A Randomized Open-Label Trial To Evaluate The Efficacy And Safety Of Triple Therapy With Aspirin, Atorvastatin, And Nicorandil In Hospitalised Patients With SARS Cov-2 Infection: A Structured Summary Of A Study Protocol For A Randomized Controlled Trial

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Research Article

Keywords: COVID-19, Aspirin, Atorvastatin, Nicorandil, randomised control trial, protocol, hospitalised patients

Posted Date: June 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-550553/v1

Version of Record: A version of this preprint was published at Trials on July 15th, 2021. See the published version at https://doi.org/10.1186/s13063-021-05361-y.

Abstract

Objectives

The pathophysiology of SARS-Cov-2 is characterized by inflammation, immune dysregulation, coagulopathy, and endothelial dysfunction. No single therapeutic agent can target all these pathophysiologic substrates. Moreover, the current therapies are not fully effective in reducing mortality in moderate and severe disease. Hence, we aim to evaluate the combination of drugs (aspirin, atorvastatin, and nicorandil) with anti-inflammatory, antithrombotic, immunomodulatory, and vasodilator properties as adjuvant therapy in covid- 19.

Trial design

Single-centre, prospective, two-arm parallel design, open-label randomized control superiority trial.

Participants

The study will be conducted at the covid centre of Dr. Rajendra Prasad Government Medical College Tanda Kangra, Himachal Pradesh, India.

All SARS-CoV-2 infected patients requiring admission to the study centre will be screened for the trial. All patients >18years who are RT-PCR/RAT positive for SARS-CoV-2 infection with pneumonia but without ARDS at presentation (presence of clinical features of dyspnoea hypoxia, fever, cough, spo2 <94% on room air and respiratory rate >24/minute) requiring hospital admission and consenting to participate in the trial will be included.

Patients with documented significant liver disease/dysfunction (AST/ALT > 240), myopathy and rhabdomyolysis (CPK > 5x normal), allergy or intolerance to statins, allergy or intolerance to aspirin, patients taking medications with significant interaction with statins, prior statin use (within 30 days), prior aspirin use (within 30 days), history of active GI bleeding in past three months, coagulopathy, thrombocytopenia (platelet count < 100000/ dl), pregnancy, active breastfeeding, patient unable to take oral or nasogastric medications, patients in altered mental status, shock, acute renal failure, acute coronary syndrome, sepsis and ARDS at presentation will be excluded.

Intervention and comparator

After randomization, participants in the intervention group will receive aspirin, atorvastatin, and nicorandil. Atorvastatin will be prescribed as 40 mg starting dose followed by 40 mg oral tablets once daily for ten days or till hospital discharge whichever is later. Aspirin dose will be 325 starting dose followed by 75 mg once daily for ten days or till hospital discharge whichever is later. Nicorandil will be given as 10 mg starting dose followed by 5mg twice daily ten days or till hospital discharge whichever is later. All patients in the intervention and control group will receive a standard of care for covid management as per national guidelines. All patients will receive symptomatic treatment with antipyretics,

adequate hydration, anticoagulation with low molecular weight heparin, intravenous remdesivir, corticosteroids (intravenous dexamethasone for 5 days or more duration if oxygen requirement increasing or inflammatory markers are raised), and oxygen support. Patients will receive treatment for comorbid conditions as per guidelines.

Main outcomes

The patients will be followed up for outcomes during the hospital stay or for ten days whichever is longer. The primary outcome will be in-hospital mortality. Any progression to ARDS, shock, acute kidney injury, impaired consciousness, length of hospital stay, length of mechanical ventilation (invasive plus non-invasive) will be secondary outcomes. Changes in serum markers (CRP, D –dimer, S ferritin) will be other secondary outcomes. The safety endpoints will be hepatotoxicity (ALT/AST > 3x ULN; hyperbilirubinemia), myalgia—muscle ache, or weakness without creatine kinase (CK) elevation, myositis —muscle symptoms with increased CK levels (3-10) ULN, rhabdomyolysis—muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin) observed during the hospital stay.

