Compassionate Use of Remdesivir and Convalescent Plasma Therapy for the Treatment of COVID-19 Infection in Nepal: A Prospective Observational Study

Report of Study Results

Study Period: 30 July- 31 October 2020

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Acronyms

AE	Adverse Event
ALT	Alanine transaminase
CBC	Complete Blood Count
CRF	Case Report Form
COVID-19	Coronavirus Infectious Disease 2019
CPT	Convalescent Plasma Therapy
CRP	C-reactive protein
DDA	Department of Drug Administration
FDA	Food and Drug Administration
GoN	Government of Nepal
IDSA	Infectious Disease Society of America
ICU	Intensive Care Unit
MoHP	Ministry of Health and Population
NBBTS	National Bureau for Blood Transfusion Service
NHRC	Nepal Health Research Council
NIH	National Institutes of Health
NPHL	National Public Health Lab
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS CoV-2	SARS Coronavirus-2
TACO	Transfusion-associated circulatory overload
TRALI	Transfusion-related acute lung injury
ULN	Upper Limit of Normal
US FDA	U.S. Food and Drug Administration

EXECUTIVE SUMMARY

Background

As of December 2020, the COVID-19 pandemic has infected over 80 million people and caused over 1.7 million deaths worldwide. Over 250 thousand cases of infection and over 1800 deaths have occurred in Nepal. An approved antiviral therapy for the treatment of COVID-19 in Nepal is not available. International infectious diseases authorities, such as IDSA (Infectious Diseases Society of America) and US NIH (United States National Institute of Health) panel, recommend Remdesivir for hospitalized patients with severe COVID-19 patients. Similarly, as an investigational treatment of COVID-19, the European Commission Directorate-General for Health and Food Safety and the United States Food and Drug Administration (US FDA) recommended convalescent plasma therapy with antibodies against SARS CoV-2. Per the Government of Nepal's Ministry of Health and Population (GoN MoHP) directives, guidelines and a study protocol for the treatment of COVID-19 with convalescent plasma was developed in May-June 2020. Subsequently, the GoN MoHP asked the Nepal Health Research Council (NHRC) to oversee the use of Remdesivir for the treatment of COVID-19. In August 2020, the protocol was amended. The amendment included Remdesivir in the study to provide a coordinated approach for the safe and effective administration of convalescent plasma and Remdesivir for COVID-19 treatment.

Methods

This was a prospective, observational study to evaluate the safety and outcomes of convalescent plasma and Remdesivir treatment of hospitalized COVID-19 patients. Patients received convalescent plasma, Remdesivir, or both treatments. Other antiviral drugs were not allowed while the patient was in the study. Other drugs necessary for patient management (such as steroids) were allowed.

Patients 18 years and older with laboratory-confirmed COVID-19 infection with positive PCR tests were enrolled from twelve NHRC approved study site hospitals. The study sites were later expanded to include over 50 hospitals.

Clinical severity of COVID-19 patients was determined by the local site investigators based on the Nepal Medical Council's COVID-19 Guidelines. Intravenous Remdesivir was administered to patients with moderate to severe COVID-19 infection based on predefined eligibility criteria. Based on severity, patients received a five-to-ten-day course of Remdesivir, with 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining therapy.

Convalescent plasma therapy (CPT) was administered to patients with severe or life-threatening COVID-19 infection, or as judged by the treating provider to be at high risk of progression to severe or life-threatening disease, or to patients who progressed to severe or life-threatening infection despite being on Remdesivir for 48 hours or longer.

This study was approved by the NHRC Ethics Review Board (ERB) and registered with ClinicalTrials.gov (NCT04570982).

Results

Between July 30, 2020 and October 31, 2020, total 1315 patients were enrolled in the study. Complete data were available for 1083 patients who had reached the study endpoint, and whose outcome was recorded. Of the 1315 patients, most were from Bagmati Province (71.1%), Lumbini Province (12.8%), and Province 2 (7.1%). Their mean age was 55.8 years (SD 15.7, range 18-99 years), 73.7% were male, 92.5% were married, and 25.6% were health care workers (HCWs). The most common comorbidities were heart disease (33%), diabetes (29.1%), hypertension (19.1%), smoking (12.7%), and chronic lung disease (11%). Fever (81.5%), cough (72.3%), and shortness of breath (80.3%) were the most common symptoms. At baseline, the mean O2 saturation was 89.6%. Baseline exam measures and labs were as expected for COVID-19 patients. Most patients were classified as having a severe infection (64%). Moderate infections were reported in 24.2% and life-threatening infections in 11.7% of patients.

More than three-quarters of the patients (1099; 83.6%) received Remdesivir alone, 76 (5.8%) patients received CPT alone, and 140 (10.6%) received both Remdesivir and CPT. The observational study ended abruptly on October 31, 2020 and was changed to a registry-only study. Thus, 209 patient outcomes were not recorded either because they were still in the

hospital at the end of the study, or the site investigators had not reported their outcome. Similarly, outcomes were not available for 23 (2.1%) patients who were transferred to another facility. Of the 1083 patients for whom outcome data were available, 801 (74%) patients were discharged in good condition, 48 (4.4%) discharged with a disability, and 234 (21.6%) patients died.

Among the 910 patients who received Remdesivir alone and whose outcome was recorded, 764 (84%) patients recovered and were discharged, and 146 (16%) died. The raw survival rates, i.e., recovery and discharge from hospital, were 98.4%, 85.2%, and 29.5% for moderate, severe, and life-threatening groups, respectively. The mean length of stay for the Remdesivir alone recipients was 10.7 days (SD 5.3 days) in the hospital, 7.9 (SD 4.8) days in ICU, and 4.3 (SD 4.4) days on a ventilator. Of the 910 Remdesivir recipients, 57.5% were admitted to the ICU, and 26.6% were on a ventilator.

