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Bird's eye view of COVID-19 clinical trials being conducted across India

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Abstract

Aim: We are in the midst of COVID-19 pandemic, with more than five lakh deaths around the globe. There is an intense search for the best medication to curtail the pandemic and prevent mortality. Ever since the pandemic broke, thousands of clinical trials are being carried out to see for a safe and effective drug in various countries. We aim to analyze various interventional clinical trials for COVID-19 infection currently being conducted in India.
Methods: The study data was downloaded on 9th June 2020 from Clinical Trials Registry-India and ClinicalTrials.gov available in public domain. The keywords used for search were COVID-19, SARS-CoV-2 and India. These studies were analyzed for type of intervention, design, study subjects and end points. The categorical variables are expressed as percentages and continuous values are expressed as interquartile range.
Results: A total of 115 studies were analyzed for study parameters. Over all 62% of total trials were randomized, 63% single center and 78% had multiple arms in the study design. Half of the clinical trials were open label with only 4 studies being double blind studies. Only two studies included pediatric age group, while the rest of the studies included subjects between 18-75 yrs. Majority of the studies have clinical cure/recovery (36.52 %) as the primary outcome, while only 18.26% looked for virological cure. Among intervention, allopathic drug and biologicals were studied in almost 40 % of the trials, of which (22.22 %) of the studies used anti-malarial drug and plasma therapy. Among studies that used AYUSH medications, Ayurvedic drugs accounted for almost 34% of intervention.
Conclusion: This study gives us a general idea of various interventions tried in the treatment and prevention of COVID-19 infection. As of June 2020 allopathic medicines have the highest share of trials being conducted in India. This preliminary data could act as a catalyst for further appropriate studies to treat and prevent COVID-19 infection.
Keywords: COVID-19, SARS CoV, interventional, clinical trials, India.

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1. Introduction

Covid-19 infection caused by single-stranded RNA virus usually found in avian and mammalian species has caused widespread morbidity and mortality around the world. On 11th March WHO declared COVID-19 a pandemic, with the rapid spread of disease [1]. Globally as of 2.25 pm CEST, 25th June 2020, there have been 9,296,202 confirmed cases of COVID-19, including 479,133 deaths, reported to WHO [2]. As per the WHO Covid-19 dashboard, the highest numbers of confirmed reported cases are from America, Brazil, India, and Russia. The clinical presentation of SARS CoV infection range from asymptomatic infection to severe symptoms like breathlessness. Some of the severe cases with old age and comorbid conditions land up in ICU with viral pneumonia and respiratory failure. The mild to moderate cases are treated with antipyretics, vitamin C, and analgesics. The progression from moderate to severe pneumonia usually takes one to two weeks after the onset of symptoms, in some even earlier. These severe patients require ICU care with oxygen support or mechanical ventilation for low oxygen saturation [3].

This time of progression from moderate to severe cases gives a crucial time for us to use various therapies to save the patient. Dealing with the management of novel coronavirus 2019 is emerging as a global challenge of the decade. Many young generations of doctors across the world are facing a pandemic of this nature the first time in their life. Huge efforts are ongoing to find the best treatment or drug for COVID-19, but we are yet to find the Holy Grail. Every country has a treatment protocol for COVID-19 which keeps changing every fortnight as new evidence appears. Many pharmaceutical companies around the world are trying to repurpose their old product for the treatment of Covid-19 infection, claimed to reduce viral load or mortality [4]. A range of products from anti-virals like Remdesivir[5], antibiotics like azithromycin [6], anti-malarials like hydroxychloroquine[7], biological [8], anti-protozoal drugs like ivermectin[9] and convalescent plasma therapy are used in the treatment of severe COVID-19 patients. The recent addition to the ever-growing list is low dose dexamethasone to reduce hospital stay and mortality [10]. Even vaccines like BCG [11] and MMR [12] are being suggested for prevention and treatment. The use of these products is based on data from use in a limited number of patients or non-randomized clinical trials. Many trial data are published in leading medical journals, which are not peer-reviewed. There were some instances of retraction of a study published from a reputed medical journal [13]. So there has been enough confusion and controversies on medications to be used in the treatment of COVID-19 infection. Every now and then we find a new drug emerging as the game- changer in treatment of COVID-19 infection. The need of the hour to tackle this issue is to conduct extensive randomized scientifically designed clinical trials to ascertain the safety and efficacy of the drugs in treatment and prevention of COVID-19 infection. The need for fast track development of drugs or vaccine has spurred huge global efforts from all concerned to conduct clinical trials around the world. Trials are being conducted not only for allopathic drugs but also other branches of medicines like AYUSH [14] aggressively to find a cure. Hence we wish to analyze the various interventional clinical trials for COVID-19 infection currently being conducted in India based on trial registration data.