Randomization

Computer-generated block randomization will be used to randomize the participants in a 1:1 ratio to the active intervention group A (Aspirin, Atorvastatin, Nicorandil) plus conventional therapy and control group B conventional therapy only.

Blinding (masking)

The study will be an open-label trial.

Numbers to be randomized (sample size)

A total of 396 patients will participate in this study, which is randomly divided with 198 participants in each group.

Trial status

The first version of the protocol was approved by the institutional ethical committee on 1st February 2021, IEC /006/2021. The recruitment started on 8/4/2021 and will continue until 08/07/2021. A total of 281 patients have been enrolled till 21/5/2021.

Trial registration

The trial has been prospectively registered in *Clinical Trial Registry – India* (ICMR- NIMS): CTRI/2021/04/032648 [Registered on: 08/04/2021].

Full protocol

The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this letter serves as a summary of the key elements of the full protocol. The study protocol has been reported under the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (Additional file 2).

Introduction

COVID-19 has presented a major threat to public health worldwide. The case fatality rate of COVID-19 is 2%–3%, but the pandemic associated with COVID-19 has been far more severe. SARS-CoV-2 is highly contagious and most individuals within the population are susceptible to infection(1).

SARS-CoV-2 is a single-stranded RNA virus (2). The viral infection is cytopathic to human cells, by binding to membrane-bound angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed abundantly on vascular endothelial cells. The endothelial dysfunction is associated with vasoconstriction, inflammation, permeability, and coagulation(3). The immune-mediated injury may play a critical role in the pathogenesis of COVID-19. In severe forms of COVID-19, the inflammatory cascade may lead to a cytokine storm. The cytokine storm is believed to be a key factor driving both ARDS and extra-pulmonary organ failure (1)

COVID-19 represents a spectrum of clinical manifestations that typically include fever, dry cough, myalgia, weakness, and fatigue, often with pulmonary involvement (1). The majority (81%) of patients had mild manifestations, 14% had severe manifestations, and 5% had critical manifestations. Older adults and those with comorbidities are believed to be at an elevated risk of complications (2). The complications of COVID-19 include pneumonia (75%), acute respiratory distress syndrome (15%), acute liver injury, acute cardiac injury, prothrombotic coagulopathy, acute kidney injury, neurologic manifestations, including impaired consciousness and acute cerebrovascular disease, and shock (4). The disease is associated with lymphopenia, elevated inflammatory markers, and abnormal coagulation parameters(3).

Different treatment modalities might likely have different efficacies at different stages of illness and in different manifestations of the disease. Viral inhibition would be expected to be most effective early in infection, while, in hospitalized patients, immunomodulatory agents may be useful to prevent disease progression and anticoagulants may be useful to prevent thromboembolic complications. Various drugs like antivirals, antibodies, anti-inflammatory agents, targeted immunomodulatory therapies, anticoagulants, and antifibrotics are being evaluated for the management of COVID-19 with limited success so far(4).

The current therapy for COVID-19 involves oxygen support, steroids like dexamethasone, anticoagulation with low molecular weight heparin, and antivirals like remdesivir. However, even with these therapeutic

agents mortality is still higher in moderate and severe disease. In patients hospitalized with COVID-19, only dexamethasone has been found to reduce the mortality (5). These therapeutic agents or regimens are not either fully effective or sufficient to combat the complete pathophysiology of the disease.

There is a need for a drug or combination of drugs that can target every component of the pathophysiology of COVID-19. Such therapeutic regimens should be easily available, low cost, and with an established safety profile. There is no single agent which can target all these pathophysiologic substrates. Hence, we aim to evaluate the combination of commonly used cardiac medication (Aspirin, Atorvastatin, and Nicorandil) with anti-inflammatory, antithrombotic, immunomodulatory, and vasodilator properties as adjuvant therapy in covid- 19. Moreover, these drugs are already extensively used, well-tolerated, and having a good safety profile in the human population.