Seventy-six patients were treated with CPT alone, and 140 patients received both CPT and Remdesivir. Of the 59 patients who received CPT alone and had outcome data, 23 (39%) patients were discharged, and 36 (61%) patients died. Among the patients who died, 22 had life-threatening infections and 13 had severe COVID-19.

Recovery and discharge rates (i.e., raw survival rates) among patients treated with CPT alone with severe and life-threatening infections were 59.4% and 15.4%, respectively. The average length of stay for the CPT recipients was 12.4 (SD 6) days in the hospital, 10.2 (SD 5.8) days in ICU, and 6.8 (SD 5.3) days on a ventilator. Among the 59 CPT recipients, 91.8% were on ICU, and 45.9% were on a ventilator.

Similarly, of the 114 patients treated with both Remdesivir and CPT, 62 (54.4%) were discharged, and 52 (45.6%) died. Among the 52 patients who died, 22 had life-threatening, 28 had severe, and 2 had moderate COVID-19 infections. Combined recovery and discharge rates among these patients were 61.1% and 33.3% for severe and life-threatening infections, respectively. The average hospital stay for these patients was 14 (SD 6.7) days in the hospital, 10.8 (SD 6.3) days in ICU, and 8.2 (SD 7.4) days on a ventilator. Among the 114 CPT and Remdesivir recipients, 94.6% were admitted to the ICU, and 59.8% were on a ventilator.

In an unadjusted model, the predicted margins for the discharge of a patient in good condition or with a disability were higher among patients who received Remdesivir (0.79; 95% CI 0.76-0.82) compared to those who received CPT alone (0.39; 95% CI 0.27-0.51) or CPT plus Remdesivir (0.51; 95% CI 0.42-0.60). Margins were not substantially altered after controlling for age, gender, severity, and steroid use.

Remdesivir was found to be safe in this population: An adverse event was reported in 34 (4.5%) patients and was recorded as "none" for 730 (95.5%). No reactions were reported to be fatal. The most common events included elevated liver enzymes (2.7%) and a rise in creatinine (1%). Of the 216 patients who received CPT, ten (4.6%) were reported to have had adverse reactions. Reactions included fever (3) and rash (1). All patients completely recovered after stopping treatment.

Conclusions

This report is based on a three-month observational study conducted in Nepal. Data on 1315 COVID-19 patients treated with Remdesivir and/or convalescent plasma therapy were reported by 30 hospitals until October 31, 2020. The observations, correlations, and associations from this study are summarized below. It is important to note that this is strictly a descriptive summary of an observational study. Any hypothesized results suggested by these data need to be verified in clinical trials.

1. Most of the hospitalized patients who received Remdesivir and/or CPT were older (mean age 55.8 years), male, married, and from Bagmati Province.
2. Most patients had pre-existing comorbidities, including heart disease, diabetes, hypertension, smoking, and chronic lung disease.
3. Most patients presented with fever, cough, and shortness of breath. Their mean O2 saturation was below 90%.
4. At baseline examination, the majority of the patients were classified as having severe COVID-19.
5. Most of the patients who had moderate infection received Remdesivir and had a good survival rate (98.4%).

6. Compared to those who received CPT alone or CPT plus Remdesivir, the majority of the patients who had severe COVID-19 and received Remdesivir alone had a better outcome. However, this difference cannot be attributed to the treatment alone because of other potential confounders. For example, as noted below (see no. 8), patients who received both CPT and remdesivir had more severe infections requiring ICU admission and/or a ventilator at baseline. As per the treatment protocol, CPT was added after many patients failed to improve with Remdesivir alone.
7. Patients classified with life-threatening infections had a high mortality rate (72.3%). In this group, patients who received CPT plus Remdesivir had the highest recovery rate followed by those who received Remdesivir alone. Patients who received CPT alone had the lowest survival rates.
8. Larger proportions of patients who received CPT alone (91.8%) or CPT plus Remdesivir (94.6%) were in the ICU compared to those who received Remdesivir alone (57.5%). Similarly, higher proportions of patients who received CPT with or without Remdesivir were on a ventilator compared to those who received Remdesivir alone. Higher severity of illness requiring ICU admission and a ventilator seem to have attributed to the higher mortality and longer duration of stay for patients who were treated with CPT with or without Remdesivir.
9. Both Remdesivir and CPT were well tolerated by the patients in this study, with adverse events reported in only 4.5% and 4.6%, respectively.

Recommendations

The study team recommends the followings:

1. Since this is an observational study, results of this study alone should not be used as conclusive. The results of this study are useful to learn and share the local experience and to compare with similar studies done elsewhere.
2. As a standard practice, a new drug approval for clinical use requires controlled clinical trials. Approval of remdesivir and convalescent plasma should be based on the results of

controlled clinical trials which are now available. We recommend continuing to collect Remdesivir data as a Registry Study until the Remdesivir is approved for COVID-19 treatment in Nepal.

3. Continue to collect data on the use of convalescent plasma therapy for COVID-19 until conclusive clinical trial results are published.
4. Correlate COVID-19 treatment outcome with antibody titer against COVID-19 for patients treated with convalescent plasma.

BACKGROUND

As of December 2020, the COVID-19 pandemic has infected over 80 million people and caused over 1.7 million deaths worldwide. Over 250 thousand cases of infection and over 1800 deaths have occurred in Nepal. An approved antiviral therapy for the treatment of COVID-19 in Nepal is not available.

