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Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness. A double-blinded controlled preliminary study

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ABSTRACT

Background: COVID-19 is highly contagious, potentially deadly current pandemic with no evidence-based cure or vaccines. The efficacy and safety of transfusion plasma of recovered patients were tested to treat patients with severe infection.

Method: In this preliminary, controlled study, 30 patients were allocated to one of two groups: Standard therapy group (control, n = 15) and recovered COVID-19 plasma group (RCP, n = 15). Control group, received standard therapy alone, while patients allocated to RCP group, were given a single dose,250 ml, of plasma of recovered COVID-19 individuals, plus standard COVID-19 therapy. Neutralizing antibodies and severe COVID-19 serum biomarkers e.g. C-reactive protein, ferritin and d-dimer were measured in all patients before and after transfusion. Our primary outcome was reduction of two or more of a four-category illness-severity scale over 5 days study period: Respiratory frequency ≥24/min, blood oxygen saturation ≤ 93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg, pulmonary infiltrates >50% of both lungs.

Results: Plasma of recovered COVID-19 resulted in improvement of laboratory and radiological findings. In RCP group, there was statistically significant improvement of clinical parameters, as well as serum ferritin, D-dimer, c-reactive protein, and the size of lung lesion compared to control group ($P \leq 0.05$). COVID-19 neutralizing antibodies appeared in serum of RCV patients, but failed to show in the control group patients during 5 days study period.

Conclusion: Plasma of recovered COVID-19 individuals is safe and effective therapeutic modality that significantly accelerated clinical improvement in patients with severe COVID-19 infection.

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COVID-19; corona virus; SARS-COV-2; neutralizing antibodies

1. Introduction

Coronavirus disease 2019 (COVID-19) is highly contagious pulmonary disease with potentially devastating end results, caused by a newly discovered strains of coronavirus family, SARS-CoV-2. It is a member of β-coronavirus family, single-stranded RNA genome consists of 4 structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The virus characteristic name, corona, stems from the S protein which is club-shaped glycoprotein radiating out of the virus envelope in a crown-like configuration. [1] The similarity of the receptor-binding sites between SARS-CoV-2 and SARS-CoV explains their shared pathogenicity and biological traits. [2]

A classic Covid-19 infection, develops after incubation period of 6 days, presents with cough, ameliorated smell and taste sensation, and low-grade fever (38.1–39°C). [3] In the majority of patients, COVID-19 takes stationery mild/moderate course that resolve within a week at home[4]. The longer the symptoms continue, the more the incidence of turning into more severe form of COVID-19, with hospitalization, intensive care admission, and invasive respiratory support. The prognosis of COVID-19 is often inconsistent, especially in geriatric populations or younger individuals with comorbidities. The clinical picture ranges from totally asymptomatic to progressively devastating consequences. [5]

At the present time, finding a cure for COVID-19 possesses an acrid challenge to the medical community due to the scarcity of evidence-based antiviral medication or vaccines. The curative benefits of the antiviral Lopinavir/Ritonavir failed to improve disease-related mortality[6]. Hydroxychloroquine, reduced fever and cough in a randomized controlled study, however, its efficacy still in question. [7] Other study claimed that adding Azithromycin plus Hydroxychloroquine decreased viremia, however on using this combination resulted in worse outcome. [8] Therefore, an effective and safe therapy for the treatment of COVID-19, is still sought after. A series of published meta-analyses studies have shown successful patient outcome after transfusion of recovered plasma: One study showed improved clinical pictures, with higher discharge rate. [9] other demonstrated conversion from seropositive to seronegative in patients' serums a week post-transfusion. [10,11]

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Nevertheless, recovered COVID-19 plasma is a modality of passive immunization that has been used with varying degrees of success as prophylactic and curative therapy in management of infectious diseases since the turn of century. [12] Plasma of recovered patients, has been used as a rescue therapy in many viral infections like H1N1 pandemic influenza A, avian influenza A (H5N1), SARS-CoV and, Ebola virus disease,[13]. Early transfusion of recovered plasma showed decreased mortality in viral-related infections like SARS-CoV, however, a failed response in Ebola virus disease was a disappointing outcome. [12]

The recovered plasma is acquired by blood apheresis of individuals with previous COVID-19 infection. Recovered plasma is an attractive therapeutic modality in the dilemma of the current COVID-19 pandemic, as it is readily available, tolerable, potentially effective, with high safety margin. [14]

There are fast-growing numbers of new COVID-19 cases every day, and disease-related morbidity and mortality is increasing. The purpose of our study was to test the efficacy and safety of transfusing plasma from patients who have recovered from COVID-19, to patients with COVID-19 with severe condition.