Review Of Literature

Aspirin

Aspirin is currently the most widely used drug worldwide since 1897. The benefit of aspirin treatment is now evident for acute coronary syndromes and secondary cardiovascular prevention(6). Aspirin is a typical non-steroidal anti-inflammatory drug with strong anti-inflammatory, anti-thrombotic, and analgesic pharmacological effects. However, prophylactic use of low-dose aspirin is currently controversial in patients with COVID-19(7).

Alveolar capillary micro thrombosis is thought to contribute to the severe lung injury and hypoxemia that occurs in COVID-19 patients. A prior study suggested that systemic anticoagulation reduces mortality in mechanically ventilated COVID-19 patients. In ARDS, aspirin has been studied with mixed results, where some studies have demonstrated benefit and others have not(8).

Acetylsalicylic Acid as an Anti-Inflammatory Drug

ASA exerts its anti-inflammatory effects mostly as a non-selective inhibitor of cyclo-oxygenase (COX-1 and COX-2) enzymes, which are involved in the production of important mediators, including PGs and thromboxane A2 (TXA2). Additionally, ASA can increase acetylation of histone proteins, regulating gene expression. It inhibits virus replication by inhibiting prostaglandin E2 (PGE2) in macrophages and up-regulation of type I interferon production(9).

Acetylsalicylic Acid as an Anti-Thrombotic Drug

Low doses of ASA (e.g., 75–100 mg/day) are sufficient to irreversibly acetylate Ser 530 of COX-1, thus preferentially inhibiting platelet generation of TXA2, a potent vasoconstrictor, and stimulator of platelet reactivity. Reduction of production of PGI2 at higher doses leads to reduced efficacy as antithrombotic. Significant inhibition of platelet activation and aggregation is achieved rapidly by using higher ASA doses ≥ 300 mg followed by lower doses of 75–100 mg daily (10).

Additional mechanisms of ASA-induced effects include down-regulation of inducible nitric oxide synthase (iNOS), oxidative phosphorylation uncoupling, and increased permeability in mitochondria. The pooled results of the Warfarin and Aspirin (WARFASA) and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trials showed that in patients with a first unprovoked venous thromboembolism, ASA reduced the risk of thrombotic event recurrence by 32% (10).

Acetylsalicylic Acid as an Antiviral Drug

ASA has significant antiviral activity against several other RNA viruses, including influenza A H1N1 virus, human rhinoviruses, and coxsackievirus subtype A9 (10). Acetylsalicylic acid (ASA), inhibit NF-κB, leading to subsequent inhibition of viral replication (11).

COVID-19 positive Veterans Health Administration patients with active aspirin prescriptions have a significantly decreased risk of mortality as indicated by unadjusted odds ratios of 0.68 (95% CI of0.57–0.80) at 14 days, and 0.68 (95% CI of 0.59–0.77) at 30 days after diagnosis (12).

A retrospective, observational cohort study of adult patients admitted with COVID-19 to multiple hospitals in the United States between March 2020 and July 2020 showed that Aspirin use had a crude association with less mechanical ventilation (35.7% aspirin versus 48.4% non-aspirin, P = .03) and ICU admission (38.8% aspirin versus 51.0% nonaspirin, P = .04), but no crude association with in-hospital mortality (26.5% aspirin versus 23.2% nonaspirin, P = .51). Aspirin use may be associated with improved outcomes in hospitalized COVID- 19 patients(13).

Potential Role of Acetylsalicylic Acid in COVID-19

Aspirin may be useful for the relief of specific symptoms of COVID-19, due to its analgesic and antipyretic effects. it may exert anti-inflammatory, antithrombotic, and antiviral effects, inhibiting the pathophysiological processes leading to the most severe clinical manifestations of COVID-19. Hence, ASA might reasonably be a therapeutic candidate to be tested in COVID-19. Timing of ASA initiation, dosing, duration of treatment, and subgroups of COVID-19 patients that can benefit most from ASA needs to be established.

Statin

Statins exert pleiotropic effects on inflammation and oxidative stress, contributing to their beneficial impact on cardiovascular diseases. Statins modulate the immune response at different levels, including immune cell adhesion and migration, antigen presentation, and cytokine production. Statins reduce reactive oxygen species and increasing antioxidants.

