2 points, SpO2 level ≥95 was recoded each day throughout the study. Laboratory assessments including RT-PCR, LFT, RFT and electrolytes and ECG were performed at baseline (Day 0), and Day of Discharge (Day 3, 6 and 10).

Statistical Analysis:

Statistical analysis was performed using R Commander for R. The continuous variables were checked for normality tests and those who did not follow normal distribution were transformed taking square root values. Continuous data was reported as mean (standard deviation) while categorical data was reported as number (percentage). Three groups were compared for different biochemical parameters using Kruskal Wallis test. Chi square test was performed to compare proportions among groups. Values were considered significant if p value <0.05.

Blinding and Randomization :

Blinding and Randomization was employed to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) were evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Participants were randomly assigned to either placebo, NVK and KSK arm by an allocation ratio of 1:1:1. Blinded treatment was used to reduce potential bias during data collection and evaluation of clinical endpoints in study. Measures were taken to ensure that the study patients and study staff were not un blinded. A placebo group was included to have an accurate assessment study treatment.

Results And Discussion

Study Subjects' Demographic Characteristics

The demographic and baseline characteristics were comparable across treatment groups. A total of 120 patients completed the study and comprised of equal number males 50% (n=60) and females 50% (n=60). The mean age of Arm I, Arm II and Arm III was found out to be 44.4, 42.8 and 39.5 years respectively and was statistically insignificant (p=0.26).

Mean Hospital Stay Time: Reduction in Hospital Stay Time

The number of patients discharged on Day 3, 6 and 10 from Arm I, II and III are summarized in Table 2. Patient was discharged from hospital if RT PCR test was negative

In Arm I (the placebo arm), no patients recovered from COVID-19 disease on day 3 after admission. On day 6, 65% (n=13) male and 20% (n=4) of female patients were discharged. Majority of patients, which

was 35% (n=7) of male and 80% (n=16) female were discharged on Day 10.

In Arm II (NVK arm), patients recovered faster in comparison to placebo hence got discharged earlier.On Day 3, 50% (n=10) of male and 30% (n=6) of female patients were discharged. Remaining patients of NVK arm were discharged on Day 6, i.e., 50% (n=10) of male and 70% (n= 14) female respectively. Since all patients recovered and discharged by Day 6 hence patient discharge on Day 10 of study was zero.

Patients in Arm III (KSK arm) showed faster recovery even when compared to the NVK arm (Arm II). On day 3, majority of the patients 65% (n=13) of male and 55% (n=11) of female were discharged on Day 3. Remaining patients, 35% of male (n=7) and 45% (n=9) of female patients were discharged on Day 6. Since all patients were discharged by Day 6, there were zero discharge on Day 10from Arm III.

Patients in placebo arm who were on decaffeinated tea along with Allopathy treatment, no patients were discharged on Day 3. Infact, majority, i.e., 23 patients (57.5%) were discharged on day 10. Interestingly, all the patients taking NVK and KSK showed early recovery signs and were discharged by Day 6. Further, the patients in KSK arm recovered even faster than NVK arm as 60% of patients of KSK arm were discharged on Day 3, as compared to only 40% in Arm II (NVK arm)on the same day.

Total number of days the patients stayed in the hospital during the treatment were recorded and compared to know if there was reduction in hospital stay time. Patients in Placebo arm stayed significantly longer (Mean [SD] = 8.4 [2.0]) as compared to the Arm II and III (Mean [SD]=4.7 [1.5] and 4.2 [1.5] respectively, Kruskal Wallis test, p=0.0001. Comparison of Hospital Stay Time Kaplan Meier Graph for Arm I, Arm II and III is presented by Figure 3.Hence, patients who were taking the siddha treatment along with allopathy treatment (Arm II and III) had spent almost half the time in comparison to placebo arm. Overall, KSK Group showed a statistically significant reduction in hospital stay time compared to standard Siddha drug NVK and placebo which is decaffeinated tea.

Reduction in viral load of SARS-CoV-2:

In order to know the viral load, RT-PCR was performed onDays 3, 6 and 10. In Arm I, all patients were RT-PCR positive on Day 3, whereas 38% of Arm II and 56% of Arm III got RT-PCR negative. On Day 6, patients tested RT-PCR negative were 38% (Arm I), 62% (Arm II) and 44% (Arm III) respectively. On Day 10, remaining 61% patients of Arm I were RT-PCR negative whereas there were no patients on Day 10 in both NVK and KSK arms, since all had got discharged by day 6. In comparison, KSK treatment arm showed early reduction in viral load as 56% of patients of this arm were RT-PCR negative even on Day 3after admission.