2. Methods

The study data was downloaded on 9th June 2020 from Clinical Trials Registry-India (CTRI) [15] and ClinicalTrials.gov [16] available in the public domain. The keywords used for search were COVID-19, SARS-CoV-2, SARS CoV-2, SARS Cov-2, and India. The downloaded data was entered in to a Microsoft Excel sheet. The study inclusion criteria were all interventional trials for the prevention and treatment of COVID-19 infection registered with clinical trials registry. The study exclusion criteria were observational studies on COVID-19 infection. The following parameters of the study were noted like trial registry number, phase of the trial, study design details, the blinding procedure followed, disease severity, primary outcome, and intervention given for trial subjects.

2.1 Statistical Analyses

All continuous values are expressed as median, range, and interquartile range. Categorical variables are expressed as percentages. All statistical procedures were performed using the SAS software.

3. Results

After entering the keywords in Clinical Trials Registry-India (CTRI) overall 175 trials were downloaded. Out of 175 registered trials 65 were excluded as they were observational studies. The number of trials from India registered in ClinicalTrials.gov (global studies) was 14, out of the 14 studies 7 were excluded as they were observational studies and two studies were also registered in CTRI. The final interventional trials analyzed from both the trials registry were 115. The above mentioned trials were downloaded on 9th June 2020.

3.1 Study Population:

Most of the study population age was 18-75 years, just two studies involved pediatric age group. The least age allowed for enrollment in these studies was 45 days and the highest age of 99 years. Sample size analysis showed 31% of the studies enrolled sample above 400 subjects (Table 1). 11 studies have a sample size of 5000 and above. The study with the least sample size was 6 and the maximum sample size was 50,000. Overall these studies will be recruiting approximately 2,37,449 individuals.

Table 1: Studies Sample distributions

Number of samples	Number of trials
< 20	6
21-40	15
41-60	15
61-100	15
101-200	22
201-400	11
> 401 to 5000	21
>5001 to 50000	10
Sample size Median (IQR)	120 (50-500)
Sample size per group Median (IQR)	60(30-300)

3.2 Study design:

62% of total trials were randomized, 33.4% were non-randomized and the rest was not applicable. Majority of the studies were single-center 63.48%, whereas only 36.52 % were multicenter studies. Maximum trials had multiple arms in the study design 78.26%, whereas 21.74% had a single

group in the trial. When looking into blinding procedures only 4 studies (3.48%) were double-blind, 10 studies were single-blind (8.70%), whereas 51.3 % of the studies were open- label (Table 2). Almost 99% of the studies were institutional-based or funded and just one study was being done by a pharmaceutical company. Majority of the trials were Phase 2 & 3, with just 6 studies (5.21%) in Phase 1.

Table 2: Trial Characteristics and summary of designs for all Interventional trials (n = 115)

Category	Information	No. of trials	Percentage
Study groups	Single group	25	21.74
	Multi group	90	78.26
Study center	Single	73	63.48
	Multi	42	36.52
Study design	Random	72	62.60
	Non-random	38	33.04
	Not mentioned	05	4.34
Masking	Open label	59	51.3
	Double-blind	04	3.48
	Single blind	10	8.7
	Not applicable	42	36.52

3.3 Study primary outcome:

Majority of the studies have clinical cure/recovery (36.52 %) as the primary outcome, while only 18.26% looked for seroconversion/virological cure. Mortality was the primary outcome in 13.04 % of studies. The other primary endpoints were ICU admission, mechanical ventilation as shown in Table 3.

