



Clinical Trials Developed in Brazil on Covid-19: What is Being Researched?

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Abstract

Background: The coronavirus disease 2019 pandemic (COVID-19) has brought great public health challenges into our lives. To date, there has been no specific therapeutic protocol for this disease, which requires a study with high-quality evidence.

Objectives: To analyze clinical trials on COVID-19 in Brazil.

Methods: Documentary research was conducted on the clinical trial registration platform. For the search strategy, the “COVID-19” keyword was established in the “condition or disease” section and “Brazil” in the “country” section. No limit on the search period was considered. Data were analyzed and presented using descriptive statistics.

Results: Of the 81 registered clinical trials, 48 met the eligibility criteria. The sample size ranged from 10 to 3,000 individuals. Most studies recruited individuals aged 18 - 64 years (48.5%) and > 65 years (48.5%). Regarding the study design, randomized (91.6%), parallel (89.5%), quadruple-blind (39.6%), and therapeutic (97.9%) types were more frequent. Most studies used standard two-arm trial (70.8%), used drugs (79.2%), placebo (58.3%), and were sponsored by pharmaceutical/biotechnology companies and universities with 33.3% and 29.2%, respectively.

Conclusions: Clinical trials under development in Brazil on COVID-19 are mostly carried out with adult and elderly participants, and regarding the study design, have a predominance of randomized allocation, parallel model, quadruple-blind masking with a therapeutic purpose. Most studies use antithrombotic agents or combinations of antithrombotic agents.

Keywords: Clinical Trial, Evidence-Based Practice, COVID-19

1. Background

The emergence and spread of a new virus at the end of 2019 brought major public health challenges worldwide (1). Health authorities in Wuhan, China, detected the first cases of atypical pneumonia attributed to a newly discovered virus, belonging to the Coronaviridae family (2), which causes the disease known as coronavirus 2019 (COVID-19) (3). Although its origin is not fully understood, it is believed to be a zoonotic disease, such as SARS-CoV's outbreaks in 2002 and MERS-CoV in 2012 (4).

The etiologic agent responsible for COVID-19 was called SARS-CoV-2 because it is similar to the etiologic agent that is caused by the severe acute respiratory syndrome (SARS)-SARS-CoV (5). It is a simple, positive, enveloped, single-stranded RNA virus belonging to the genus *Betacoronavirus* (betaCoV). SARS-CoV-2 has a high mutation rate and rapid spread (6) and has been declared as a pandemic (7). The recent data on August 23, 2020, show COVID-19 in 216 coun-

tries with more than 23 million infected individuals and 800 thousand deaths (8). With more than 12 million cases in total, the United States and Brazil are currently the most COVID-19-stricken Countries (8).

SARS-CoV-2 transmission occurs through expelled respiratory droplets or contact with exposed surfaces (2, 9). The most common symptoms of COVID-19 include fever, cough, and fatigue, followed by myalgia, increased sputum production, shortness of breath, chest pain, chills, headache, and sore throat (10). As a complication, the disease can progress to acute respiratory distress syndrome (ARDS), heart failure, shock, and renal failure (10). Specific groups of patients, such as the elderly and individuals with chronic diseases, have the worst prognosis (11).

Although COVID-19 is included in the list of priority diseases for research and development in the emergency context of the World Health Organization (WHO) (12), no specific therapeutic protocol has yet been approved for

the disease (13). Some recommended treatments include antivirals, antiretrovirals, corticosteroids, and gamma globulin, probiotics, quinolones, and cephalosporins (13). Some drugs such as chloroquine, hydroxychloroquine, azithromycin, and favipiravir are being tested in clinical trials to treat the severe cases caused by SARS-CoV-2 (13).

Randomized clinical trials represent the gold standard for evaluating interventions and contribute to evidence-based practice (14). Since 2004, the International Committee of Medical Journal Editors (ICMJE) has recommended the registration of all clinical trials in publicly-available databases before being considered for publication (15).

