Clinical Efficacy of Early Administration of Convalescent Plasma among COVID-19 Cases in Egypt

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Abstract

BACKGROUND: The rapid worldwide spread of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) or COVID-19 pandemic from its epicenter; Wuhan was first reported in December 2019. Egypt reported its first COVID-19 case on February 14, 2020. Thereafter, Egypt scaled-up preventive measures, with a partial lockdown starting on March 25. Several therapeutic agents along with convalescent plasma transfusion (CPT) are under investigation and data from CPTs have been receiving a lot of attention, after Emergency approvals from the Food and Drug Administration suggesting that it may provide a clinical effect in the treatment of SARS-COV-2.

METHODS: This is an interventional, single-arm, and non-randomized clinical trial conducted in Egypt from April 15 to July 21, 2020. Settings: This was a multi-center study conducted in three hospitals in Egypt. Participants: A total of 94 patients were enrolled who received CPT either within 7 days or after 7 days of hospitalization.

RESULTS: A total of 94 patients were enrolled who received CPT either within 7 days or after 7 days of hospitalization. 82 were severely ill and 12 were critically ill. The average age remained 58 years (±standard deviation 15.1 years). Male were 69% and 49% patients got cured while 51% died with case fatality rate 51%. Seventy-five percent deaths were among the COVID-19 patients who received CPT within 7 days.

CONCLUSIONS: Among patients with COVID-19 and severe or critical illness, the use of CPT along with routine standard therapy resulted in a statistically significant improvement when administered within seven days of hospital admission. However, plasma transfusion, irrespective of days to transfusion may not help treat critically ill patients. The overall mean time to cure in severely ill patients was 15 days if CPT provided within 7 days with 65% cure rate.

Trial Registration: Clinical Intervention identifier: MOPH_COVID-19_Ver1.1 registered April 2020.
in 46 reported COVID-19 deaths by the end of March 2020 [2], [3]. Thereafter, Egypt scaled-up preventive measures, with a partial lockdown starting on March 25 [4]. Quantitative real-time polymerase chain reaction (qRT-PCR) was performed extensively for symptomatic patients while patients with a high rate of suspicion; the test was repeated after 48 h [4]. The current treatment for COVID-19 is generally supportive. Several therapeutic agents along with convalescent plasma transfusion (CPT) are under investigation and data from CPT have been receiving a lot of attention, after Emergency approvals from the Food and Drug Administration (FDA) suggesting that it may provide a clinical effect in the treatment of SARS-CoV-2 [4].

The Egyptian MOH adopted a clinical COVID-19 management protocol for patients with COVID-19 by the Egyptian Ministry of Health COVID-19 scientific steering committee (according to the condition of the patient) [5]. It included paracetamol, hydroxychloroquine, oseltamivir if needed, empiric antibiotic when suspected secondary bacterial infection, oxygen, fluids, with steroids for severe cases, non-invasive and invasive mechanical ventilation if PaO2 < 60 mm Hg, O2 saturation <90% despite oxygen, progressive hypercapnia, respiratory acidosis (pH< 7.3), and progressive or refractory septic shock [5].

Passive immunization therapies treating infectious diseases date back to the 1920s' [6], providing instantly available therapeutic strategies for conferring direct immunity to susceptible individuals. Blood from an individual who has recovered from the disease is drawn and screened for high titers neutralizing antibodies, convalescent plasma containing these neutralizing antibodies is then administered in individuals with the infectious disease. Antibodies bind to the pathogen and directly neutralize its effectivity through antibody-mediated pathways, such as complement activation, antibody-dependent cellular cytotoxicity, and/or phagocytosis. Non-neutralizing antibodies that bind to the pathogen contribute to reducing symptoms and mortality, as they do not interfere in the pathogen’s ability to replicate within in vitro symptoms [6].

The use of CPT against coronaviruses was first tested during SARS1 outbreak in 2003 [7]. One of the largest SARS1 studies involved a total of 80 patients in Hong Kong. Results showed that patients treated before 14 days had improved outcomes [7], [8]. Eventually, convalescent plasma became established as an empirical treatment during the outbreaks of influenza A (H1N1) [7], where treatment of severe infection with convalescent plasma (n = 20 patients) as associated with reduced respiratory tract, viral load, serum cytokine response, and mortality [7]. Treatment protocols with convalescent plasma became further established for Ebola virus in 2014, and Middle East Respiratory Syndrome (MERS) in 2015 [7].