Infection with SARS-CoV results in increased induction of the myeloid differentiation primary response 88 (MyD88) gene, which activates the nuclear factor (NF)-kB pathway and induces inflammation. Statins inhibit the MyD88 pathway and tend to preserve MyD88 levels during hypoxia and under stress, which may confer a protective effect in COVID-19 patients (14).

Large observational studies have reported the effectiveness of statin treatment in reducing influenza-related hospitalizations and deaths. An association between outpatient statin use and reduction in disease severity among patients hospitalized during the 2009 H1N1 pandemic has also been demonstrated.

Statins also interfere with ACE2 signaling. After initial entry through ACE2, SARS-CoV-2 down-regulates ACE2 expression, and causing an unopposed angiotensin II accumulation, leading to organ injury. Statins are known to up-regulate ACE2. An increase in ACE2 might prove beneficial for COVID-19 patients (15). A large analysis from an epicentre of the COVID-19 pandemic demonstrated that antecedent statin use was associated with significantly lower rates of in-hospital mortality within 30 days(16).

In this Danish nationwide cohort study, recent statin exposure in patients with COVID-19 infection was not associated with an increased or decreased risk of all-cause mortality or severe infection(17). Statins might mitigate the effects of COVID-19 infection in selected patients based on its associated coagulopathy, endothelial dysfunction, and dysregulated inflammation (18).

A meta-analysis of 9 studies (case series and retrospective cohort studies), with a total of 3449 patients were included in the analysis. The meta-analysis showed that statin use did not improve severity outcome [OR 1.64 (95% CI 0.51e5.23), p ¼ 0.41, I2 ¼ 93%, random-effect modelling] nor mortality rate from COVID-19 infection [OR 0.78 (95% CI 0.50e1.21), p ¼ 0.26, I2 ¼ 0%, fixed-effect modelling]. This study has several limitations. Analysis was limited to retrospective studies only and confounding conditions like comorbidities were not considered (19). Further randomized studies are needed to establish the role of statins in patients with COVID-19.

Nicorandil

Nicorandil (N-[2-hydroxyethyl]-nicotinamide nitrate) is a therapeutic agent used clinically for the treatment of angina. Nicorandil acts by increasing nitric oxide (NO) availability and by opening ATP-sensitive K channels (K+ ATP). NO can attenuate the viral receptor (ACE2) interaction through inducing morphological changes in the viral spike (S) protein and may inhibit viral replication through diminishing viral RNA production (20).

Inflammation and Oxidative stress and modulation by nicorandil

Nicorandil aborted inflammatory cytokine formation and suppressed apoptosis. Nicorandil inhibits superoxide anion production by the activated neutrophils. The immunomodulatory effect of nicorandil and lung tissue protection against apoptosis is reflected in improved arterial oxygen saturation and oxygen partial pressure. Nicorandil causes bronchodilation and reduces vascular permeability. NO can inhibit the replication cycle of SARS-CoV(20).

Nicorandil can abort the inflammatory process by suppressing monocyte-endothelial adhesion. Nicorandil protected HPAECs from hypoxia-induced apoptosis. Nicorandil has an anti-apoptotic effect

through activation of mitoKATP channels and increased eNOS expression, with subsequent inhibition of the NF-κB pathway and the mitochondrial apoptotic pathway(21).

Anti -fibrotic potential of nicorandil

The SARS-CoV2 infection has a high tendency for pulmonary parenchymal and interstitial fibrosis(22). The beneficial actions of nicorandil are signaled by a decrease in the profibrotic marker, transforming growth factor-β (TGF-β). Immunohistochemical examination revealed that nicorandil-treated rats exhibited significant diminutions in protein expression levels of transforming growth factor beta-1(TGF-β1) and inducible nitric oxide synthase (iNOS) and enhanced pulmonary protein expression of endothelial NOS (eNOS)(23).