Cycle threshold (Ct) values in RT PCR were analysed at Baseline (Day 0) and Day 3 and results are summarized in Table 3. At baseline, Ct values of three arms showed no significant difference (Placebo=20.5, NVK=21.2 and KSK=20.8, p=0.56). Ct values of patients in all three arms were analysed again at the time of discharge and compared using Kruskal Wallis test. On Day 3, mean Ct values were found to be significantly different among 3 arms (Placebo=25.1, NVK=31.5 and KSK=33.1,

p=0.0001).Statistically significant reduction in viral load of SARS-CoV-2 was recorded in both the Siddha treatment arms NVK and KSK compared to placebo (decaffeinated tea).

Time Taken for Patients to Become Asymptomatic:

The average time taken for a patient to become asymptomatic from symptomatic in the standard Siddha treatment NVK and KSK arms, was significantly less when compared to that taken by those in the placebo drug (decaffeinated tea) arm (Figure 4). Time taken by patients to get asymptomatic from symptomatic were 2.5 mean days in NVK arm; 1.7 in KSK arm and 4.2 days in the placebo arm (Kruskal Wallis test, p=0.0001). Similarly, patients in NVK arm and KSK arm took significantly lesser time (mean days) compared to placebo for both sore throat (NVK arm; 1.3, KSK arm; 1.3, placebo arm; 3.5, p value =0.0005) and short breath (NVK arm; 1.3, KSK; 1.3, placebo arm; 3.2, p value =0.0001 respectively).

Safety Evaluation:

In all three groups, only two adverse events (AEs) were reported. Mild episodes of AEs of vomiting and diarrhoea were observed for a single day in Arm I and II. Both the episodes were reversed within a day and treatment was continued. AEs were notified to trial site IEC and DSMB (Data Safety and Monitoring Board, Ministry of AYUSH, Govt. of India), within the reporting timelines. No serious adverse events (SAEs) were reported throughout study.

Mean Variation in IL-6 Value:

One of the significant markers in COVID-19 disease is IL-6 which is indicative of immune response. During the study course, IL-6 values were recorded at baseline and on the day of discharge from the hospital (endpoint) as summarized in Table 4. Baselines IL-6 mean values were recorded as 7.5 of Arm I, 5.7 of Arm II and 7.1 of Arm III. On the day of discharge (endpoint), IL6 values were showed significant difference(Arm I;4.0, Arm II;2.6 and Arm III;2.2 and Kruskal Wallis test, p=0.02)from baseline. This revealed an overall improvement in the IL-6 scores.

Mean Variation in Biomarker parameters

To evaluate the overall improvement across the three arms, the other biomarker parameters considered for evaluation were LDH, Ferritin, D-Dimer and CRP. These parameters were recorded at time of admission (baseline) and at time of discharge from hospital (endpoint) as summarized in Table 4.Total mean value of LDH was17at baseline and 16.4 at endpoint. Total mean values of Ferritin, D-Dimer and CRP were 11.7, 1.6 and 3.6 at baseline showing an overall improvement at the endpoint with the mean values of 11.1, 2.4 and 3.2 respectively. Overall change in CRP, LDH, Ferritin and D-Dimer was found to be non-significant ($p>0.05$) amongst the all 3 arms.

Conclusion

This is the first randomized controlled clinical trial to study the effectiveness of two classical Siddha herbal formulations, NVK and KSK, along with the standard Allopathy treatment for COVID-19. Patients of NVK (Arm II) and KSK (Arm III), recovered faster than patients of placebo (Arm I) and spent less number days in hospital than those in the placebo arm (Arm I). All patients of both NVK and KSK arms were discharged by Day 6 whereas maximum patients of placebo arm were discharged only on Day 10. Similarly, RT-PCR test was negative by Day 6 in both Arms II & III, whereas for the placebo group, 61% were RT PCR positive. Additionally, patients of Arm II and III took significantly less time to become asymptomatic compared to placebo arm. Between the Siddha treatments, KSK arm showed more promising results than NVK arm, as over 50% patients were discharged and found RT-PCR negative even on Day 3. Patients of KSK spent least time in hospital among all 3 arms. IL6 markers of Siddha treatment arms showed statistically significant difference in comparison to placebo arm. No SAEs were recorded throughout the study. The results of this trial suggest that NVK and KSK are safe and effective drugs in the management of mild to moderate COVID-19 disease when taken along with Allopathy treatment.