2. Materials and methods

The present study was conducted during the period from June 2020 to August 2020 at Qena University Hospital, COVID- 19 isolation ward, after approval from faculty of medicine, ethical committee. Written informed consent was obtained from the patient or a legal relative on behalf of the patient. The study was registered with ClinicalTrials.gov Identifier: NCT04530370

Figure 1, outlines the study flow chart. Thirty eligible patients were randomly allocated to one of two groups: Recovered COVID-19 (n = 15, RCP group) and standard therapy groups (n = 15, control group). Patients allocated to RCP group, were given a single dose of plasma of recovered COVID-19 individuals, 250 ml, plus standard COVID-19 therapy. The control group, received standard therapy alone. Available standard therapy, when appropriate, included: supplemental oxygen, noninvasive and invasive ventilation, antibiotic medication, inotrope drugs, renal-replacement therapy, anticoagulants, glucocorticoids, intravenous fluids, interferon, and extracorporeal membrane oxygenation (ECMO). COVID-19 neutralizing antibodies (Qualitative assay), was measured in donors' serum before donation and in the recipient serum a day before and every day for 5 days after recovered COVID-19 plasma transfusion. Neutralizing Antibody, Cusabio, ELISA Kit Catalog Number. CSB-EL23253HU for the qualitative determination of (SARS-CoV-2).

3. RCP recipient eligibility criteria

Inclusion criteria to receive recovered COVID-19 plasma (RCP) were: hospitalized patients ≥18 years, with confirmed positive nasopharyngeal/oropharyngeal covid-19 swab, and have two or more of a four-category illness-severity scale:

1. Respiratory frequency ≥24/min.
2. Blood oxygen saturation ≤ 93% on room air,
3. Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg,
4. Pulmonary infiltrates occupying more than 50% of both lungs. Any patient with prior allergic history to plasma or plasma products or septic shock or multiple organ failure was excluded from the study.

4. RCP donor eligibility criteria

Recovered plasma (CRP) was accepted from donors who had a history of COVID-19 infection confirmed by positive nasopharyngeal swab/oropharyngeal swab test, and have complete recovery of symptoms for at least 2 weeks prior to donation, documented with negative nasopharyngeal/oropharyngeal swab. All blood products followed standard blood handling and processing procedures and regulations.

5. Randomization and masking

Using website software, enrolled patients were randomized in a 2:1 ratio to receive standard therapy alone, versus receiving standard therapy plus plasm of recovered COVID-19 individuals. Treatment allocation were assigned using randomized block design to provide symmetrically distributed base on key outcome-related characteristics. Plasma of recovered COVID-19 individuals was given and clinical data were monitored by the attending team, that was not aware of the research scheme. Radiological reports and laboratory parameter were registered by the administrative staff who was unaware of research protocol. The blood bank staff was blinded to group assignment. Patients were blinded to the intervention.

6. Primary outcome

At least 50% improvement of the severity of illness at any time during 5 days study period after transfusion, was our primary end point. 50% Improvement of severity of illness was defined as achieving a minimum of two-point reduction on the four-category illness-severity scale: Respiratory frequency ≥ 24/min; blood oxygen saturation ≤ 93% on room air; partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg; pulmonary infiltrates occupying more than 50% of both lungs, during 5 days study period.