Clinical trial data from previous studies suggest that using similar CPT protocols could be beneficial in patients infected with SARS-CoV-2. However, there is a lack of robust evidence, generated from the data of large clinical trials that confirm the efficacy of this treatment modality.

The objective of the study was to assess the clinical efficacy of early start of convalescent plasma among SARS-CoV-2 patients as well as to observe intensive care unit (ICU) characteristics and fatality among severe and critically ill patients diagnosed with SARS-CoV-2.

Methods

An interventional, single-arm, non-randomized, and multi-center clinical trial was conducted from April 15 to July 21, 2020, in Egypt. The study was approved by the Ministry of Health and Population Ethics Committees (MOHP-EC) and was registered in Egypt NO. MOHP_COVID-19_Ver1.1.

Initially, 30 patients were enrolled and later extended where a total of 102 patients tested positive, using qRT-PCR in Central laboratories and on their admission to the hospital either with severe or life-threatening disease they were included in the study. A total of 94 patients were finally enrolled in the study after exclusion of patients who did not meet the criteria and written informed consent was taken. All patients included in the study have laboratory proven as SARS-CoV-2 and had bilateral infiltrates>50% and categorized as severely ill when having hypoxia and critically ill in case of mechanical ventilation use. Patients had received a combination of antiviral agents, antibiotics, and steroids according to the SARS-CoV-2 treatment protocol by Ministry of Health.

All patients received two convalescent plasma units (Each unit is 200cc) (Figure 1).

Symptomatic patients were tested for SARS-CoV-2 using nasopharyngeal or oropharyngeal swabs through-PCR - a validated assay protocol approved by the World Health Organization (WHO).

Convalescent plasma donors

Donors between the ages 18–60, with a clinical and laboratory-confirmed recovery diagnosis of SARS-CoV-2 were selected. PCR kits were used to confirm cases. Selected donors had complete resolution of symptoms at least 14 days before donation and negative results for SARS-CoV-2 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from the blood. Neutralization antibodies are measured by microneutralization technique [9]. Donors with a measurement of neutralizing antibody titers more than 1:320 (accepted till 1:80) along with an FDA approved defined serum SARS-CoV-2 specific chemiluminescence antibody titer higher than 1:320...
were included in the study. The investigators tested donor units using the Ortho VITROS SARS-CoV-2 total antibodies as per approved FDA guidelines [10]. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the Ortho VITROS SARS-CoV-2 total antibody are considered low titer units.

The volume of donated plasma was 800 cc and all donors’ samples were routinely virology screened for HBsAg, HCV Ab, HIV Ag/Ab, and Syphilis Ab using Chemiluminescence technique and were also screened by NAT for HBV DNA, HCV RNA and HIV ½ RNA. All donors provided consent and container labels of convalescent plasma units included the following statement, “Caution: New Drug--Limited to investigational use.”

**Statistical analysis**

Independent variables included age, timing of plasma administration, and severity of illness. Dependent variables included complications, number of days of ICU stay, number of days to cure and mortality. Descriptive and inferential analyses were performed. For the quantitative variables; frequencies, averages, and standard deviations were calculated. For the timing of the convalescent plasma administered variable coding was done as 1 for CP administration within 7 days of hospitalization and 2 for CP administration after 7 days of hospital administration. Student’s T test was applied for comparing continuous variables as the mean duration to cure and ICU stay among the categories of the timing of CP administration. Level of significant was selected as 0.05 and significance values (p) compared. N-1 Chi-square test was also applied for categorical variables. IBM® SPSS® was used for analysis.

**Results**

**Patient demographics and clinical characteristics**

A total of 94 COVID-19 patients including 82 (87%) severely ill and 12 (13%) critically ill were enrolled in the current study and administered two units of CPTs, within 24 h, either within 7 days or after 7 days of hospitalization. Patients were divided into three groups; < 40 years, 40–60 years, and greater than 60 years of age. Each group included 13 (16%), 30 (37%), and 39 (47%) severely ill patients while 1 (8%), 4 (33%), and 7 (58%) critically ill patients, respectively.

The average age remained 58 years (± standard deviation [SD] 15.1 years) Among the 94 enrolled patients the average age among <40 years, 40–60 years, and >60 years remained 32 (± SD 4), 51 (± SD 6), and 71 (±S D 6). Among the total patients, 65 (69%) were male. A total of 46 (49%) patients got cured while 48 (51%) died. The symptoms were dyspnea (55%), fever (52%), cough (46%), and loss of taste and smell (21%), and cyanosis (15%).