In spite of the limited sample size, the effects of Siddha decoctions, both NVK and KSK, along with standard of care Allopathy compared to placebo has been confirmed. The effects of these drugs were also statistically significant and proved the efficacy of an integrative approach with Allopathy for COVID-19 management. This trial also complies with the National Health Policy 2017 of integrative approaches of Allopathy with traditional systems of Medicines especially with Siddha medicines. The result of this trial encourages integration of Siddha medicines with Allopathy in combating pandemics like COVID-19 and also in the repurposing existing Siddha drugs. Large-scale, multi-centric clinical trial can help making it robust and reproducible.

Declarations

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Authors Contribution:

MR, AS conceived the study. MR, AS and VN initiated and conducted the study. VG contributed to incorporate all lab investigations. MR, AS, VN, SS and RU contributed in conduction of trial. JK performed statistical analysis of the trial.MR, AS, SS, VN and JK helped in the finalization of the study report. SP and KK provided the technical guidance and administrative support for the conduction of study. AV contributed to administrative support and provision of study drugs.

Authors Information:

AS, SS, RU and VG possess the background of Allopathy

KK, SP, MR, AV and VN possess the background of Siddha System of Medicine.

JK possesses the background of Biostatistics and Biotechnology.

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Availability of Data and Materials:

All participants' data will be kept confidential and personal identifiers of the study participants will not be disclosed to the public. Only the investigators will have access to the trial data. All the procedures will be carried out by strict adhering to the Good Clinical Practices (GCP). The monitors will have access to the study documents.

Ethics Approval and consent to participate:

The trial received the ethical approval from the Institutional Ethical Committee of Siddha Clinical Research Unit, Safdarjung Hospital, New Delhi on 20.07.2020 and trial site Ethics Committee on 04.08.2020.

This is to state that the appropriate ethical committee approval was taken.

Written consent was taken from all eligible and willing participants before their participation.

Consent for Publication: Not Applicable

Conflict of Interest: The authors declare that they have no Conflict of Interest.

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Tables

Table 1a & 1b: Composition and Polyherbal Decoction Ingredients of Nilavembu Kudineer (NVK) and Kaba Sura Kudineer (KSK) as per Siddha Formulary of India Guidelines[20]

Table 1a: Composition of NVK

S. No	Botanical name	Siddha Name	Family	Part Used	Parts
1	Andrographis paniculata *(Burm.f.)*	Nilavembu	Acanthaceae	Whole Plant	1 Part
2	Vetiveria zizanioides L.	Vettiver	Poaceae	Whole Plant	1 Part
3	Santalum album L.	Santhanam	Santalaceae	Wood	1 Part
4	Zingiber officinale *Roscoe.*	Chukku	Zingiberaceae	Rhizome	1 Part
5	Piper nigrum *L.*	Milaku	Piperaceae	Dry fruits	1 Part
6	Cyperus rotundus *L.*	Korai kilanku	Cyperaceae	Rhizome	1 Part
7	Hedyotis corymbosa *L.Lam*	Parpadagam	Convolvulaceae	Whole Plant	1 Part
8	Plectranthus vettiveroides *(K.C.Jacob) N.P.Singh & B.D.Sharma*	Vilamichamver	Lamiaceae	Root	1 Part
9	Trichochanthes cucumerina L.	Peipudal	Cucurbitaceae	Whole Plant	1 Part