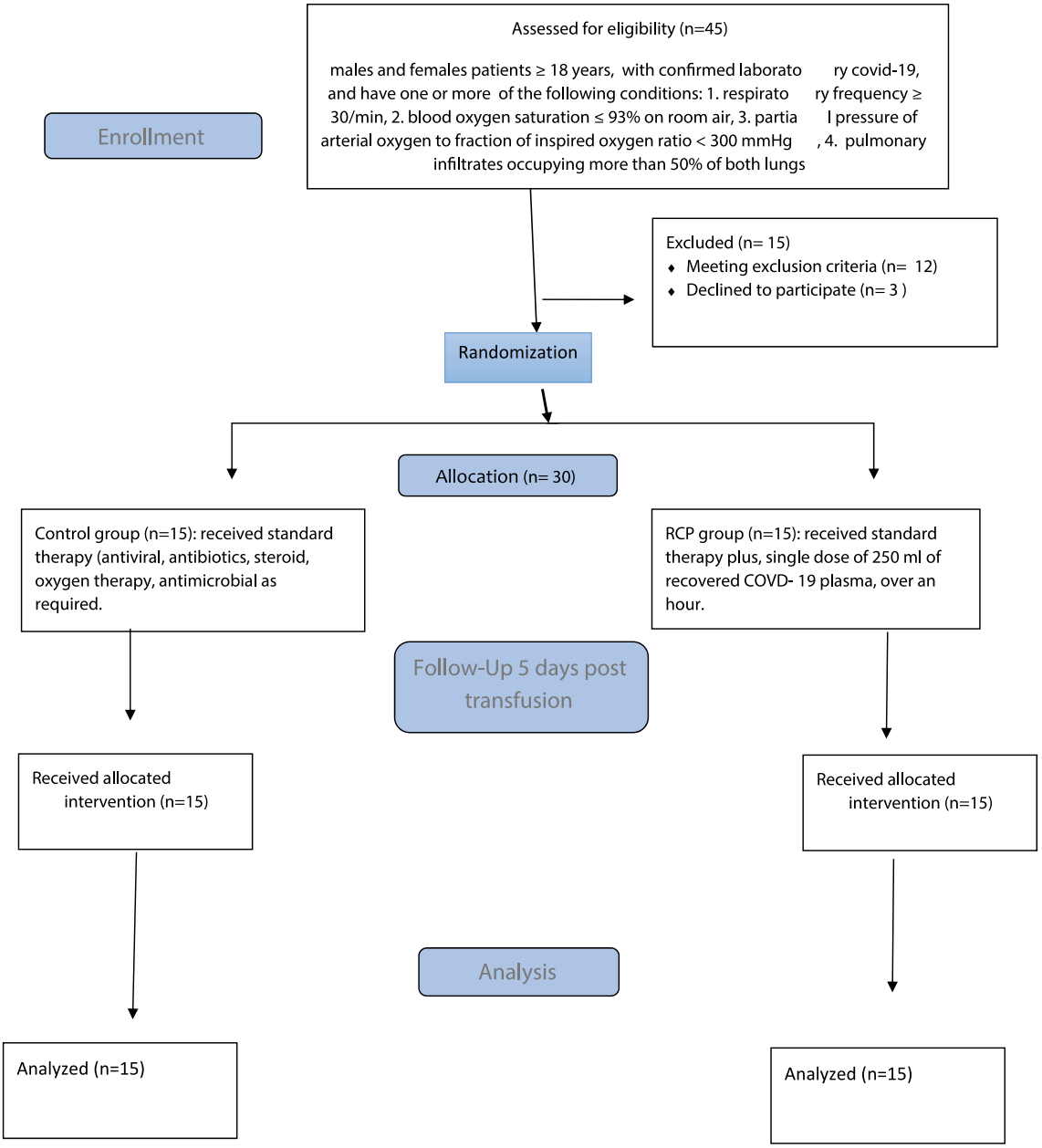

Figure 1. Study flow chart.

7. Secondary outcomes

Improvement of laboratory parameters of severe COVID-19 infection, and detection of neutralizing antibodies in COVID-19 patients within 5 days after RCP transfusion were our secondary end points as well as transfusion-related complications. Laboratory biomarkers of severe COVID-19 infections were assessed at baseline (after randomization) and every day during study period, and included Serum levels of: ferritin, D-dimer, troponin, lactic dehydrogenase creatine phosphokinase, lymphocytic count, and C-reactive protein. Other routine laboratory parameters were checked but data not show. All RCP recipients were hospitalized in isolation ward/ICU and received antiviral therapy antibacterial, and antifungal treatment according to the co-infections existed. All patients received steroid and oxygen supportive therapy as required. None of them was ventilated. Unwanted events and complications associated with recovered plasma transfusion were monitored by a nurse/clinician. During the transfusion, patients were under continuous supervision, with vital signs checked every 15 min during the transfusion and every hour for 6 hours after transfusion.