The average age remained 58 years (± standard deviation [SD] 15.1 years) Among the 94 enrolled patients the average age among <40 years, 40–60 years, and >60 years remained 32 (± SD 4), 51 (± SD 6), and 71 (±S D 6). Among the total patients, 65 (69%) were male. A total of 46 (49%) patients got cured while 48 (51%) died. The symptoms were dyspnea (55%), fever (52%), cough (46%), and loss of taste and smell (21%), and cyanosis (15%). The most common
co-morbidities among the <40 years remained diabetes mellitus (21%) and asthma (14%). Among 40–60 years age group hypertension (56%), diabetes mellitus (39%), and among >60 years age group hypertension (57%), chronic heart disease (24%), and chronic kidney disease were the most frequently reported co-morbidities.

**Severely Ill cases**

Among the total 94 cases, 82 (87%) were severely ill cases out of them 46 (56%) cured (95% confidence interval [CI] = 45%–67%) while 36 (44%) died (95% CI = 33%–55%). A total of 52 (63%) received CPT within 7 days of hospital admission while 30 (37%) cases received CPT after 7 days. The average days to cure remained 15 days (± SD 7.3) among those who received CPT within 7 days while the average days to cure remained 23 (± SD 9.4) who received CPT after 7 days and difference remained statistically significant p = 0.007.

Among the severely ill cases the cure rate among the cases who received CPT within 7 days was 65% (95% CI= 51%–78%) while among those who received CPT after 7 days remained 40% (95% CI= 23%–59%). Odds ratio for cure= 1.63 (95% CI = 1.01–2.64) the difference remained 25% which is statistically significant (p = 0.016).

**Severely Ill-cured**

Among the total 82 severely ill cases 46 were categorized as severely ill – cured. The average age of severely-cured patients remained 57.3 years (±SD 15 Years). Male were 33 (72%) and female were 13 (28%). Clinical sign and symptoms remained as dyspnea 44 (96%), cough 38 (82%), fever 34 (74%), cyanosis 10 (21%), and loss of taste and smell 7 (15%). Reported co-morbidities remained as hypertension 23(50%), diabetic 13 (28%), heart disease 6 (13%), asthma 5 (11%), COPD 4 (9%), kidney disease 3 (7%), and chronic liver disease 2 (4%).

Out of the total 45 (97%) patients treated with antibiotics and steroids, while 36, (78%) patients were treated with combination of hydroxychloroquine and 4 (9%) patients were treated with oseltamivir and lopinavir/ritonavir. The mean lowest SPO2, S/F ratio, PAO2, and P/F ratio reported across all age groups were 68.96, 155, 56.67, and 129.8, respectively (Table 1).

Among the 46 severely-ill cured cases, 34 (74%) received plasma within 7 days while 12 (40%) cured cases received plasma after 7 days. The average days to cure the cases who received plasma within 7 days remained 15 days (± SD 7 days) while the average days to cure who received plasma after 7 days remained 23 (±SD 9). The mean difference remained significantly different among both groups (p = 0.007). Similarly, the cases who received plasma within 7 days the average ICU stay remained 6 days (± SD 4 days) while the cases who received plasma after 7 days the average ICU stay was 11 days (± SD 7 days). The difference in the average ICU stay remained significant (p = 0.008) (Table 2).

**Severely Ill-dead**

Among the total 82 severely, ill cases of 36 s were categorized as severely ill - died, patients across all age groups. The average age remained 59 years (± SD 17 Years). Male were 22 (61%) and female were 14 (39 %). Clinical sign and symptoms remained as dyspnea 33 (92%), cough 30 (83%), fever 29 (81%), cyanosis 14 (39 %), and loss of taste and smell 7 (19%). Reported co-morbidities remained as hypertension 17(47%), diabetic 11(31 %), heart disease 5 (14%), and kidney disease 3 (8%). All patients (n=36, 100%) treated with antibiotics and 35 patients (97.2%) treated with steroids. A combination of hydroxychloroquine was administered to 69% (n = 25) of the subjects and lopinavir/ritonavir was given to 11% (n = 4) of the subjects. The mean lowest SPO2, S/F ratio, PAO2, and P/F ratio reported across all age groups were 68.96, 155, 56.67, and 129.8, respectively (Table 3).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Timing of plasma transfusion</th>
<th>n</th>
<th>Mean (±SD)</th>
<th>Significant (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to cure</td>
<td>Within 7 days</td>
<td>34</td>
<td>15.2647 (± 7.34974)</td>
<td>0.007</td>
</tr>
<tr>
<td>Days to stay in ICU</td>
<td>Within 7 days</td>
<td>34</td>
<td>5.8524 (± 4.45016)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Among the severely ill died cases 18 (50%) received plasma within 7 days while 18 (50%) received...
plasma after 7 days. The cases who received plasma within 7 days the average ICU stay remained 7 days (± SD 5 days) while the cases who received plasma after 7 days the average ICU stay was 4 days (± SD 3 days). The difference remained significant (p = 0.04) (Table 4).