The convalescent plasma from patients who have recovered from viral infections has been a standard therapy for patients with severe to life threatening infection with COVID-19 in Nepal. Published literature suggests the transfusion of convalescent plasma has been used safely and successfully. A metanalysis by investigators from Mayo Clinic showed that convalescent plasma reduced mortality by 57% compared to matched patients receiving standard treatments. However, this modality of treatment is considered as investigational therapy at present.

Remdesivir is an RNA polymerase inhibitor with antiviral activity against COVID-19. Clinical studies to date have shown that Remdesivir decreases clinical recovery time in COVID-19 patients with moderate to severe infection. Remdesivir had initially received emergency use authorization (EUA) for COVID-19 by US FDA, European Commission, Indian Health Service, and many other countries. Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen. Remdesivir finally received full approval by the US FDA in November 2020.

International infectious diseases authorities, such as IDSA (Infectious Diseases Society of America) and US NIH (United States National Institute of Health) panel, recommend Remdesivir for hospitalized patients with severe COVID-19 patients. Similarly, as an investigational treatment of COVID-19, the European Commission Directorate-General for Health and Food Safety and the United States Food and Drug Administration (US FDA) recommended convalescent plasma therapy with antibodies against SARS CoV-2.

Per the Government of Nepal's Ministry of Health and Population (GoN MoHP) directives, guidelines for treatment of COVID-19 with convalescent plasma was initially developed by a joint effort of Nepal Public Health Research Laboratory (NPHL) and an expert clinical team. These guidelines were subsequently approved by the MoHP in May 2020. This was followed by

development of a study protocol under Nepal Health Research Council's (NHRC) oversight by a joint clinical study group consisted of an expert clinical team, Nepal Public Health Research Lab (NPHL) team, and NHRC researchers in June 2020. Subsequently, when Remdesivir became available for import from neighboring countries in August 2020, the GoN MoHP asked NHRC to oversee the use of Remdesivir for treatment of COVID-19 as a study drug in Nepal. The protocol was amended to add Remdesivir in the study with a goal to provide a coordinated approach for the safe and effective administration of convalescent plasma and Remdesivir for COVID-19 treatment. This protocol amendment was approved by NHRC's Ethics Review Committee (ERB) at the end of August 2020.

Objectives and Scope

The objective of this compassionate use study was to provide access, monitor safety, and evaluate the outcomes of Remdesivir and COVID-19 convalescent plasma use in hospitalized patients with COVID-19. This study was designed to provide a coordinated approach and guidance for distribution and administration of convalescent plasma and remdesivir, and to monitor their safety and patient outcomes. Followings are the specific objectives of this study.

Specific Objectives

1. Provide access to convalescent plasma therapy for hospitalized patients with severe COVID-19 infection (compassionate use, expanded access program)
2. Monitor safety of the therapy with convalescent plasma containing antibodies against SARS CoV-2.
3. Monitor safety of remdesivir for treatment of hospitalized patients with COVID-19 infection.
3. Evaluate outcomes of patients who received convalescent COVID-19 plasma therapy alone, Remdesivir alone, and both agents.

Scope

As per GoN MoHP directives, this protocol was developed to provide a coordinated approach for safe and effective administration of convalescent plasma and remdesivir for treatment of appropriate patients with COVID-19 infection in all hospitals of Nepal.

A separate protocol was developed to provide guidance for a coordinated approach for the collection, processing, and distribution of convalescent plasma with antibodies against SARS CoV-2 for treatment of COVID-19 patients in Nepal.

METHODS

I. Study Design

This was a prospective, multicentered, observational study designed to evaluate the safety and outcomes of convalescent plasma therapy (CPT) and remdesivir for hospitalized patients with COVID-19 infection. Hospitalized patients received convalescent plasma therapy (CPT) alone or remdesivir alone or both for treatment of COVID-19 based on their clinical status as determined by the treating physicians. Addition of convalescent plasma was allowed if patients continued to get worse even after receiving Remdesivir for more than 48 hours.

Randomization was not done considering ethical issues in the absence of a standard antiviral treatment. This was also a decision based on the Government of Nepal, Ministry of Health's instructions to provide access to both modalities of treatment.

Other antiviral drugs were not allowed in the study patients. Other drugs necessary for management of patient (such as steroids, immunomodulator therapy, etc) were allowed based on patients need and what was considered the standard treatment at the time.

This study was approved by the NHRC Ethics Review Board (ERB). This study was the first multicentered, national level study of Nepal to be registered with ClinicalTrials.gov (NCT04570982).

II. Enrollment

Patients meeting eligibility criteria as listed below were enrolled from all COVID-19 treating hospitals of Nepal participating in this clinical study. All hospitalized patients with moderate to severe or life threatening COVID-19 infection who met eligibility criteria as noted below were qualified for the study.

Convalescent plasma donors were identified and recruited with the help of hospital records from where they were discharged. The COVID hospitals were be asked to collect names of recovered patients who voluntarily showed interest to donate plasma. These donors were screened as noted under "Donor Eligibility Criteria" below.