Table 1b: Composition of KSK

S. No	Botanical name	**Siddha Name**	Family	Part Used	Parts
1	Zingiber officinale *Roscoe.*	Chukku	Zingiberaceae	Rhizome	1 Part
2	Piper longum *L.*	Milagu	Piperaceae	Fruit	1 Part
3	Syzygium aromaticum*(L,)&L.M Perry*	Kirambu	Myrtaceae	Flower Bud	1 Part
4	Anacyclus pyrethrum *L.*	Akkarakaram	Asteraceae	Rhizome	1 Part
5	Tragia involucrate *L.*	Siru kanjori	Euphorbiaceae	Leaves	1 Part
6	Solanumanguivi *Lam*	Karimulli	Solanaceae	Leaves	1 Part
7	Terminalia chebula *(Gaertn.)*	Kadukkai	Combretaceae	Fruit Rind	1 Part
8	Justicia adathoda Linn.	Adathoda	Acanthaceae	Leaves	1 Part
9	Anisochilus carnosus (*L.f) Wall,ex Benth*	Karpoora valli	Lamiaceae	Whole Plant	1 Part
10	Costus speciosus *(J.Koing)Sm*	Koshtam	Costaceae	Rhizome	1 Part
11	Tinospora cordifolia *(Thunb.) Miers,*	Seenthil	Menispermaceae	Whole Plant	1 Part
12	Clerodendrum serratum *(L.)*	Siru Theku	Verbanaceae	Leaves	1 Part
13	Andrographis paniculata *(Burm.f.)*	Nilavembu	Acanthaceae	Whole Plant	1 Part
14	Cyperus rotundus *L.*	Korai Kilanku	Cyperaceae	Rhizome	1 Part
15	Sida acuta*(Burm.f.)*	Sitramutti	Malvaceae	Whole plant	1 Part

Procurement and Preparation: NVK and KSK were procured from the GMP certified pharmacy (Central Pharmacy – CCRS, Chennai). 5 mg coarse powder of NVK or KSK was boiled in 240 ml of water and reduced to one-fourth (60ml), followed by filtration, to obtain NVK or KSK decoctions

Table 2: Numbers of Patients Discharged in Arm I, Arm II and Arm III on Day 3, 6, and 10

Time patient discharged Days	Arm I: Placebo n=40	Arm II: NVK n=40	Arm III: KSK n=40
Day 3	0 (0%)	16 (40%)	24 (60%)
Male (n=20)	0 (0%)	10 (50%)	13 (65%)
Female (n=20)	0 (0%)	6 (30%)	11 (55%)
Day 6	17 (42.5%)	24 (60%)	16 (40%)
Male (n=20)	13 (65%)	10 (50%)	7 (35%)
Female (n=20)	4 (20%)	14 (70%)	9 (45%)
Day 10	23 (57.5 %)	0 (0%)	0 (0%)
Male (n=20)	7 (35%)	0 (0%)	0 (0%)
Female (n=20)	16 (80%)	0 (0%)	0 (0%)

Table 3: Cycle Threshold (Ct) Values Analyzed on Day 0 and Day3

Ct Values	Arm I: Placebo Mean (SD)	Arm II: NVK Mean (SD)	Arm III: KSK Mean (SD)	p-value
Day 0 (n=38, 37, 39)	20.5 (4.3)	21.2 (2.8)	20.8 (4.3)	0.56
Day 3 (n=34, 33, 35)	25.1 (3.79)	31.5 (5.11)	33.1 (4.57)	0.0001

Units: Cycle threshold,

Ct values were not analyzed on Day 6 and 10 as all the patients of Arm II and Arm III were discharged.

Table 4: Biomarker Parameters Recorded at Time of Admission (Baseline) and at Time of Discharge from Hospital (Endpoint)

	Arm I: Placebo Mean (SD)	Arm II: NVK Mean (SD)	Arm III: KSK Mean (SD)	p-value
IL 6 Baseline (n=38, 39, 34)	7.5 (4.4)	5.7 (4.2)	7.1 (4.0)	0.09
IL 6 Endpoint (n=38, 39, 38)	**4.0 (2.9)**	**2.6 (2.5)**	**2.2 (1.3)**	**0.02**
LDH Baseline (n=26, 25, 22)	17.2 (3.5)	16.6 (4.6)	17.3 (5.8)	0.61
LDH Endpoint (n=24, 17, 13)	17.4 (5.6)	17.3 (3.9)	13.2 (5.6)	0.10
Ferritin Baseline (n=26, 25, 21)	10.5 (4.5)	11.7 (5.3)	13.2 (5.8)	0.25
Ferritin Endpoint (n=23, 16, 11)	11.4 (5.0)	11.0 (5.7)	10.6 (5.3)	0.95
D Dimer Baseline (n=26, 21, 13)	0.9 (0.7)	1.9 (3.6)	2.7 (6.8)	0.79
D Dimer Endpoint (n=16, 15, 7)	2.6 (4.8)	1.6 (2.6)	3.7 (7.5)	0.53
CRP Baseline (n=24, 25, 22)	3.5 (2.8)	3.0 (2.4)	2.6 (1.5)	0.84
CRP Endpoint (n=22, 19, 15)	3.9 (3.2)	2.5 (1.6)	3.1 (4.7)	0.26

