Original Article

Impact of Steam Inhalation, Saline Gargling, and Povidone-Iodine Gargling on Clinical Outcome of COVID-19 Patients in Bengaluru, Karnataka: A Randomized Control Trial

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Abstract

Context: In the absence of any specific treatment available for COVID-19, people started practicing traditional nonpharmacological preventive home remedies such as salt water gargling and steam inhalation. The available research evidence on some of these measures opines that steam inhalation, saline gargling, and povidone-iodine gargling does have virucidal properties and do provide symptomatic relief. **Aims:** The aim is to test this hypothesis, and the present trial was undertaken with an objective to assess the effect of steam inhalation, saline gargling, and povidone-iodine gargling among the COVID-19-positive patients with respect to early test negativity and clinical recovery. **Methodology:** Open-labeled, parallel, randomized controlled trial was conducted among asymptomatic or mild COVID-19-positive patients in Bangalore from September 2020 to February 2021. In each group of steam inhalation, saline gargling, povidone-iodine gargling, and control, twenty participants were allocated. Daily follow-up was done for 21 days to assess early test negativity and clinical recovery. Trial Registry Number: Clinical Trial Registry India/2020/09/027687. **Results:** Among 80 participants recruited, 65 (81.3%) were symptomatic. Early test negativity was seen in povidone-iodine gargling group of 6 days (KaplanMeier survival curve, BreslowGeneralized Wilcoxon test $P = 0.7$ as per the intention-to-treat and as per-protocol $P = 0.8$). Significant clinical recovery was seen in saline gargling group (4 days, $P = 0.01$). **Conclusion:** Povidone-iodine gargling was effective in providing early test negativity, whereas saline gargling was effective in early clinical recovery.

Keywords: COVID-19, povidone-iodine gargling, randomized control trial, saline gargling, steam inhalation

Introduction

The WHO declared COVID-19 as a pandemic on March 11, 2020.[1] As the pandemic progressed and with better understanding of the disease, it was realized that asymptomatic, mild-and-moderate cases could be managed under home isolation. Accordingly, Indian government changed the guidelines from institution isolation to home-based care[2] to reduce the burden on the health-care system.

COVID-19 is an infectious viral disease with respiratory droplets as the main transmission route. The initial viral load in the nasopharyngeal specimens is a predictor of clinical outcome with respect to severity, disease progression, and mortality which in turn makes it very important to intervene in the early stage of the disease.[3] The viral load in throat swabs is highest just before symptom onset, and peak infectivity is seen on or before the onset of symptoms and viral load declines gradually by day 21.[4]

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In the absence of specific treatment, people are advised to practice social distancing, wearing mask, and maintain hand hygiene to contain the infection spread. COVID-19 mimicking common cold/flu, people started practicing traditional nonpharmacological home remedies such as salt water gargling and steam inhalation. The evidence says that steam inhalation, saline gargling, and povidone-iodine gargling do have virucidal properties.[5-8] Furthermore, studies have shown that gargling and steam inhalation do help in symptomatic improvement.[9] Many observational studies on non-COVID and few studies on COVID-19 infection have opined to conduct randomized control trials (RCTs) to support or refute the effect of these practices.[10] Exploiting the knowledge from the existing literature, this RCT was undertaken with an objective to assess the effect of steam inhalation, saline gargling, and povidone-iodine gargling among the COVID-19-positive patients with respect to early test negativity and clinical recovery.

Methodology

An open-labeled, parallel block, randomized controlled trial was conducted after obtaining institutional ethical clearance and registered in Clinical Trial Registry India. The study was conducted from September 2020 to February 2021 in seven urban primary health centers of South division, Municipal Corporation, Bangalore. Patients aged more than 18 years, asymptomatic or mild cases of COVID-19 who were under home isolation and who gave written informed consent for the study were included. Patients with a known history of immunosuppressive disorders, thyroid disorders, pregnant and lactating women, nasal polyps, recurrent nasal bleeding, known allergy to iodine and its compounds, and on lithium therapy were excluded. The sample size was calculated based on similar study,[11] at 95% significance level and 90% power with expected difference of 3 days in symptoms recovery between intervention and control groups. The total sample size calculated was 80 (20 in each group).