III. Study Eligibility

A. Inclusion Criteria

All patients:

1. Minimum 18 years or older

2. Confirmed diagnosis of COVID-19 infection with PCR test positive for SARS-CoV-2

3. Hospitalized patients admitted to an acute care facility for the treatment of COVID-19

4. Signed informed consent provided by the patient or patient's healthcare proxy

For Remdesivir:

5. Moderate to severe COVID-19 infection who require to be on oxygen supplement

For convalescent plasma therapy (CPT):

6. Severe or life-threatening COVID-19 infection, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease

7. Patients who progress to severe or life-threatening infection despite being on remdesivir for 48 hours or longer

The following definitions were used to define severe and life threatening COVID-19 infection:

Severe COVID-19 infection: defined by one or more of the following criteria-

1. Shortness of breath (dyspnea)

2. Respiratory frequency ≥ 30/min

3. Blood oxygen saturation ≤ 93%

4. Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300

5. Lung infiltrates increased more than 50% within 24 to 48 hours

Life-threatening COVID-19 infection: defined as one or more of the following-

1. Respiratory failure

2. Septic shock

3. Multiple organ dysfunction or failure

B. Exclusion Criteria

1. Under 18 years of age (excluded due to lack of data supporting use of Remdesivir and COVID-19 plasma in children)

2. Not confirmed with PCR test for COVID-19 infection

3. Patients not meeting criteria for severe or life-threatening COVID-19 infection

4. Contraindications for receiving plasma transfusion (exclusion for CPT)

5. Contraindications for receiving Remdesivir (exclusion for remdesivir)

6. Patient's declination to enroll in the study

IV. Outcome Measures (End Points)

1. Availability of convalescent plasma
2. Adverse events of convalescent COVID-19 plasma
3. Adverse events of remdesivir therapy
4. Disposition of patients including discharge in good condition, discharge with disability, and death
5. Hospital and ICU length of stay

V. Procedure for Obtaining the Convalescent Plasma

ABO compatible COVID-19 Convalescent Plasma was collected and made available by Blood Banks in the respective provinces as designated by NPHL/NBBTS in collaboration with Nepal Red Cross based on the availability of plasma donations from recovered COVID-19 patients. The following procedures as outlined in Part II of the MOHP guidelines for "Collection and

preparation of Convalescent Plasma for COVID-19" were followed by the physicians to treat COVID-19 patients who were eligible for the convalescent plasma therapy.

1. When a COVID-19 patient was identified as a potential convalescent plasma recipient, the treating physician ordered ABO typing so that the blood bank had a validated ABO type on the patient before the rest of the process was started.

2. A locally designated person explained and obtained patient consent. A signed copy was kept for record. (Form no. 1 used from NPHL website: www.nphl.gov.np)

3. Physician placed "Order Convalescent Plasma" (Form no. 2 from NPHL website: www.nphl.gov.np) for the specific patient to the hospital blood bank to order convalescent plasma from supplier (Red Cross, or any registered Blood Centers in the province where patient is admitted) as per standard operating practices. The local physician were instructed to work out this ordering process with the respective blood bank regarding the available plasma via. NPHL website: www.nphl.gov.np.

4. Blood bank informed recipient's patient care team that convalescent plasma was available and ready to transfuse for the patient identified on the prior request, per hospital's standard processes and procedures.

5. The hospital blood bank/respective blood bank thawed and issued the convalescent plasma after receiving the transfuse convalescent plasma order.

6. Plasma unit was transfused at bedside and administered according to hospital procedures after having the informed consent (Form. 3)

7. Any patient safety issues, expected or unexpected Serious Adverse Events (SAEs) that occurred between 4-hour post-transfusion through 7 days, and patient progress after transfusion were documented and reported to NPHL/NBBTS by the treating physician or his/her designee.

VI. Administration of Convalescent Plasma and Remdesivir

A. Convalescent Plasma:

Based on available study data and experience from other centers, the following administration procedures were recommended:

1. The treating physician or a designee document properly obtained informed consent, read through the protocol and appropriately direct the use of the convalescent plasma.

2. The physician or designee checked the label to verify that the information on the label as it relates to the transfusion to the intended patient is correct.

3. ABO compatible COVID-19 Convalescent Plasma was administered according to standard hospital procedures based on compatibility chart.

4. The transfusion was administered through a peripheral or central venous catheter and was given according to standard institutional medical and nursing practices for the administration of plasma.

5. Based on currently available study data and experience from other centers, one unit containing 200 mL of ABO compatible COVID-19 convalescent plasma was administered.

6. The duration of infusion usually took 1 to 2 hours (rate of 100 to 250 mL/hr).

7. Before administration of plasma, the use of any premedication such as acetaminophen and diphenhydramine were allowed based on patient's history and per clinical judgement of the clinician.

8. Biohazard information for staff was provided. The convalescent plasma was to be handled as if capable of transmitting infectious agents and standard (or universal) precautions were followed. Use of mask and gloves was recommended while handling this product outside the patient's room.

9. In addition, appropriate PPE was used before entering a COVID-19 patient's room.

B. Remdesivir

In August 2020, the Department of Drug Administration (DDA) provided permission to three brands of remdesivir manufactured in India (by Cipla, Hetero and Mylan) and one brand manufactured in Bangladesh (by Beximco Pharmaceuticals) to be used as study drugs for treatment of COVID-19.

1. Obtaining Remdesivir – All hospitals with admitting facilities for severe COVID-19 patients could procure DDA approved Remdesivir from suppliers in Nepal at DDA published rates or at a negotiated rate whichever was less. The Government of Nepal, Ministry of Health and Population, reimbursed the cost for patients who received Remdesivir following NHRC study protocol.

2. Storage and handling: Ambient vials of the lyophilized formulation of Remdesivir was stored below 30°C preferably in locked rooms. Temperature records were maintained by the site to demonstrate drug was stored appropriately.

3. Dose preparation: The lyophilized formulation was reconstituted and then diluted into IV infusion fluids (250mL or 500mL Normal Saline) before use. After reconstitution, the total storage time before administration (including any time before or after dilution) was not to exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C).