**Critically ill-dead**

Out of the total 12 patients were categorized as critically ill - died, patients across all age groups. The average age remained 57 years (± SD 12 years). Male were 10 (83%) and female were 2 (17 %). Clinical sign and symptoms remained as dyspnea 12 (100%), cough and fever 9 (75%), cyanosis 6 (50%), and loss of taste and smell 2 (17%). Reported co morbidities remained as hypertension 6 (50%), diabetic 4 (33 %), heart disease, kidney diseases and asthma remained 2 (17%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Age groups</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&lt; 40</td>
<td>40–60</td>
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</table>

<table>
<thead>
<tr>
<th>Plasma characteristics</th>
<th>n</th>
<th>Mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, n (%)</td>
<td>36 (100)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Plasma administered within 7 days, n (%)</td>
<td>18 (50)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Mean days to die (± SD)</td>
<td>12.5 (± 6.6)</td>
<td>12 (8.4)</td>
</tr>
<tr>
<td>Plasma administered after 7 days, n (%)</td>
<td>18 (50)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Mean days to die (± SD)</td>
<td>16 (± 7.1)</td>
<td>16 (± 7.11)</td>
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<tr>
<td>ICU characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Mean duration of ICU stay before transfusion (±SD)</td>
<td>5.4 (± 3.6)</td>
<td>4.1 (± 2.6)</td>
</tr>
<tr>
<td>Mean duration of ICU stay after transfusion (±SD)</td>
<td>6.6 (± 6.8)</td>
<td>6.8 (± 9.7)</td>
</tr>
<tr>
<td>Mean duration of ventilator stay after transfusion (±SD)</td>
<td>6 (± 7.6)</td>
<td>3.2 (± 3.8)</td>
</tr>
</tbody>
</table>

**Complications**

| AKD, n (%) | 3 (8) |
| Pharmacological treatment | | |
| Antibiotics | 34 (95) | 6 (100) | 11 (92) | 17 (94) |
| Hydroxychloroquine | 25 (69) | 4 (67) | 10 (83) | 11 (61) |
| Lopinavir/ritonavir | 4 (11) | 0 | 3 (25) | 1 (8) |
| Steroids | 35 (97) | 6 (100) | 12 (100) | 17 (94) |

| Case fatality**

Out of the total 94 COVID-19 cases 46 cases got cured while 48 cases died (case fatality rate 51% 95% CI = 41%–62%). Among the total died cases, the average age remained 58 (± SD 15). The most frequent age among died cases was 73 (Mode), 25% deaths were under 45 years of age (First quartile), 50% deaths were up to 61 years of age (Second Quartile), 75% deaths were up to 70 years of age (Third Quartile), and 25% deaths were above the 70 years of age. About 67% male were died and 33% female died. Respiratory complications were more reported among the dead cases.

**Discussion**

The current study has shown that early administration of convalescent plasma in COVID-19 patients remained a critical measure for its clinical efficacy in severely ill patients. However, plasma transfusion, irrespective of days to transfusion may not be helpful in treating critically ill patients.

In history, several studies [11], [12], [13] have reported treatment with CPTs for viral infections. Similar results were provided by a study published in China on April 2020, a total of 10 severely ill COVID-19 patients were enrolled in the study and single dose of 200 ml plasma was administered to each of the subject and there was significant improvement in the clinical symptoms [14].

Some other published studies also provided the plasma transfusion should be done during...
the early phase of the diseases and will be more beneficial [15], [16]. China provided the usefulness of plasma transfusion among the critically ill COVID-19 cases. In this study, 5 critically ill cases were enrolled and received transfusion body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172–276 before, and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion [17].