Units: IL 6; Picogram per milliter (pg/mL), LDH: units per liter (U/L), Ferritin; micrograms per liter (mg/L), D Dimer; nanograms per milliliter (ng/mL), CRP; milligrams per decilitre (mg/dL)

TABLE 5: List of Abbreviations

Abbreviation
AEs - Adverse Events
ARDS - Acute Respiratory Distress Syndrome
BA - Bronchial Asthma
CCRSs - Central Council for Research in Siddha
CKD - Chronic Kidney Disease
CRP - C-Reactive Protein
CTRI - Central Council for Research in Siddha
COVID 19 - Coronavirus Disease
CT Value - Cycle Threshold Value
DM - Diabetes Mellitus
DSMB - Data Safety and Monitoring Board
EC - Ethics Committee
GCP - Good Clinical Practice
GIMS - Government Institute of Medical Sciences
GFR - Glomerular Filtration Rate
HT - Hypertension
HPTLC - High Performance Thin Layer Chromatography
ICU - Intensive Care Unit
IL6 - Interleukin 6
ICMR - Indian Council for Medical Research
KSK - Kaba Sura Kudineer
LDH - Lactate Dehydrogenase
LFT - Liver Function Test
mmHg - millimetre of mercury
mg/L - micrograms per liter
mg/dL - milligrams per decilitre
NVK - Nilavembu Kudineer
NKA - National Kidney Association
ng/mL - nanograms per milliliter