4. Drug Administration: The total volume of administration was either 250 mL or 500 mL of Normal Saline. The infusion was to be administered over a period of between 30 minutes and 2 hours. Based on the guidelines, hospitalized patients received following doses of intravenous

5. Disposition of unused product: Remdesivir had to be used only for patient who it was intended for. Records of doses dispensed were kept by local site staff and provided to study staff to NHRC upon request. If any unopened study packages remained at the end of the study the local study, pharmacy staff were instructed to contact NHRC for further instructions.

6. Maintenance of inventory logs: Used of doses were tracked and recorded on drug disposition logs for use during accountability procedures by study staff. Records of when doses were dispensed or destroyed were to be kept in these logs.

VII. Monitoring for Adverse Events and Patient Outcomes

As a standard procedure for documentation of transfusion related adverse reaction, any patient safety, expected or unexpected Serious Adverse Events (SAEs) that occurred between 4-hour post-transfusion through 7 days after transfusion were documented and reported to the NHRC and NPHL/NBBTS.

In addition, all clinical or laboratory related adverse reactions noted after convalescent plasma transfusion or remdesivir administration were recorded and reported to the NHRC. Clinical study teams in participating sites were trained to identify and manage transfusion related SAEs.

All patients who were reported to have any adverse events (AE) or serious adverse events (SAE) were followed up. For this purpose, a follow up form was developed in collaboration with DDA to determine association vs. causation, and to record final AE related outcomes. The study team reviewed these records and made final determination on the association.

VIII. Drug Discontinuation and Patient Withdrawal

Patient's medical team were solely responsible for decisions about the patient care and safety all the time. Medical teams were allowed to deviate from the allocated treatment arm if it was necessary for patient care. The study drug was stopped if the local clinical team suspected any serious expected or unexpected adverse reactions that was potentially life-threatening.

Patients were free to withdraw completely from the study at any time or they could request to stop treatment only but remain in the study for data collection purpose only. Patients were free to withdraw from the whole study at any time without any consequences and could continue to take only local standard of care.

IX. Coordination Committee

A coordination committee was formed under the umbrella of NHRC. The following team oversaw, coordinated, and provided guidance for the Convalescent Plasma Therapy:

- Core clinical team consisting of independent clinicians including infectious disease experts
- NHRC officials, researchers, and data managers
- NPHL / Blood Bank representatives
- One or more designated COVID Hospital physician(s)

X. Data Collection and Analysis

This protocol was administered as a prospective observational study. All donor related and recipient patient related data were collected from blood banks obtaining plasma and COVID-19 hospitals administering the convalescent plasma in the appropriate forms.

All patient information were collected by participating hospitals' study teams and entered into a central electronic database developed by NHRC team.

Patients were divided into three treatment groups including CPT alone, remdesivir alone, and CPT plus remdesivir group. Patient's baseline information at the time of enrollment including demographic data, co-morbidities, clinical and laboratory findings, and severity of infection were compared. Study endpoints included death or discharge of patients in a good condition or discharge with disability. All patients who received at least one dose of remdesivir or plasma and had an outcome entered into the electronic database were considered for outcome analysis. The three treatment groups were compared for patient disposition at the end of

hospitalization and for durations of hospital stay, ICU stay and ventilator. Patient outcomes at the end of hospitalization were compared between the three treatment groups controlling for severity, age, sex, comorbidities, and steroid use. Adverse events associated with convalescent plasma and remdesivir were reported as a proportion of all patients who received each therapy.

On initial sample size calculations, the required sample size was determined to be 400 patients minimum. Given the uncertainties of the pandemic, plan was to include all patients in 3 months study period which would allow a better comparison between the groups.

Stratified analyses and regression analyses were performed to compare patients on two arms and to compare patients with different severities. Safety of the convalescent plasma therapy and remdesivir were analyzed and expressed as percentage of total patients who received each therapy. Treatment outcomes for each type of treatment as a single agent and in combination were evaluated. Patient data were analysed for the following end points and variables.

End Points and Variables:

1. Availability of convalescent plasma

    - availability of convalescent plasma for treatment of appropriate COVID-19 patients

    - additionally, when available, donor plasma antibody titer against SARS CoV-2

2. Adverse events related to convalescent COVID-19 plasma

    - any expected and unexpected adverse reactions to CPT during or after treatment from 4 hours to 7 days after transfusion

3. Adverse events related to remdesivir therapy

    - any suspected adverse events (AE or SAE) related to remdesivir

4. Disposition of patients including survival

    - Condition at discharge: discharge in good condition, discharge with disability, or death

5. Hospital and ICU length of stay

- Number of days of hospital stay and ICU stay

XI. Data Monitoring and Safety Board

All safety data, patient's baseline and clinical outcome data, and donor data were reported by the site clinician and his/her team in a pre-instructed electronic case report form (CRF) via a designated website. All participating site staff were trained and given instructions and reminders from time to time via webinars.

An independent Data Monitoring/ Safety Board was formed which consisted of the following members:

- Expert physician
- ICU physician
- Pharmacologist
- Statistician
- DDA representative

This board met and reviewed the data after administration of convalescent plasma and Remdesivir in October and November 2020. A report of the interim analysis of preliminary data was submitted and presented to the NHRC Ethics Review Committee on October 13th, 2020.

RESULTS

Between July 30, 2020 and October 31, 2020, total 1315 patients were enrolled in the study. Complete data were available for 1083 patients from 31 hospitals who had reached the study endpoint, and whose outcome was recorded.