There is a wide range of clinical trial registry databases, among which is the International clinical trials registry platform (ICTRP). The ICTRP Search Portal combines the registration of studies provided by 17 data providers, including the ClinicalTrials.gov (16). This database is maintained by the National Library of Medicine (NLM) of the National Institute of Health (NIH) (17). It provides the registration of 349,708 studies in 216 countries, with information on diseases, interventions, and study design (17).

2. Objectives

The present study aimed to analyze the clinical trials on COVID-19 under development in Brazil.

3. Methods

Documentary COVID-19 research was conducted on the clinical trials registration platform (<https://clinicaltrials.gov/>). For the search strategy, the "COVID-19" keyword was established in the "condition or disease" section and "Brazil" in the "country" section.

We analyzed all the registered clinical trials and excluded those studies with suspended, withdrawn, and terminated recruitment status, observational studies, studies that did not include diagnosis of COVID-19 among its criteria, and those that mentioned the use of healthy patients. Data were collected in August 2020 by a single previously trained researcher.

The following information was collected: Study location, number of participants, age groups of subjects, allocation, intervention model, masking, purpose, diagnostic criteria for COVID-19, other eligibility criteria, recruitment status, numbers of arms, type of intervention, phase, presence of placebo, comparison arm, and sponsor.

Drugs, biological intervention, and other experimental groups' interventions were identified and classified using the WHO's Anatomical Therapeutic Chemical Classification System (18). We use the information on the company's website for the drugs that were not included in the WHO's ATC.

Data were tabulated and analyzed using Microsoft Excel 2016 for Windows (Microsoft Press, Redmond, WA, USA) and presented via descriptive statistics (absolute and percentage distributions).

4. Results

Overall, 3,099 records involving COVID-19 were found, of which 81 (2.6%) are being developed in Brazil. Two suspended, one withdrawn, one terminated, sixteen observational studies, nine that did not include diagnosis of COVID-19, and finally four studies that used healthy patients were excluded. Thus, 48 clinical trials met the eligibility criteria and were analyzed.

Fifteen clinical trials (31.3%) had international collaboration, covering 20 different countries. Some studies involve more than one collaborating country simultaneously, predominantly the United States of America (11 studies), followed by Mexico and Spain (6 studies each), Argentina and Russia (5 studies each), Italy and Canada (4 studies each), France, Germany and the United Kingdom (3 studies each), Belgium, South Africa, Chile, and Japan (2 studies each), Peru, Kenya, Australia, Israel, Holland, and Poland (1 study each).

There was great variability in the number of participants with a minimum of 10 and a maximum of 3,000 individuals. Most clinical trials recruited adults and the elderly, with similar percentage distribution between those aged 18 - 64 years (48.5%) and those aged 65 years or older (48.5%). Studies involving children and adolescents are minority representing only 3%.

Regarding the distribution of participants, four studies (8.4%) did not use randomized allocation. The most frequent intervention model was parallel (89.5%). Regarding the type of masking, the quadruple-blind study (39.6%) was the most prevalent, followed by an open model (31.3%). Therapeutic studies are predominant (97.9%), and more than two thirds (68.8%) consider the confirmed diagnosis for COVID-19 as an inclusion criterion (Table 1).

Given the identification and classification of drugs, biological interventions, and other interventions, 44 clinical trials used monotherapy interventions and 11 used combinations. In monotherapy, most studies used antithrombotic agents (7 studies), followed by antimalarials, antiviral and immunosuppressants (5 studies each), anticancer (3 studies), antiparasitic and corticosteroids (2 studies each) and plasma (1 study). Studies using combinations used antithrombotic agents (2 studies), antivirals (1 study), antivirals/antimalarials (1 study), antivirals/immunosuppressants (1 study), and corticosteroids/antithrombotic agents (1 study) (Table 2).