Randomization technique

Computer-generated block randomization was done by one investigator using Microsoft Excel with equal allocation ratio. Sample size of 80 was randomized into eight blocks of unequal size, each varying between 8 and 12. Allocation was concealed using opaque sealed and sequence-labeled envelopes. After obtaining the written informed consent, eligible participants were recruited by one of the investigators. Another investigator revealed the allocation by opening the above-labeled envelopes. Intervention type and procedures were revealed and assigned to the four intervention groups, namely, Group A (steam inhalation), B (saline gargling), C (povidone-iodine gargling), and D (control group) [Figure 1: Flowchart]. Blinding could not be followed for the participants and the investigator as the interventions were performance based. Only the analyzer was blinded by data coding.

Intervention

The patients under home isolation received the study interventions in addition to the standard therapy for COVID-19. Patients in control group were not given any interventions apart from standard therapy.[12] Participants were advised to practice these interventions thrice daily for 21 days.

Group A: Inhalation with electronic, automated steam inhalers for 3–5 min (effective exposure of 3 min).[13]

Group B: Gargling with 20 mL of hypertonic saline for 15 s.[14]

Group C: Gargling with 36 ml of 0.5% w/v povidone-iodine for 30 s.[15]

Group D: Antipyretic, antibiotics, zinc supplements, and Vitamin C as per the standard treatment guidelines.[12]

To reduce the experimenter bias, the four participants group were followed up by four different investigators. Data were collected from the patients of each group by the respective investigator and directly shared with the PI, thereby preventing the inter investigator discussion and its expected experimenter bias. The study participants were trained through video conferencing by different investigators for each group. Compliance and adherence to the concerned procedures were monitored through photos/videos/messages/phone call.

Follow-up

Patients were followed up daily for subjective clinical improvement (history taking and visual analog scale) and objective assessment (temperature and oxygen saturation monitoring) over the phone. Nasal and oropharyngeal swabs were collected once in 3 days at the patient's residence following standard precautions.[16] The primary objective was assessed by RT-PCR swab testing till test negativity or completion of home isolation of 21 days (whichever was earlier). A minimum gap of 3 h was ensured between intervention and swab collection.

End point

1. Test negativity- Two consecutive negative samples of RT-PCR swab test. (in exceptional cases, few patients showing alternate negative and positive results, few inconclusive results, and refusal for further tests, for them, the last test result was considered the final test report for analysis)
2. Clinical/symptom recovery– Reduction in symptom score (Symptoms were scored by giving weightage of 1 mark for each symptom and summed up. Symptom score reduction from the date of starting intervention to date of score reaching zero was considered the number of days taken for clinical improvement).

Statistical analysis

Data were analyzed according to an intention-to-treat and also per-protocol strategy. Chi-square test and KruskalWallis test were used for categorical data. The number of days required for the test to be negative among the different interventions were assessed by using KaplanMeier curve, and difference between the groups was verified by BreslowWilcoxon test.