Demographics and Co-morbidities

The mean age of the patients was 55.8 years (SD 15.7, range 18-99 years), 73.7% were male, 92.5% were married, and 25.6% were health care workers (HCWs). [TABLE-1]

Of the 1315 patients, most were from Bagmati Province (71.1%), Lumbini Province (12.8%), and Province 2 (7.1%). [TABLE-2]

Ethnicity of patients based on Nepal government's classification system was recorded for 875 patients, which revealed most of the patients were Brahmins (28.1%), Newars (25.8%) and Kshatriyas (15.5%), whereas only smaller number of patients belonged to the Janjati (10.3%), dalits (4%), and terai ethnicities (11.4%). [TABLE-3]

The most common comorbidities were heart disease (33%), diabetes (29.1%), hypertension (19.1%), smoking (12.7%), and chronic lung disease (11%). [TABLE-4]

Baseline Clinical Findings and Severity Classification

Fever (81.5%), cough (72.3%), and shortness of breath (80.3%) were the most common symptoms. Diarrhea (8.1%) and altered sense of taste and smell (9.5%) were reported in a small proportion of patients. [TABLE-5]

At baseline, the mean O2 saturation was 89.6% (SD 8) and mean temperature was 37.6 C (SD 0.8). Lab results showed elevated mean CRP, ALT and AST. Rest of the baseline exams and lab findings were as expected for hospitalized COVID-19 patients. [TABLE-6 and 7]

Most patients were classified as having a severe infection (64%). Moderate infections were reported in 24.2% and life-threatening infections in 11.7% of patients. [TABLE-8]

Treatment and Outcomes

Of the 1315 patients, a large majority of the patients (1098; 83.6%) received Remdesivir alone, 75 (5.7%) patients received CPT alone, and 140 (10.7%) received both Remdesivir and CPT. [TABLE-9]

The observational study ended on October 31st, 2020 and was changed to a registry study. When the study data was retrieved for analysis on November 5th, outcome data for 209 patients was not available either because the patients were still in the hospital, or the site investigators had not reported their outcome yet. Similarly, outcome results were not available for 23 (2.1%) patients who were transferred to another facility.

Of the 1083 patients for whom outcome data were available, 801 patients were discharged in good condition, 48 discharged with a disability, and 234 patients died. [TABLE-10]

Among the 910 patients who received Remdesivir alone and whose outcome was recorded, 764 (84%) patients recovered and were discharged, and 146 (16%) died. The raw survival rates, i.e., recovery and discharge from hospital, were 98.4%, 85.2%, and 29.5% for moderate, severe, and life-threatening groups, respectively. [TABLE-11]

The mean length of stay for the Remdesivir alone recipients was 10.7 days (SD 5.3 days) in the hospital, 7.9 (SD 4.8) days in ICU, and 4.3 (SD 4.4) days on a ventilator. Of the 910 Remdesivir recipients, 57.5% were admitted to the ICU, and 26.6% were on a ventilator. [TABLE-12]

Seventy-six patients were treated with CPT alone, and 140 patients received both CPT and Remdesivir. Of the 59 patients who received CPT alone and had outcome data, 23 (39%) patients were discharged, and 36 (61%) patients died. Among the patients who died, 22 had life-threatening infections and 13 had severe COVID-19. [TABLE-11]

Recovery and discharge rates (i.e., raw survival rates) among patients treated with CPT alone with severe and life-threatening infections were 59.4% and 15.4%, respectively. The average length of stay for the CPT recipients was 12.4 (SD 6) days in the hospital, 10.2 (SD 5.8) days in ICU, and 6.8 (SD 5.3) days on a ventilator. Among the 59 CPT recipients, 91.8% were on ICU, and 45.9% were on a ventilator. [TABLE-12]

Similarly, of the 114 patients treated with both Remdesivir and CPT, 62 (54.4%) were discharged, and 52 (45.6%) died. Among the 52 patients who died, 22 had life-threatening, 28 had severe, and 2 had moderate COVID-19 infections. Combined recovery and discharge rates among these patients were 61.1% and 33.3% for severe and life-threatening infections, respectively. [TABLE-11]

The average hospital stay for these patients was 14 (SD 6.7) days in the hospital, 10.8 (SD 6.3) days in ICU, and 8.2 (SD 7.4) days on a ventilator. Among the 114 CPT and Remdesivir recipients, 94.6% were admitted to the ICU, and 59.8% were on a ventilator. [TABLE-12]

In an unadjusted model, the predicted margins for the discharge of a patient in good condition or with a disability were higher among patients who received Remdesivir (0.79; 95% CI 0.76-0.82) compared to those who received CPT alone (0.39; 95% CI 0.27-0.51) or CPT plus Remdesivir (0.51; 95% CI 0.42-0.60). Margins were not substantially altered after controlling for age, gender, severity, and steroid use.

Adverse Events

Remdesivir was found to be safe in this population. An adverse event was reported in 34 (4.5%) patients and was recorded as "none" for 730 (95.5%) patients. None of the reactions were reported to be fatal. The most common events included elevated liver enzymes (2.7%) and a rise in creatinine (1%). Follow up data reveled that these lab abnormalities returned to normal levels after stopping remdesivir. [TABLE-13A]

Of the 216 patients who received CPT, ten (4.6%) were reported to have had adverse reactions. These transfusion related reactions included fever (3) and rash (1). All patients were reported to have complete recovery after stopping the treatment. [TABLE-13B]

CONCLUSIONS AND RECOMMENDATIONS

This report is based on a three-month observational study conducted in Nepal. Data on 1315 hospitalized COVID-19 patients between July 30 and October 31, 2020 and treated with remdesivir and/or convalescent plasma therapy were reported by 30 hospitals. The observations, correlations, and associations from this study are summarized below.