Anti-Coagulant effect of nicorandil

NO inhibits platelet activation and limits endothelial-leukocyte adhesion. Nicorandil protected pulmonary endothelium from the thrombus formation and induction of apoptosis, accompanied by both upregulations of endothelial NOS expression and downregulation of cleaved caspase-3 expression(24). Nicorandil prevented sirolimus-induced thrombus formation, presumably due to the reduction of reactive oxygen species (ROS) and endothelial protection(25).

Based on the modulatory role of NO on the interstitial lung thrombo-inflammation, NO can be used as adjuvant therapy. The American Food and Drug Administration (FDA) has recently granted the safety of NO-releasing drugs as supportive therapy in COVID-19 treatment.

Cardiovascular manifestation in covid-19 and nicorandil

The involvement of myocardial injury may be linked to the cardiac ACE2 expression. The inflammatory storm caused by SARS-CoV2 infection, respiratory dysfunction, and hypoxemia may be other precipitating factors for the COVID-19 induced cardiac injury. The myocardial dysfunction was described without evidence of obstructive coronary disease. Nicorandil prevents cardiac fibroblast proliferation. The inhibitory effect might be associated with the opening KATP channels, by interfering with the generation of ROS (26). Nicorandil protected cardiac tissues by normalization of cardiac biochemical and oxidative stress parameters and amelioration of histopathological changes(27).

Nephroprotective effect of nicorandil

The pathologic hallmark of COVID-19 is proximal tubular injury and loss of brush border due to direct involvement. Other factors mediating acute kidney injury, include systemic hypoxia, coagulopathy, and possible drug nephrotoxicity. Nicorandil administration significantly restored mitochondrial enzymes and oxidative phosphorylation efficacy mediated through enhanced mitoKATP channel function. Based on the various possible benefits of nicorandil therapy in the COVID-19 management, Nicorandil possesses multiple potential modulatory properties on the currently known pathogenesis of the disease(28).

Method And Materials

Objectives

To test whether triple therapy with aspirin, atorvastatin, and nicorandil is superior to usual care in SARS-CoV-2 infected patients in improving outcome.

To find out the safety of triple therapy in SARS-CoV-2 infected patients.

Study Design: Single-centre, prospective, two-arm parallel design, open-label randomized control superiority trial.

Place of Study: The study will be conducted at the covid centre of Dr. Rajendra Prasad Government Medical College Tanda Kangra, Himachal Pradesh India, converted into a dedicated COVID-19 management centre since August 2020.

Eligibility criteria

Inclusion criteria:

All SARS-CoV-2 infected patients requiring admission to the study centre will be screened for the trial (figure 1). All patients >18years who are RT-PCR/RAT positive for SARS-CoV-2 infection with pneumonia but without ARDS at presentation (presence of clinical features of dyspnoea hypoxia, fever, cough, spo2 <94% on room air and respiratory rate >24/minute) requiring hospital admission and consenting to participate in the trial will be included.

Exclusion criteria:

Patients with documented significant liver disease/dysfunction (AST/ALT > 240), myopathy and rhabdomyolysis (CPK > 5x normal), allergy or intolerance to statins, allergy or intolerance to aspirin, patients taking the following medications: cyclosporine, HIV protease inhibitors, hepatitis C protease inhibitor, telaprevir, fibric acid derivatives (gemfibrozil), niacin, azole antifungals (itraconazole, ketoconazole) clarithromycin, and colchicine, prior statin use (within 30 days), prior aspirin use (within 30 days), history of active GI bleeding in past three months, coagulopathy, thrombocytopenia (Platelet count < 100000/ dl), pregnancy, active breastfeeding, patient unable to take oral or nasogastric medications will be excluded. The patients in altered mental status, shock, acute renal failure, acute coronary syndrome, sepsis, and ARDS at presentation will be excluded.

Investigation

Baseline investigations like complete blood count, liver function test, renal function test, fasting blood sugar, LDH, D-dimer, CRP, serum ferritin, BNP, Trop-I, CPK, PT/INR, procalcitonin - will be done at admission. RFT, LFT, CPK, Trop-I, BNP, D-dimer, CRP, serum ferritin will be repeated on the 5^{th} day and at the time of discharge.