PPVC - Peripheral Pharmacovigilance Center

pg/mL - Picogram per milliter

RFT - Renal Function Test

ECG - Electrocardiogram

RT PCR - Reverse Transcription Polymerase Chain Reaction

SD - Standard Deviation

SARS COV 2 - Severe Acute Respiratory Syndrome Coronavirus 2

SAE - Serious Adverse Events

TLC - Thin Layer Chromatography

OECD - Organisation for Economic Co-Operation and Development

U/L - Units per liter

Figures

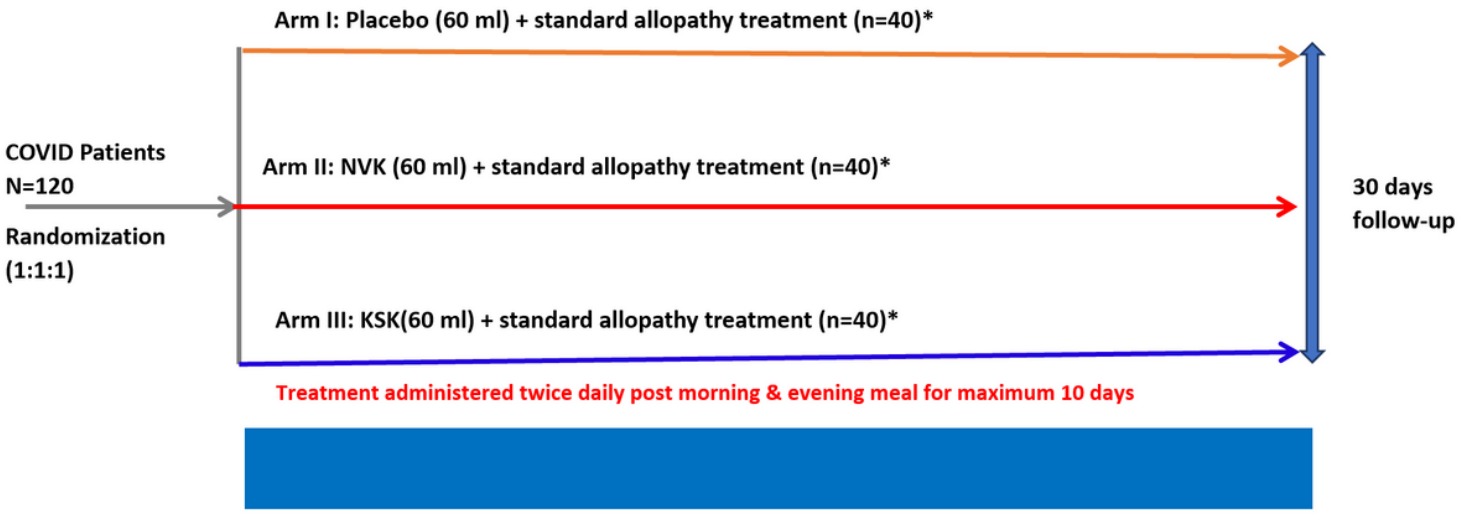

Figure 1

Study Design Displaying Treatment Allocation for Each Arm *Standard allopathy treatment: Doxycycline/Hydroxychloroquine and Ivermectin/Fabiparavir and patients with moderate disease also received steroids (Methyl prednisolone/Dexa methasone)and low molecular weight Heparin.#Clinical symptom assessment for fever, breathlessness, respiratory rate, Oxygen saturation and cough were recoded daily.

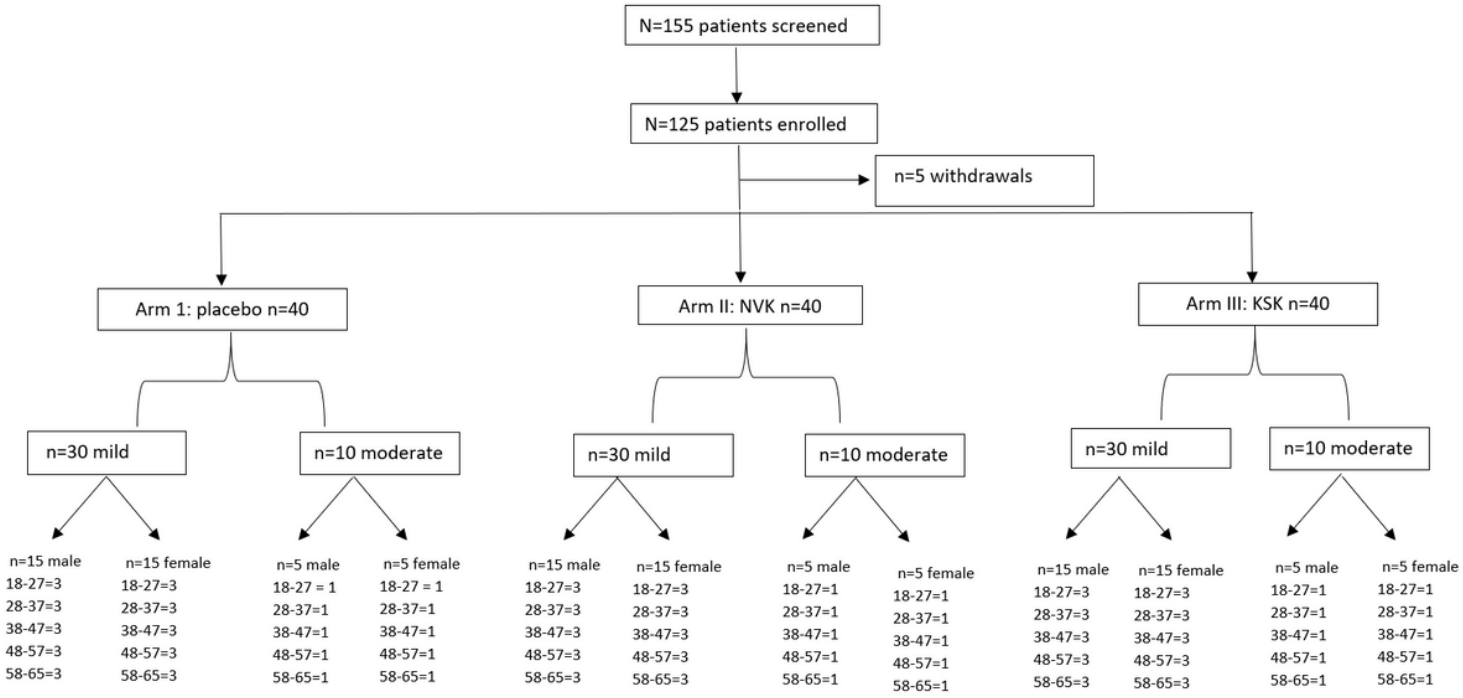

Figure 2

Subject Disposition Displaying Screening and Treatment Allocation of Participants Out of 120 patients, all were equally allotted into 3 groups each 40. In that 40, further divided 3:1 ratio for mild and moderate cases (Based on ICMR, Min.of Health COVID 19 Criteria). Here Male/Female patients were also equally distributed to all three groups. Randomization done by Simple Stratified Randomization.