Table 3: Primary outcome measures

Category	Number of trials	Percentage
Clinical cure/ Recovery	42	36.52
Seroconversion/ Virological cure	21	18.26
Incidence of COVID-19 infection	52	45.21
All cause mortality	15	13.04
ICU admission	03	2.67
Mechanical ventilation	02	1.74
Misc./ Diagnostic	01	0.87

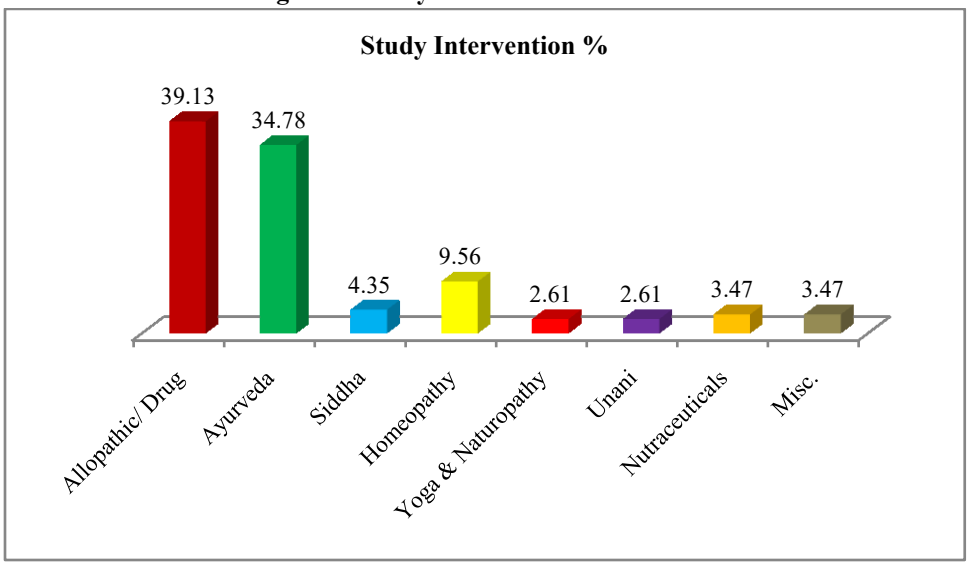
3.4 Symptoms severity:

Studies that enrolled SARS-CoV-2 positive cases were 55.65 % and the rest were being done in SARS-CoV-2 negative subjects. Analysis of severity of symptoms in SARS-CoV-2 positive cases being enrolled showed 50.34% of cases had mild symptoms, 35.65% moderate symptoms, and 16.52% severe symptoms. Almost 13.91 % of SARS-CoV-2 positive cases being enrolled are asymptomatic. The studies that enrolled SARS-CoV-2 negative subjects include usually health care workers, police, healthy volunteers, high-risk individuals and quarantined individuals.

3.5 Interventions studies:

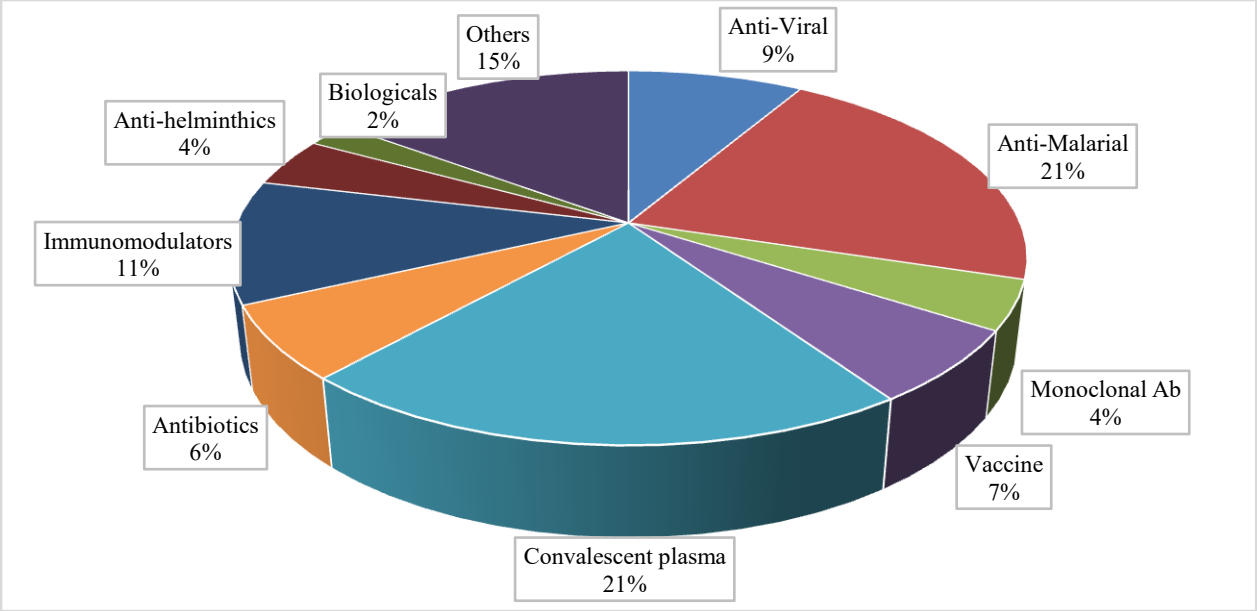
Majority of the studies enrolled were using the allopathic drugs (39.13%) as an intervention for treatment or prevention of COVID-19 infection. The rest of the studies were using AYUSH intervention. Among AYUSH, the ayurvedic drugs accounted for almost 34.78 % of intervention followed by homeopathy (9.56 %) as shown in Figure 1.