Randomization

Enrollment eligibility will be accessed by the person admitting patients. Before assigning groups to eligible individuals to participate in the study, written informed consent will be taken by the medical officer posted in the covid centre. Block randomization technique will be used to assign patients to the standard care (control) or current intervention (intervention group). We will use a block size of four study participants during the randomization process. Allocation to intervention or control group will be done by the treating team in the covid centre. Allocation concealment is done by the treatment team.

Blinding

This will be an open-label study. In this study, all participants are aware of participating in the study and enroll in the study after consent. The participants will be aware of the group assigned. Patients receive aspirin, atorvastatin, nicorandil in the intervention group(A) over and above the standard of care, and patients in the control group (B) will receive standard of care only. The health care personal, data collecting officials, and those who evaluate the outcome are aware of the grouping of patients.

Sample size

A total sample size of 396 was calculated assuming alpha error=0.05, power 80%, death in the control group of 20% (5), the death rate in the treatment group =15%, a superiority margin of 5%, and a nonresponse rate (loss to follow up) of 10% using sample size calculator http://riskcalc.org/samplesize/.

Outcome and measurement

Data collection is done by the specially trained nursing officers of the hospital. Patients' demographic data and clinical data including age, sex, comorbidities, baseline vital information, saturation, treatment received, type of oxygen support, baseline and follow-up investigation information, outcome, and safety endpoint information will be recorded on structured proforma.

Primary outcomes

The primary outcome will be in-hospital mortality.

Secondary outcomes

The secondary outcomes will be any progression to ARDS, shock, acute kidney injury, impaired consciousness, and length of hospital stay, length of mechanical ventilation (invasive plus non-invasive). Changes in serum markers (CRP, D –dimer, S ferritin) will be other secondary outcomes.

Safety endpoints

Hepatotoxicity (ALT/AST > 3x ULN; hyperbilirubinemia), myalgia—muscle ache or weakness without creatine kinase (CPK) elevation, myositis—muscle symptoms with increased CPK levels (3-10)ULN,

rhabdomyolysis—muscle symptoms with marked CPK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin), minor Bleeding (BARC bleeding type 1 and 2 or major Bleeding (BARC bleeding type 3 –5) will be safety endpoints observed during the hospital stay.

Intervention groups

Intervention group

Atorvastatin will be prescribed as 40mg starting dose followed by 40 mg oral tablets once daily for ten days or till hospital discharge whichever is later. Aspirin dose will be 325 starting dose followed by 75mg once daily for ten days or till hospital discharge whichever is later. Nicorandil will be given as 10 mg starting dose followed by 5mg twice daily for ten days or till hospital discharge whichever is later. In addition, all patients will receive symptomatic treatment with antipyretics, adequate hydration, anticoagulation with low molecular weight heparin, intravenous remdesivir, corticosteroids (intravenous dexamethasone for 5 days or more duration whenever indicated, if oxygen requirement increasing or inflammatory markers are raised), and oxygen support. Patients will receive treatment for comorbid conditions as per guidelines.

Control group

All patients in the control group will receive symptomatic treatment with antipyretics, adequate hydration, anticoagulation with low molecular weight heparin, intravenous Remdesivir, corticosteroids (intravenous dexamethasone for 5 days or more duration whenever indicated, if oxygen requirement increasing or inflammatory markers are raised), and oxygen support. Patients will receive treatment for comorbid conditions as per guidelines.

Follow-up

All study participants will be prospectively followed up during the hospital stay or 10 days whichever is later. Patients will be evaluated telephonically post-discharge till ten days.

Withdrawal from the study

Complete and accurate follow-up is extremely important for the duration of the study. The participant, however, may decline to continue protocol-related assessments at any time however every attempt will be made to continue contact by telephone. This does not constitute withdrawal from the study. The reason for withdrawal will be documented for all participants withdrawn from the study. If the vital status is known before hospital discharge, the participant will not be considered lost to follow up.