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5. Discussion

The scientific community is making a great effort to clarify the therapeutic modality with clinical efficacy in the treatment of COVID-19 (2). Properly designed clinical trials can reduce biases, allowing the identification of cause-effect relationships between intervention and result (19). Sharing these data is essential as it contributes to the advancement of knowledge and in decision making (20).

The significant number of clinical trials on COVID-19 registered with clinical trials reflects the current challenge of medical research and clinical practices and the demand for effective and safe intervention. However, we should pay attention to the dissemination of scientific research of poor quality conducted with small and unrepresentative sample size, without control or comparison group, non-randomized and non-multicentric, which can be amplified as a consequence of pressure from governments, from large pharmaceutical companies, and from the society for immediate results, and of inadequate research infrastructure conditions (21). Thus, it is important to analyze the clinical trials' design to identify those that provide the best scientific evidence.

Most included studies are being developed in collaboration with researchers from the United States. In July 2020, the USA were the leading country by publishing papers related to the COVID-19 (22). This leadership in biomedical research is supported by huge public funding, dominated by NIH (23), which demonstrates the urgency in relation to the severity with which the disease has reached the country.

In this work, most of the studies included adult and elderly individuals in their samples, with randomized allocation, parallel intervention model, and quadruple-blind masking type. The age group's choice may be related to the lower likelihood that younger individuals, particularly those under 17, are contaminated or presenting milder symptoms than adults and the elderly when the test is positive for COVID-19 (24). In turn, randomization and masking are important characteristics because they provide a well-designed clinical trial, enabling adequate comparison between different groups, tending to produce impar-

tial results, since by the process of masking, the participant and/or researcher unaware of the treatment he/she is going to receive and do not influence the results, reducing research bias and providing higher quality evidence, which increases the possibility of clinical success.

The predominance of studies with therapeutic purposes and evaluated drugs as intervention demonstrates the concern with the current worldwide contagion scenario and the urgent need for clinical trials to assess which interventions are more effective in an adequate and quick way against COVID-19. Regarding the use of the placebo group in part of the studies analyzed and the lack of proven therapeutic methods, this technique is ethically acceptable.

The most frequent sponsors were pharmaceutical/biotechnology companies and universities. Clinical trials conducted by industries must be critically judged since the pressure to show a favorable result may result in less robust data. However, even without operationalization and financial contribution (25), universities stand out in conducting this type of study in Brazil.

The results of this study show that the majority of clinical trials on COVID-19 under development in Brazil employ antithrombotic agents or combinations of antithrombotic agents. COVID-19, through the direct or indirect effects of the disease, due to severity and hypoxia, can predispose patients to thrombotic events (26). It is worth noting that other drugs currently under study such as Lopinavir/Ritonavir, Tocilizumab, among others, can interact with antiplatelet or anticoagulant agents (26). Therefore, the study of these drugs is justified.

This study emphasizes the importance of registering clinical trials in a publicly accessible database, enabling scientific transparency in conducting research (27). Our findings may help researchers identify gaps and more promising interventions, consequently contributing to scientific knowledge advancement. Up to the present time, a lot of medications were identified that possessed definite antiviral effects against COVID-19; however, a long-run and well-designed study is necessary to obtain the best possible answer (28, 29).

5.1. Conclusions

Clinical trials under development in Brazil on COVID-19 employ adult and elderly participants and have a predominance of randomized, parallel, quadruple-blind design with a therapeutic purpose. Most studies use antithrombotic agents or combinations of antithrombotic agents.

Footnotes

Authors' Contribution: Study concept and design: AFCC and ALC. Design: ICCL, AFCC, and ALC. Analysis and inter-

pretation of data: ICCL, AFCC, and ALC. Drafting of the manuscript: ICCL. Critical review: ICCL, AFCC, and ALC.