Similar results were observed in influenza A (H1N1) patients, where patients who received plasma transfusions (n = 20) had significantly fewer deaths when compared to controls (n = 73) deaths (20% vs. 54.8%; p = 0.01) [18]. These positive effects of plasma transfusions in viral infections can be attributed to the humoral immunity established in recovered patients containing a large quantity of neutralizing antibodies capable of neutralizing SARS-CoV-2 and eradicating the pathogen from blood circulation and pulmonary tissues. In this multi-center non-randomized study, 94 patients (82 severely ill and 12 critically ill) with SARS-CoV-2 were treated with convalescent plasma. As assessed by days to transfusion (before and after 7 days) from date of admission, clinical symptoms such as dyspnea, cyanosis, fever, and cough improved within days of transfusion of plasma. This response time may have impact on pandemic economy as shorter duration of hospital stay leads to reduced cost. A study was published to examine the economic consequences of hospital admissions. And it is evident that with long stay there is a significant implication of the economics and increase of the out of pocket [19]. The current study provided that clinical respiratory parameters also improved in all cured patients. The results, therefore, support the initial hypothesis stating that CPT at an early stage may be effective in treating SARS-CoV-2. Similar results were provided by a study published during June 2020 in China. This study comprehensively evaluated the effectiveness, safety, and indications of CPT therapy for severe or critical COVID-19 patients. It is provided that 70% of the cases with severe respiratory symptoms showed improvement and removed oxygen supports within 7 days after CPT [20].

Our study also reports the deaths of critically ill patients who were placed on invasive mechanical ventilation before plasma transfusions. All 12 patients in this group died and they had respiratory system complications predominantly including pneumonia. All patients, irrespective of days to plasma transfusions had prolonged ICU stay similar to other studies. Similar results are evident form a meta-analysis published during May 2020 and provided that among the fatal cases the prevalence of respiratory co morbidities is higher [10.89% (95% CI: 7.57%, 15.43%)] as compared to the total cases [3.65% (95%CI: 2.16%, 6.1%)] [21].

In previous studies [22], viral load was linked to severity of SARS-COV-2. Thereby, supporting the current clinical evidence that suggests, clinical benefit is most likely in patients treated early in the course of the disease during viremia stage. Another study in 2018 was based on viral load and sequence analysis provided that viral load is significantly associated with the severity of diseases [23].

These results are comparable with other SARS-CoV-2 CPT studies that have been published since the beginning of this pandemic [16], [24], [25]. Shen et al. conducted one of the first plasma transfusions studies with a small sample size of five patients. The results reported, the PAO2 levels ranged from 172 to 276 before transfusion which was improved among four of five patients within seven days after transfusion (overall range: 206–290), and improved substantially (range: 284–366) on the 12th day after the plasma treatment. Chen et al. also reported improvement of clinical symptoms (fever, cough, shortness of breath, and chest pain) in all ten patients within 1 to 3 days of plasma transfusions [17].

Accordingly, results show promising effect of CPT on prognosis of COVID-19 infection. However, it is still too early to have a clinically relevant implication on guidelines for management of COVID-19 by CPT. There is still a limited understanding of mechanism and precise therapeutic components of convalescent plasma. Still there is no evidence-based rationale for donor selection and quality control of convalescent plasma.

**Limitations**

Due to the clinical features of included patients; the investigators could not conduct a randomized controlled trial. However, we understand that a controlled study may further help in establishing the dynamics of the viremia of SARS-CoV-2 while capturing the optimal transfusion time point. In addition, all patients were also treated with multiple pharmaceutical agents including antibiotics, antivirals, and steroids requiring robust comparative analyses to clearly establish the effect of each treatment modality individually and collectively as well.

**Conclusions**

This non-randomized clinical trial demonstrates the clinical efficacy of early convalescent plasma in treating SARS-CoV-2 infected patients. The study results indicate that cure rates are significantly better when plasma is administered within the first seven days of hospital admission for severe cases. The overall cumulative mean time to cure remained 15.2 days if CPT provided within 7 days with 65% cure rate as compared to 22.8 days if CPT administered after
7 days with 40% cure rate. For critically ill patients, the study reports that plasma transfusions may not be beneficial, due to the rapid progression of the infection and associated complications. We recommend well-designed randomized studies to further establish its efficacy in the future.

**Ethics Approval and Consent to Participate**

The study was approved by the Ministry of Health and Population Ethics Committees (MOHP-EC) and was registered in Egypt no. MOHP_COVID-19_ver1.1, all participants provided written consent before enrolment in the study.

**Availability of Data and Material**

The datasets generated and/or analyzed during the current study are not publicly available due to Egypt lows inhibit sharing personal information but are available from the corresponding author on reasonable request.

**Authors’ Contributions**

NA Performed the study design, analysis plan, data management, design data collection tools and performed critical review of the manuscript. HM planned the study and critical review of the manuscript. IS conceptualized the Idea and preparation of convalescent plasma. All other authors contributed equally in study.

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All clinical coordinators participated in coordinating field work and data entry.

**References**

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