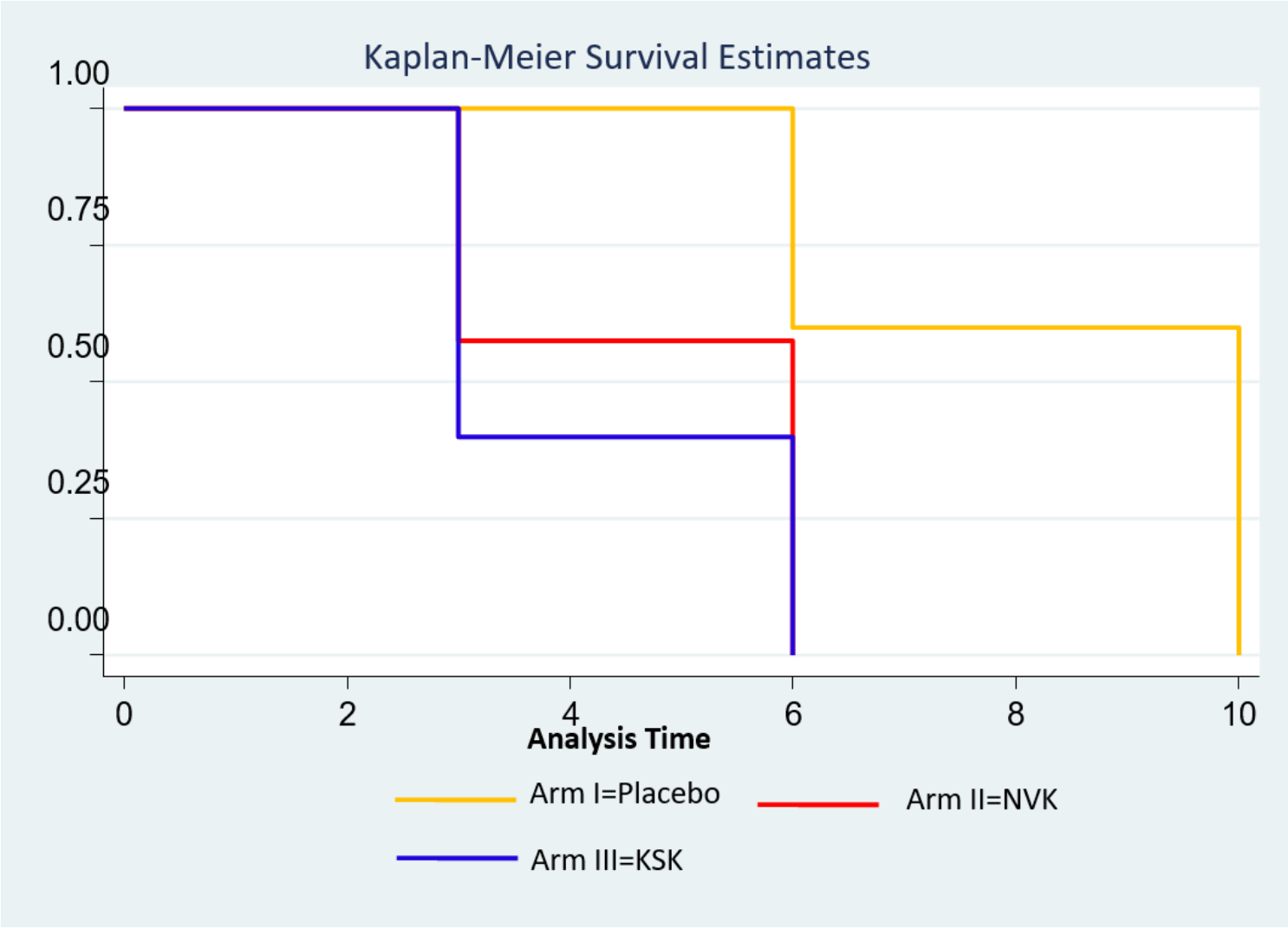

Figure 3

Comparison of Hospital Stay Time Kaplan Meir Graph for Arm I, Arm II and III Patients in Arm I stayed significantly longer (Mean [SD]=8.4 [2.0]) as compared to the Arm II and III (Mean [SD]=4.7 [1.5] and 4.2 [1.5] respectively, Kruskal Wallis test, p=0.0001.