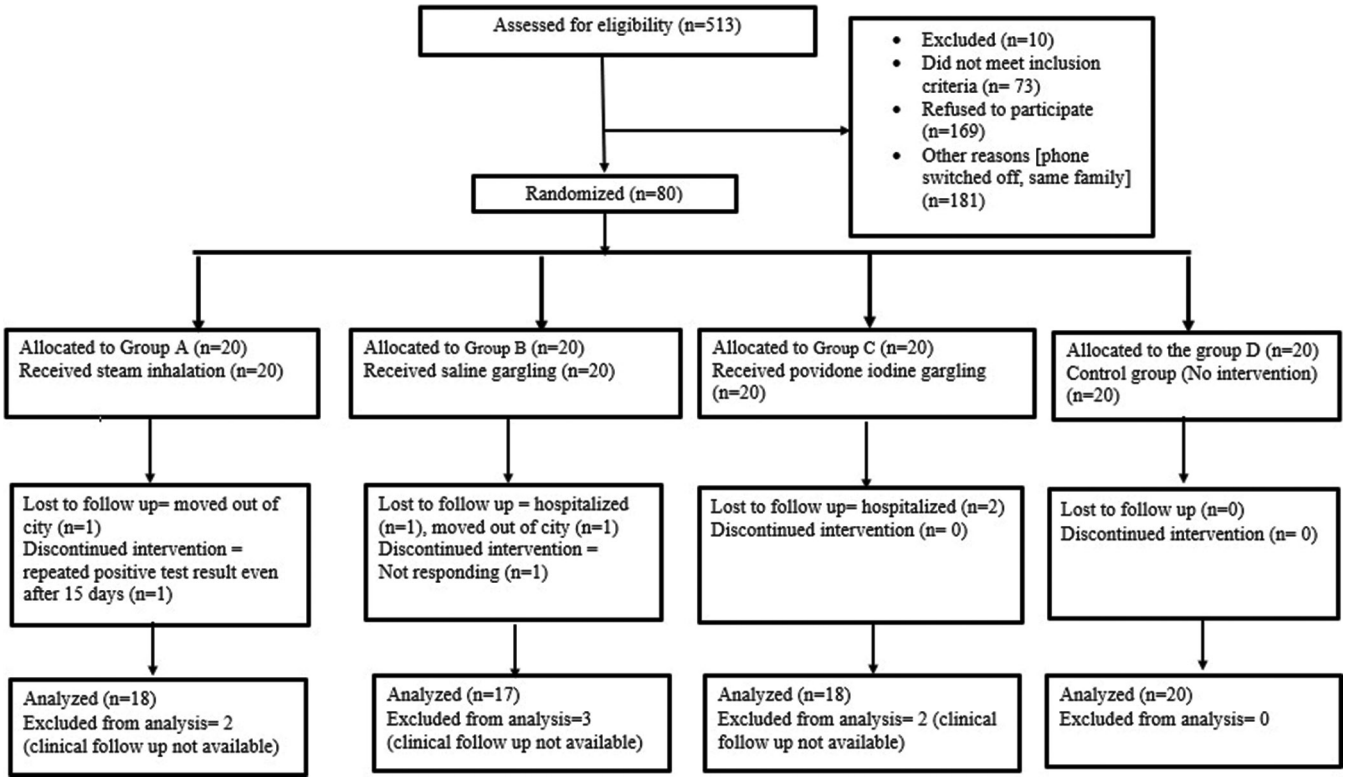

Figure 1: Consort flow diagram of SISPIG study

Results

We conducted RCT among asymptomatic and mild symptomatic COVID-19-positive patients under home isolation. Out of 513 patients assessed, 80 were recruited and randomized into four different intervention groups, each having 20 participants [Figure 1].

The total attrition observed was seven. One in Group B (no improvement of symptoms) and 2 in Group C (developed breathing difficulty) were hospitalized. One each in Group A and B moved out of the city. One discontinued each in Group A and B.

Mean age of the study population was 38.6 years (standard deviation ± 12.1) with median age of 39 years (interquartile range: 26–48) and 48 (60%) were males. Sociodemographic and baseline clinical characteristics of participants in four intervention groups were comparable [Table 1]. Majority were symptomatic (81.3%), and fever (43 [53.8%]) was the most common. Contact history with confirmed positive cases was present among 15 (18.8%). Comorbidities present among 10 (12.5%) (diabetes mellitus [5], hypertension [4], and asthma [1]). Tobacco consumption was present among seven participants (for a period of 5–20 years) and 12 participants with alcohol consumption (for a period of 2–20 years).

Effect of interventions on test negativity

Based on per-protocol analysis, our study revealed that those who were in Group C took on an average of 6 days for the RT-PCR test negativity while other group participants took 9 days for the same. However, it was not statistically significant $P = 0.8$ [Table 2]. Most of the test results were negative between 2 and 22 days among all four intervention groups. There was one person with positive report even after 21 days (Group A = 1). One person was continuously positive till 4th test and refused further tests (Group D = 1). One person with alternate negative and positive results (Group B = 1) till 5th test and refused further tests. Hence, for all these, final test results were considered positive till end of the analysis. Three individuals had alternate negative and positive results (Group A = 1, C = 1, and D = 1), but all of them had their last test report as negative.