It is important to note that this is strictly a descriptive summary of an observational study. Because of missing data, unaccounted for treatment variations and protocol changes, lack of longitudinal observations, follow-up after discharge, and other important clinical and patient variables, direct comparison between treatment groups based on the findings in this report alone can be misleading. The results of this study alone should not be used to establish clinical effectiveness of the studied treatments. Any hypothesized results suggested by these data need to be verified in clinical trials.

1. Most of the hospitalized patients who received Remdesivir and/or CPT were older (mean age 55.8 years), male, married, and from Bagmati Province.
2. Most patients had pre-existing comorbidities, including heart disease, diabetes, hypertension, smoking, and chronic lung disease.
3. Most patients presented with fever, cough, and shortness of breath. Their mean O2 saturation was below 90%.
4. At baseline examination, the majority of the patients were classified as having severe COVID-19.
5. Most of the patients who had moderate infection received Remdesivir and had a good

7. Patients classified with life-threatening infections had a high mortality rate (72.3%). In this group, patients who received CPT plus Remdesivir had the highest recovery rate followed by those who received Remdesivir alone. Patients who received CPT alone had the lowest survival rates.
8. Larger proportions of patients who received CPT alone (91.8%) or CPT plus Remdesivir (94.6%) were in the ICU compared to those who received Remdesivir alone (57.5%). Similarly, higher proportions of patients who received CPT with or without Remdesivir were on a ventilator compared to those who received Remdesivir alone. Higher severity of illness requiring ICU admission and a ventilator seem to have attributed to the higher mortality and longer duration of stay for patients who were treated with CPT with or without Remdesivir.
9. Both Remdesivir and CPT were well tolerated by the patients in this study, with adverse events reported in only 4.5% and 4.6%, respectively.

Recommendations

The study team recommends the followings:

1. Since this is an observational study, results of this study alone should not be used as conclusive. The results of this study are useful to learn and share the local experience and to compare with similar studies done elsewhere.
2. As a standard practice, a new drug approval for clinical use requires controlled clinical trials. Approval of remdesivir and convalescent plasma should be based on the results of controlled clinical trials which are now available. We recommend continuing to collect Remdesivir data as a Registry Study until the Remdesivir is approved for COVID-19 treatment in Nepal.
3. Continue to collect data on the use of convalescent plasma therapy for COVID-19 until conclusive clinical trial results are published.
4. Correlate COVID-19 treatment outcome with antibody titer against COVID-19 for patients treated with convalescent plasma.

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APPENDICES

Appendix-1: Data Tables

Appendix-2: List of Investigators

Appendix 1. DATA TABLES

Table-1: Demographics- All Patients (N=1315)

	Mean	SD	Min	Max
Age	55.8	15.7	18	99

	Variables	Number	Percent	Remarks
Gender	female	346	26.3	
	male	969	73.7	
Marital status	married	835	92.5	
	unmarried	59	6.5	
	widow	3	0.3	
Health worker	Yes	243	25.6	

Table-2: Distribution by Province- All Patients (N=1315)

Distribution by Province			
	Frequency	Percent	Remarks
Province No. 1	33	2.75	
Province No. 2	85	7.1	
Bagmati Pradesh	853	71.1	
Gandaki Pradesh	56	4.7	
Lumbini Pradesh	154	12.8	
Karnali Pradesh	3	0.25	
Sudurpashchim	15	1.25	
Total	1199	100	
Missing	116	(8.8%)	

Table-3: Distribution by Ethnic Groups (N=875)

Distribution by Ethnicity			
	Frequency	Percent	Remarks
Hill Brahmin	246	28.1	
Hill Chhetri	136	15.5	
Hill Dalit	14	1.6	
Hill Janajati	68	7.8	
Muslim	16	1.8	
Newar	226	25.8	
Terai Brahmin/Chhetri	57	6.5	
Terai Dalit	21	2.4	
Terai Janajati	22	2.5	
Other	35	4.0	
Total	875	100	
Missing	440		

Table-4: Comorbidities- All Patients (N=1315)

Comorbidity	Number	Percent	Remarks
Smoking	106	12.7	
Diabetes	268	29.1	
HTN	251	19.1	
Heart Disease	293	33	
Chronic Lung Disease	94	11	
Chronic Liver Disease	13	1.6	
Asthma	29	3.5	
TB	3	0.4	
HIV	2	0.24	
Cancer	13	1.6	
Transplant	8	1	

Table-5: Clinical Symptoms- All Patients (N=1315)

Symptoms	Number	Percent	Remarks
Fever	1073	81.5	
Cough	951	72.3	
Shortness of breath	1056	80.3	
Sore throat	199	15.1	
Diarrhea	107	8.1	Reported as diarrhea or loose stools
Altered taste or smell	125	9.5	
Headache	37	2.8	
Bodyache, Myalgia	82	6.2	
Loss of Appetite	13	1	
Nausea, Vomiting	20	1.5	
CNS changes	20	1.5	e.g., altered consciousness, agitation, etc.