Statistical Analysis:

Descriptive statistics will be used to summarize variables. All primary and additional endpoints will be analysed both on intention-to –treat (ITT) basis and on a per-protocol (PP) basis for the study. The ITT

population set consists of all patients who have provided informed consent and have been randomized to a treatment group. All patients will be analysed according to the assigned treatment group, regardless of the treatment received.

The PP population set will consist of all patients who have provided informed consent and have been randomized to a treatment group, and who have received only the assigned study treatment, without any major protocol deviation. Participants who do not receive a study treatment, or who receive any treatment other than the study treatment to which they were randomized, will be excluded from the PP population. All participants will be analysed according to the treatment that they received. A supportive analysis of the primary endpoint and all secondary clinical endpoints will also be conducted in the PP population. Wilcoxon rank-sum test will be used for nonnormal distribution. Time-to-event will be compared using the Kaplan-Meier curve and log-rank test. The Cox proportional hazards model will be used to calculate the hazards ratio and 95% Confidence Interval. Safety outcomes will be compared between the groups using Chi-square or Fisher's exact test.

Data Recording and Record-Keeping

All trial data will be entered by trained nursing officials on the Microsoft Excel worksheet. Participants will be provided with a unique identification number. The data received by the researchers will not include any personally identifiable information. The data will be kept for 10 years.

Abbreviations

ACE2 Angiotensin converting enzyme2

ALT Alanine transaminase

ARDS Acute respiratory distress syndrome

ASA Acetyl salicylic acid

AST Aspartate transaminase

BARC British academic research consortium

BNP Brain natriuretic peptide

CAD Coronary artery disease

CKD Chronic kidney disease

COPD Chronic obstructive airway disease

COVID -19 Coronavirus disease of 2019

CPAP Continuous positive airway pressure

CPK Creatin phosphokinase

CRP Creactive protein

CVA Cerebrovascular accident

DBP Diastolic blood pressure

DM Diabetes mellitus

HFNC High flow nasal cannula

HIV Human immunodeficiency virus

HPAECs Human pulmonary artery endothelial cells

HTN Hypertension

iNOS Inducible nitric oxide synthase

ITT Intention to treat

LDH Lactate dehydrogenase

LFT Liver function test

NF-Kb Nuclear factor -kb

NO Nitric oxide

NRM Non rebreathing mask

OR Odds ratio

PAD Peripheral arterial disease

PGE2 Prostaglandin E2

PGI2 Prostaglandin I2

PP Per protocol

RAT Rapid antigen test

RFT Renal function test

RNA Ribonucleic acid

RT-PCR Reverse Transcription Polymerase Chain Reaction

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

SBP Systolic blood pressure

TGF-β Transforming growth factor -beta

TXA2 Thromboxane A2

ULN Upper limit of normal

VTE Venous thromboembolism

WHO World health organization

Declarations

Ethical approval and consent to participate

The authors confirm that this trial has received ethical approval from the Dr. Rajendra Prasad Government Medical College Tanda Kangra, Himachal Pradesh 176001 institutional ethical committee as described above. Written informed consent will be obtained from participants before involvement in the trial in the Hindi/English language.

Consent for publication

Written informed consent will be obtained from all participants/subject's legally acceptable representatives before inclusion in the trial for collecting data, analysis, storage, and publishing it.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Authors declare that they have no competing interests.

Funding

We disclose that the study has not received any financial, material, or any other support from any source.

Authors' contribution

All authors have contributed to writing the structured summary.

AS: Conceptualization, Methodology, Data curation, Visualization, Writing- original draft preparation, Writing - Review & Editing, Project Administration, Supervision; CS: Project Administration, Methodology, Investigation, Resource; SR: Original draft preparation, Methodology, Investigation; DS: Methodology, Investigation; BS: Software, Formal Analysis, Validation, Supervision; VD: Project Administration, Supervision; SG: Project Administration, Supervision; SB: Project Administration; VS: Project Administration.

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Acknowledgments

We are sincerely thankful to matron Nirmal and nursing officers Richa and kajal for data acquisition.