The cumulative duration for test negativity among intervention groups was assessed and plotted using KaplanMeier survival curve assessed with value = 0. On day zero, all were infected. Among the study participants, 50% were cured (tested negative) and depicted by the black line (median value). Median number of days required for the test to turn negative was 9, 12, 6, and 9 days in intervention Groups A, B, C, and D, respectively [Figure 2]. BreslowGeneralized Wilcoxon test $P = 0.7$ (intention-to-treat analysis)

Effect of interventions on clinical recovery

Out of 80 participants, 73 were available for follow-up of symptoms, of whom 65 had one or more symptoms and 8 of them continued to be asymptomatic throughout the intervention period. Totally, 13 symptoms along with any other symptom details were collected. The minimum and maximum symptom scores at the beginning of intervention were 1 and 9. The

Table 1: Sociodemographic and baseline clinical characteristics of study participants (*n*=80)

Parameters	Group A (*n*=20)	Group B (*n*=20)	Group C (*n*=20)	Group D (*n*=20)	Test value *P*
Age (years), median (IQR)	32.5 (26-47.3)	31 (25-44.5)	39 (26.3-52.5)	42 (36.8-47.5)	3.4[a] *P*=0.3
Gender					
Male	11	12	15	12	χ^2=2.9, *P*=0.4
Marital status					
Married	12	12	13	17	χ^2=3.9, *P*=0.3
Occupation risk with respect to COVID-19					
High risk[b]	7	5	5	2	χ^2=3.5, *P*=0.3
Comorbidity					
Present	3	5	1	1	χ^2=5.0, *P*=0.2
Smoking					
Present	5	2	0	0	χ^2=10.5, *P*=0.01
Alcohol					
Present	6	5	0	1	χ^2=10.2, *P*=0.01
Symptoms					
Present	17	14	17	13	χ^2=3.5, *P*=0.3

[a]Kruskal-Wallis test, [b]High risk includes health-care workers and frontline workers. IQR: Interquartile range

Table 2: Duration for test negativity among the study participants (*n*=73)

Intervention group	Number of days taken for test negativity, median (IQR)	Minimum and maximum days	Test
A (18)	9 (5.8-12.8)	2-21	Kruskal-Wallis test *P*=0.8
B (17)	9 (6-15)	3-18	
C (18)	6 (6-13.2)	3-21	
D (20)	9 (6-14.2)	3-22	

IQR: Interquartile range

minimum and maximum number of days required to recover from symptoms are 1 and 18 days. Our study results revealed significant early clinical/symptom recovery among Group B compared to other intervention groups ($P = 0.01$). Significant symptom relief was seen with respect to fever, cough, malaise, and nasal congestion among Group B [Table 3].

Discussion

The primary objective of our study was to assess the effect of interventions on early test negativity, and we observed that participants using 0.5% povidone-iodine gargle took 6 days to become test negative, although it was not statistically significant ($P = 0.8$). Few studies have explained about the virucidal property of povidone-iodine and opined that they provide protective oropharyngeal measure.[17] Similar RCT showed 100% severe acute respiratory syndrome-coronavirus-2 viral clearance on day 6 among participants using 1% povidone-iodine gargle ($P = 0.01$).[18] An observational study conducted on steam inhalation in COVID-19 revealed that 62% of participants were tested negative after 10 days of starting intervention.[19] While in our study, the number of days taken for the test to be negative was 9 days among the steam inhalation group.

The secondary outcome results of our study revealed the saline gargling is beneficial in early symptom recovery (4 days [$P = 0.01$]). In another study, it took 5.6 days for saline gargling group ($P = 0.05$), suggesting its role in early symptom recovery.[20]

A similar study to know the effect of steam inhalation on COVID-19 patients showed that none of the asymptomatic patients progressed to develop any symptoms during 14 days to 2 months of follow-up. Among the mild symptomatic people, 3 days was needed to become asymptomatic, whereas among the severe symptomatic, they took 7–10 days to return to normal.[20] Our study revealed a duration of 5.5 days for overall symptom recovery among the steam inhalation group.

A single-center and open-label study on the efficacy of steam inhalation in 10 health-care professionals with COVID-19 showed that all were cleared of all the symptoms following the steam inhalation protocol.[21]

The present trial was conducted in a community-based setting. Even though the results of such community trials are usually generalizable, but the current COVID-19 pandemic situation warranted strict social distancing and quarantine measures which in turn affected the direct supervision of intervention performance by the participants. This situation could have also led to the occurrence of various biases. All attempts were made to reduce such biases wherever feasible. All the processes of randomization, patient recruitment, consent, allocation revealed, instructions to the procedure, follow-up,

Table 3: Effect of interventions on the duration of symptoms recovery (*n*=73)