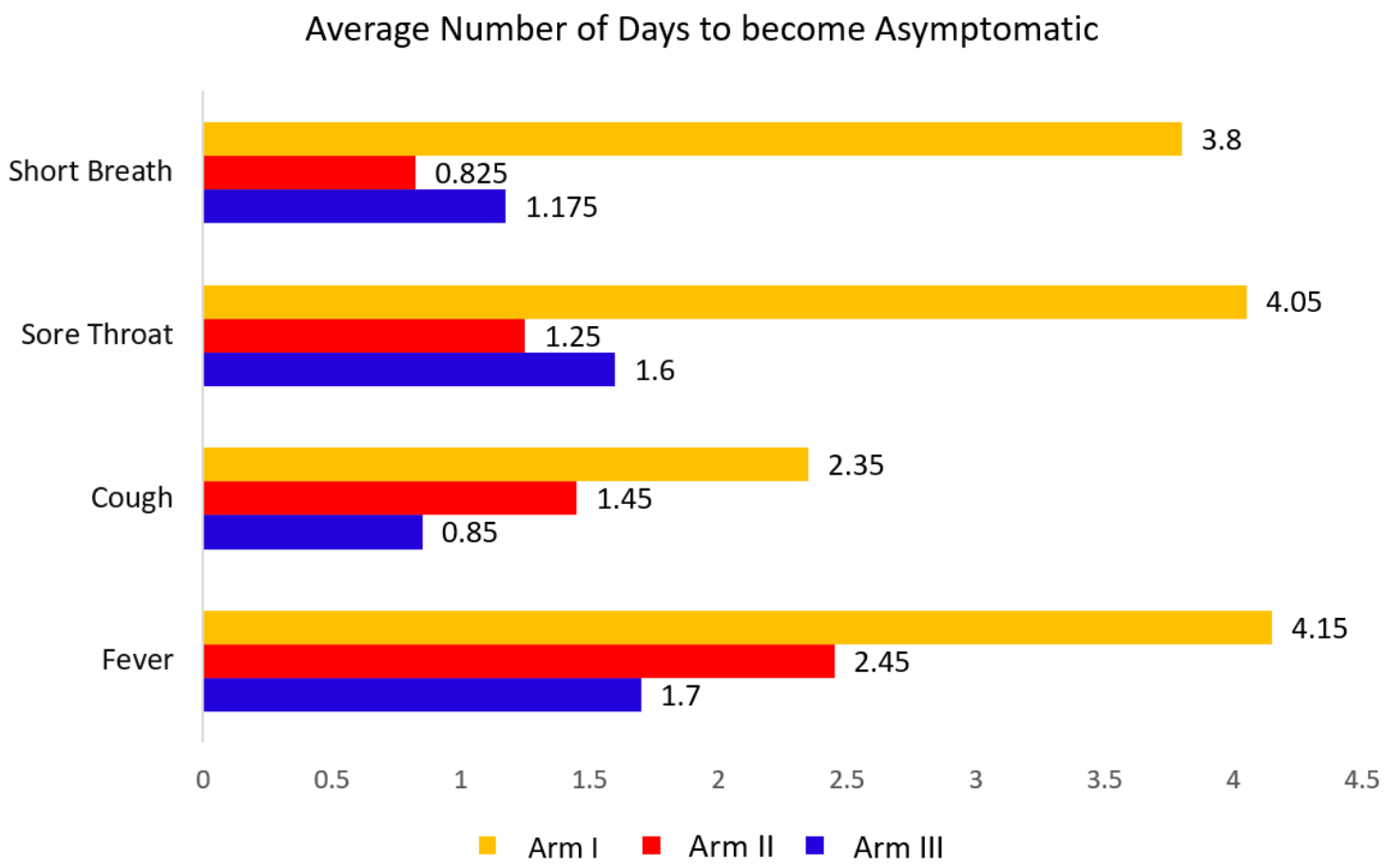

Figure 4

Time Taken to Convert Patients from Symptomatic to Asymptomatic for Arm I: Placebo, Arm II: NVK and Arm III: KSK

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- EquatorReportingStandardsCONSORT2010ChecklistMSWord.doc