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Figures

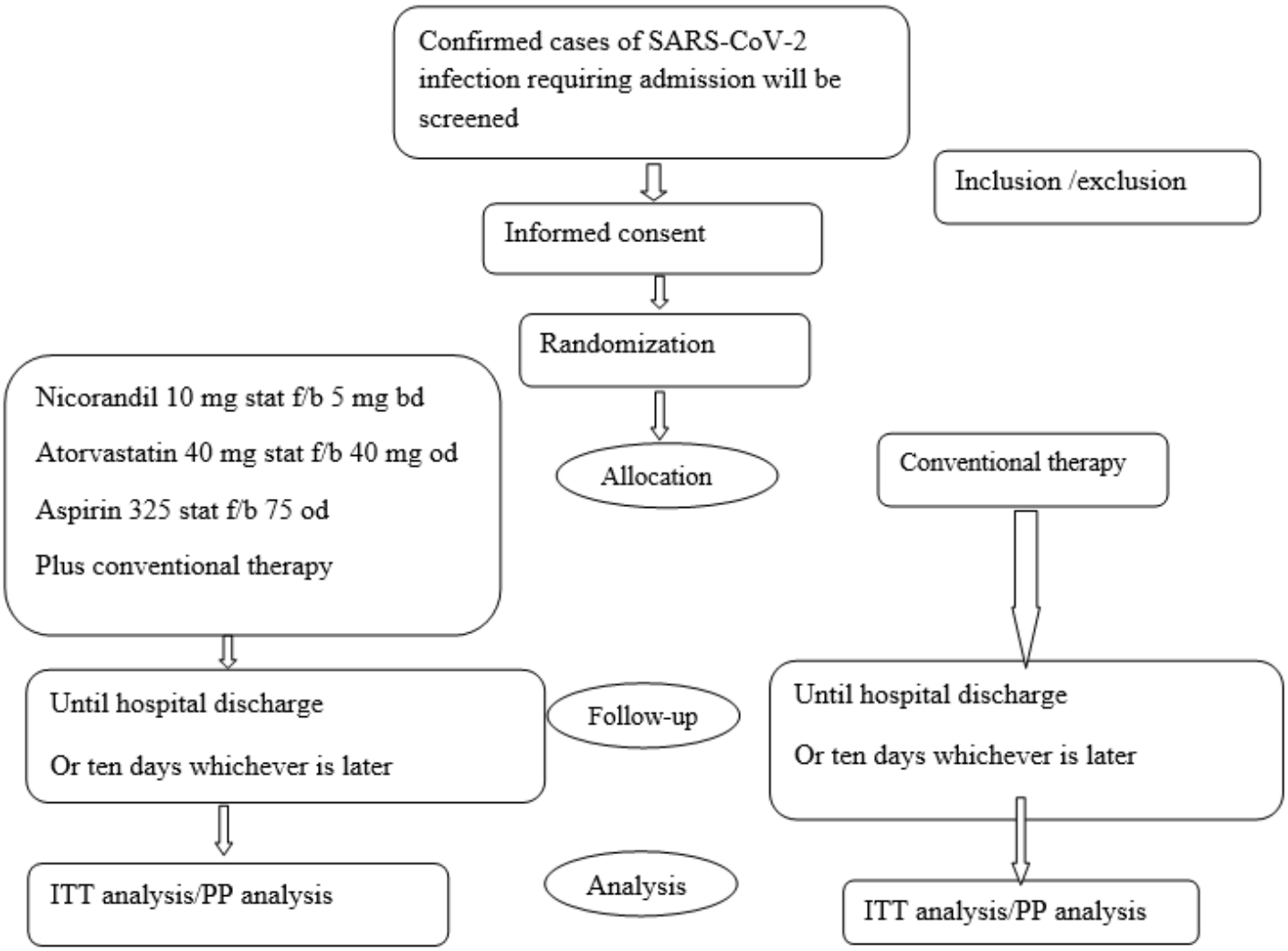

Figure 1

Schematic study design

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