Symptoms (*n*)	Median (IQR) (days)				Test value (χ^2, *P*)
	Group A	Group B	Group C	Group D	
All symptom score (65)	5.5 (4-12)	4 (2-5.5)	9 (6.25-10)	7 (5.2-8)	10.9, 0.01
Fever (39)	5.5 (3.5-8.2)	2 (1-3)	6 (2.5-7.5)	2 (1-3)	12.1, 0.01
Cough (24)	5.5 (3.5-8.2)	1	9 (2.5-12.5)	2 (1-1.75)	7.8, 0.05
Sore throat (25)	3 (1-7)	1 (1-1.7)	5 (3-8.5)	3 (1.5-3.5)	7.3, 0.06
Malaise (33)	7 (4.7-9)	3 (1.7-3.2)	5 (2.5-7.5)	3 (2.2-3)	12.5, 0.01
Loss of taste (13)	6.5 (4-)	4.5 (1.7-12.5)	14.5 (14-)	3 (2-3.5)	6.3, 0.1
Loss of smell (12)	9 (5-)	5 (4-)	11.5 (8-)	2 (1-3.75)	7.5, 0.1
Aches and pains (13)	5.5 (4.2-8.2)	1	4 (3.2-5.5)	3 (3-4.5)	6.5, 0.1
Nasal congestion (17)	4 (1.5-11)	1 (1-1)	1 (1-1)	1 (1-1)	9.1, 0.03
Headache (17)	2.5 (1-8)	1.5 (1-)	2 (2-2)	3 (2.5-3.5)	1.4, 0.7

IQR: Interquartile range

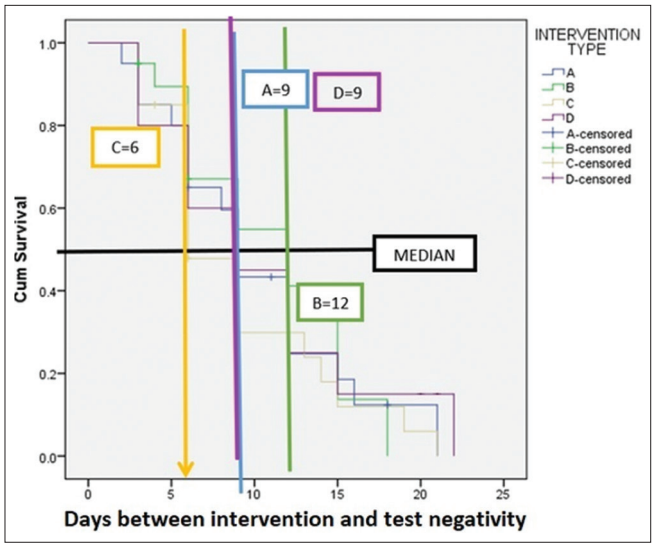

Figure 2: Kaplan-Meier curve depicting duration taken for test negativity after intervention

and data collection were conducted by different members of the investigation team, thereby reducing the selection bias. Information bias was reduced by keeping constant touch with the patients through phone, sharing photos, videos, or recordings with the investigator. To reduce the performance bias, prerecorded videos of assigned interventions were shared with the participants. They were in turn asked to share videos/photos to ensure that the assigned interventions were performed as per the instructions. Two well-trained swab collectors were assigned for the swab collection to minimize the measurement bias.

The key limitation of this trial was inability to conduct the study under a controlled setting such as isolation hospitals. Although standard treatment was followed by all 80 participants, the effect of these standard treatments on COVID symptoms recovery cannot be negated.

COVID-19 is a novel disease and has become pandemic with an impact on economic, political, and social concerns at global level. We have realized that COVID-19 is here to stay with its new variants/strains and resultant secondary waves which in turn continue to affect mankind in the days to come. Hence, in the absence of a potent antiviral agent for the treatment of COVID-19, the results of our study have provided additional evidence that these interventions can be practiced safely by public to curb the transmission of the disease and also to provide symptomatic improvement to patients across the globe, which in turn can decrease the demand of already overburdened health resources. Our study also acts as a base for further research on a larger scale.

Conclusion

Among the interventions, early test negativity was observed among povidone-iodine gargling group (6 days, $P = 0.8$), whereas overall significant early clinical recovery was seen among saline gargling group (4 days, $P = 0.01$). We conclude that povidone-iodine with its virucidal property will help in early test negativity and saline gargling is effective in early clinical recovery. Povidone-iodine gargling can be practiced to contain the transmission of infection and saline gargling can be practiced for individual's symptomatic relief.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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