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Table 1. Sample Characteristics and Study Design of Clinical Trials^a

Variables	Values
Age groups, y^b	
0 - 17	3 (3.0)
18 - 64	48 (48.5)
> 65	48 (48.5)
Allocation	
Randomized	44 (91.6)
Non-randomized	2 (4.2)
N/A	2 (4.2)
Intervention model	
Single group assignment	2 (4.2)
Sequential assignment	1 (2.1)
Parallel	43 (89.5)
Factorial	2 (4.2)
Masking	
Blind	3 (6.2)
Double-blind	8 (16.7)
Triple-blind	3 (6.2)
Quadruple-blind	19 (39.6)
Open label	15 (31.3)
Purpose	
Diagnostic	1 (2.1)
Treatment	47 (97.9)
Diagnostic Criteria for COVID-19	
Confirmed	33 (68.8)
Suspect	5 (10.4)
Confirmed or suspect	10 (20.8)
Recruitment Status	
Completed	2 (4.2)
Recruiting	38 (79.2)
Active, not recruiting	4 (8.3)
Not yet recruiting	4 (8.3)
Numbers of Arms	
1	2 (4.2)
2	34 (70.8)
3	7 (14.6)
4	3 (6.2)
5	1 (2.1)
6	1 (2.1)
Type of Intervention	
Dietary supplement	1 (2.1)
Drug	38 (79.2)
Biological	4 (8.3)
Device	1 (2.1)
Diagnostic test	1 (2.1)
Ventilation strategy	1 (2.1)
Others	2 (4.2)
Phase	
1	2 (4.2)
2	11 (22.9)

3	14 (29.2)
4	3 (6.2)
1 e 2	1 (2.1)
2 e 3	8 (16.7)
N/A	9 (18.7)
Presence of placebo	
Yes	28 (58.3)
No	20 (41.7)
Comparison arm	
Yes	16 (80.0)
No	4 (20.0)
Sponsor	
University	14 (29.2)
Pharmaceutical/biotechnology company	16 (33.3)
Research organizations	8 (16.7)
Hospital	10 (20.8)

^aValues are expressed as No. (%).

^bSome studies involved more than one age group.

Table 2. Interventions Used in Experimental Groups of Registered Clinical Trials On COVID-19

Interventions and Classes	N ^a
Antithrombotic agents	7
Heparin	4
Acetylsalicylic acid	1
Therapeutic anticoagulation	1
Rivaroxaban	1
Antimalarials	5
Chloroquine or hydroxychloroquine	5
Antivirals	5
Atazanavir	1
Daclatasvir	1
Galidesivir	1
Lopinavir/ritonavir	1
ABX464	1
Immunosuppressants	5
Tocilizumab	2
Methotrexate	1
Baricitinib	1
Sarilumab	1
Anticancer	3
Ruxolitinib	2
PTC299	1
Antiparasitic	2
Nitazoxanide	1
Ivermectin	1
Corticosteroids	2
Methylprednisolone	2
Plasma	1
Others	14
Renin-angiotensin system inhibitors	2
Cannabidiol	2
Brazilian green propolis extract (EPP-AF)	1
BCG	1
NestaCell®	1
Sirukumab	1
ANG-3777	1
BLD-2660	1
Losmapimod	1
M5049	1
Otilimab	1
SAR443122	1

Antithrombotic agents combinations	2
Heparin + enoxaparin	1
Rivaroxaban + heparin/enoxaparin	1
Antivirals combination	1
Sofusbuvir + daclastavir	1
Antivirals + antimalarials	1
Hydroxychloroquine sulfate + lopinavir/ ritonavir	1
Antivirals + immunosuppressants	1
Remdesivir + tocilizumab	1
Corticosteroids + Antithrombotic agents	1
Methylprednisolone + heparin	1
Other combinations	5
Hydroxychloroquine + azithromycin	2
Ivermectin + losartan	1
Dutasteride + ivermectin + azythromycin	1
Proxalutamide + ivermectin + azythromycin	1

^aSome studies used several interventions.