Table-6: Baseline Exams - All Patients and By Treatment Group

	All Patients (N=1225)		CPT Group (N=73)		Remdesivir Group (N=1016)		CPT+Remdesivir (N=136)		Remarks
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BP systolic	123.5	16.6	124.3	19.6	122.8	16.3	128.3	16.4	
BP diastolic	76.3	10.3	75.3	11	76.5	10.3	75.3	10.4	
Temperature	37.1	0.8	37.5	0.9	37.5	0.8	37.1	0.7	
Pulse rate	92	16.7	97	15.5	91.4	16.4	94.2	18.9	
Respiratory Rate	25	5.7	24.3	6.9	24.9	5.5	26.7	6.2	
O2sat	89.6	8	87.9	7.8	89.7	7.9	89.4	8.4	
PAO2	102.3	90.3	104.2	82.2	104.8	98.8	96.9	75.7	(N=135 only)
SOFA score	4.2	2.7	5.5	0.7	4.4	2.9	3.43	2.6	(N=25 only)

Table-7: Baseline Labs - All Patients and By Treatment Groups

	All Patients (N=1098)		CPT Group (N=68)		Remdesivir Group (N=902)		CPT+Remdesivir (N=128)		Remarks
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
WBC (x1000)	9.9	8.9	11.2	4.6	9.5	8.5	11.3	12.5	
HGB	12.9	1.9	12.3	2.4	12.9	1.8	13.2	2.2	
Neutrophils	78.7	11.5	78.6	14.1	78.2	11.2	82.1	11.7	
Lymphocytes	16.9	10.3	15.2	10.6	17.3	10.1	14.4	11.3	
Platelets (x1000)	231.6	139.4	249	296	231.8	132.7	225.3	100.8	
CRP	86.4	426.3	118.1	135	86.4	426.3	74.6	72.2	
ALT	59.3	62.5	94.8	108.3	59.3	62.5	60.3	43.9	
AST	62.6	70.9	71.8	52.7	62.6	70.9	55.9	33.1	
Bili Total	1.2	4.3	0.8	0.4	1.2	4.3	0.9	1.06	
Ferritin	0.9	1.1	1308	681.7	0.9	1.1	792.4	652.2	(N=52)

Table-8: Clinical Classification (Severity) of COVID-19 - All Patients (N=1315)

Clinical Classification		
Severity	**Frequency**	**Percent**
Life Threatening	154	11.7
Severe	841	64
Moderate	318	24.2
Total	1313	100.0
Missing data	2	

Table-9: Treatment Groups by Severity- All Patients (N=1315)

	Intervention Groups (Frequency)				Intervention Groups (%)			
Clinical Classification	CPT	REM	CPT+REM	Total	CPT	REM	CPT+REM	Total
Life Threatening	32	87	35	154	20.8	56.5	22.7	100
Severe	41	706	94	841	4.9	83.9	11.2	100
Moderate	2	305	11	318	0.6	95.9	3.5	100
Total	75	1098	140	1313	5.7	83.6	10.7	100
Missing				2				

Table-10: Overall Outcome - All Patients (N=1315)

OUTCOME	FREQUENCY	PERCENT
Transfer	23	1.8
Death	234	17.8
Discharge in good condition	801	60.9
Discharge with Disability	48	3.7
Missing*	209	15.9
Total	1315	100.0
* Missing values included patients who had not reached study end points at study closure or end points were not entered by the study site		

Table-11: Final Outcome by Severity and Interventions (N=1083)

Clinical Classification	Outcome	Intervention Groups				
		CPT	REM	CPT+REM	Total	Remarks
Life Threatening	Death	22	55	22	99	
	Discharge	4	23	11	38	
	Total	26	78	33	137	
Moderate	Death	1	4	2	7	
	Discharge	0	239	7	246	
	Total	1	243	9	253	
Severe	Death	13	87	28	128	
	Discharge	19	502	44	565	
	Total	32	589	72	693	
All Patients	Death	36	146	52	234	
	Discharge	23	764	62	849	
	Total	59	910	114	1083	

Table-12: Length of Stay by Type of Intervention (N=1098)

Patient Groups	Type of Care			Length of Stay (Days)				Remarks
		N	%	Mean	SD	Min	Max	
All Patients	Hospital	1098	100	11.1	5.6	1	45	
	ICU	694	63.2	8.5	5.3	1	30	
	Ventilator	341	31.1	5.3	5.4	1	29	
CPT Group	Hospital	61	100	12.4	6	2	27	
	ICU	56	91.8	10.2	5.8	2	27	
	Ventilator	28	45.9	6.8	5.3	1	23	
Remdesivir Group	Hospital	925	100	10.7	5.3	1	44	
	ICU	532	57.5	7.9	4.8	1	30	
	Ventilator	246	26.6	4.3	4.4	1	26	
CPT+REM	Hospital	112	100	14	6.7	2	45	
	ICU	106	94.6	10.8	6.3	2	30	
	Ventilator	67	59.8	8.2	7.4	1	29	

Table-13(A): Remdesivir Adverse Events Reported by Study Sites (N=764)*

Reported Adverse Events	Frequency	Percent
Abnormal LFT	21	2.7%
Rise in creatinine	8	1.0%
Dizziness/ Weakness	4	0.5%
GI problems ("heartburn")	1	0.1%
Total AE	34	4.5%
None	730	95.5%
* Presence or absence of adverse Events were documented for 764 patients		

Table-13(B): Transfusion Reaction Reported - All Patients Who Received CPT (N= 216)

	Frequency	Percent	Types of Reaction
Yes	10	4.6%	Rash 1 Fever 3 Not described 7 **All were non-fatal reactions**
No	199	92.1%	
Missing Data	7	3.3%	
Total	216	100	

APPENDIX-2: STUDY TEAMS

I. Core Clinical Team:

1. Prof. Dr. Janak Koirala, Principal Investigator
2. Prof. Dr. Sanjib Sharma, BPKIHS
3. Prof. Dr. Yuba Raj Sharma, PAHS
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5. Dr. Karishma Malla Vaidya, NPHL

III. NHRC Team:

1. Dr. Pradip Gyanwali, Executive Chief
2. Dr. Meghnath Dhimal, Chief Scientist
3. Mr. Saroj Bhattarai, Study Coordinator
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7. Dr. Suman Pant

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V. Data Monitoring/ Safety Board

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