Figure 1: Study intervention distribution



Among allopathic intervention maximum (21%) of the studies used anti-malarial drug and plasma therapy for the treatment of COVID-19 infection. The next common interventions tried were immunomodulators (11%), followed by antiviral drugs, vaccines, antibiotics, monoclonal antibodies, and anti-helminthic drugs as shown in Figure 2 below. Four studies were registered with nutraceutical as an intervention.

Figure 2: Breakdown of Allopathic Intervention used in the trials



4. Discussion

The above analyzed studies show there were only 62% of the studies randomized. The most accepted scientific study design is randomized studies, the advantages being it removes selection bias and truly allows for a direct comparison between two treatment groups. Only four studies registered had a double-blind approach, this could be due to the contagious nature of the infection. Hence most of the studies registered were open-label. All most 40% of the trials were evaluating an allopathic drug, antimalarial drug, and plasma therapy dominated the intervention studied.

A similar study was done by Jihan Huanget et al [17] from China, where 76 % of the trials were randomized parallel trials and 24 % were double-blind studies. 22 % of trials considered an improvement in symptoms as primary endpoint and 16% virus negative status. Chemical drugs and biologicals accounted for almost 40 % of trials being conducted, with anti-virals accounting for 15 % and antimalarial drugs for 8.4 %. In this study, 27.9% of the registered studies used traditional Chinese medicine. In our study, ayurvedic drugs were most commonly studied from traditional medicine.

Recently one of the AYUSH medications has claimed to found cure to Covid-19, based on trials on a limited number of patients. Later the study data was questioned by both experts and government on the quality of the trials conducted. The said product sale was put on hold by the local authority. Such trials have evoked widespread skepticism and alarm because it can pose a danger to the lives and health of people [18]. Some of the drugs like Remdesivir from Gilead have been given conditional approval by EMA for adults and adolescents from 12 years of age who are also suffering from pneumonia and require oxygen therapy [19]. This conditional marketing authorization allows the drug to be sold a year in 27 nation bloc before all necessary data on its efficacy and side effects are available.

The WHO Solidarity trial[20] and UK's RECOVERY trial [21] are two of the world's leading scientific efforts providing cutting edge research in the battle against COVID-19.The solidarity trial was launched on 18th March by WHO to compare four untested treatment options for Covid-19. The treatment arms are remdesivir, lopinavir/ritonavir, lopinavir with interferon beta-1alpha, and chloroquine or hydroxychloroquine. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine in RECOVERY trial.

We have to accept the fact that as of a date no drug or vaccine used or being used in COVID-19 treatment has a strong scientific base to show efficacy and safety. Only multi-centric large scale randomized trials will tell the truth. As we keep searching for various treatment options its best to rely on evidence-based medicine and robust clinical trials. The idea is to get the right medication or vaccine which is safe and efficacious to all.

5. Limitation of the study

This study only includes data from studies registered up to 9th June, 2020, we are sure many more studies were enrolled later to this date. We could not look in to the results of these studies enrolled for comments.

6. Conclusion

This study gives us a general idea of various interventions tried in the treatment and prevention of COVID-19 infection from all medical branches. As per clinical trials registry data, allopathic medicines have the highest share of trials being conducted in India. In the allopathic segment, anti-malarial drug and plasma therapy for the treatment of COVID-19 infection are extensively being studied. This preliminary data could act as a catalyst for further appropriate studies to treat and prevent COVID-19 infection.

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