8. Statistical analysis

The sample size was decided based on a pilot study, of 10 patients who received RCP with improved clinical outcomes. [15] we conducted a priori power analysis which showed that to achieve 80% power of study with two-tailed test, α- error = 0.05, ß-error = 0.2,

effective size = 0.8, allocation ratio = 1, standard deviations of the pilot study ranged from ± 0.9 to ± 1.4, the sample size would be total of 30 patients, 15 on each arm. Data entry and analysis were done using SPSS 20.0 statistical software. Quantitative continuous data were calculated using Student t-test for comparison between two independent values or the non-parametric Mann-Whitney test. Categorical variables were statistically analyzed using chi-square or Fisher exact test. In order to detect independent identifiers of the clinical improvement, multiple linear regression analysis was applied after evaluating normality, and analysis of variance was applied to analyze full regression models were done. Statistical significance was considered at p-value <0.05.

9. Results

9.1. Demographic data

There was no statistically significant difference between the two groups as regard, age, sex, coexisting conditions, clinical status, standard treatment, days from the onset of clinical picture to hospitalizations, or days from hospitalization to randomization, Table 1.

9.2. Primary end point

Table 2 shows that, during the 5 days observation, number of patients who experienced shortness of breath, was significantly less in RCP group on PTD1, PTD2, PTD3, PTD4, PTD5 (46.3, 33.3, 33.3, 44, and 26% in the mentioned order) compared to control group (80, 66.3, 54.3, 66.3, and 53%, respectively) (P < 0.001). As with the incidence of dyspnea, the incidence of hypoxia was 40, 20, 20,26, and 20% on PTD1, PTD2, PTD3, PTD4, and PTD5, respectively, significantly better compared to control group of (53%, 60%,46.3%,53.3%, and 53.3%, on PTD1, PTD2, PTD3, PTD4, and PTD5 in the mentioned order) (P < 0.001). Nevertheless, In the control group, the incidence of hypoxia was not significantly different from the baseline. Table 2, also showed similar pattern of improvement over the 5 days study period, as regard the incidence of patients who had partial pressure of arterial oxygen to fraction of inspired oxygen ratio<300 mmHg, in RCP group, there was a statistically significant improvement compared to control group (P < 0.001). Likewise, the incidence of patients with lung lesions, was (40%) on PTD1, (33%) on PTD3 and (33%) on PTD5 significantly better compared to the control group of 66.3% on PTD1, PTD3 and PTD3, respectively (P < 0.001). Control group failed to show statistically significant change in lung lesion during the 5 days study period (P > 0.05) compared to baseline value. Figure 2, is a graphic representation of illness severity scale, during the trial period, in both control and RCP group. As shown in Figure 2(a) there was gradual decrease in illness severity during the study period in RCP group, P < 0.001, compared to baseline value. This trend was

Table 1. Patients` profile (original).

Patient traits	Total (n = 30)	Controlled group (n = 15)	RCP group (n = 15)
Age, median (IQR) – yr.	57.0 (50.0–66.0)	57.0 (50.0–67.0)	58.0 (49.0–68.0)
Male sex – no. (%)	21 (70)	10 (66.6)	11 (73.33)
Coexisting conditions – no. (%)			
Diabetes	9 (30%)	4 (26.6.1)	5 (33.0)
Cerebrovascular disease	13 (43.3)	5 (33.0)	8 (53.3)
Bronchial asthma	5 (16.6)	3(20)	2 (13.3)
Body temperature, median (IQR) – °C	36.7 (36.4–37.0)	36.5 (36.4–37.0)	36.5 (36.5–36.8)
Fever >38°C – no. (%)	20 (66.6)	11 (73.33)	9 (60)
Four category illness severity scale -no. (%)			
(1) Respiratory rate >24/min –	23 (67.6)	12 (80)	11 (73.0)
(1) Blood oxygen saturation ≤ 93% on room air	19 (63.3)	10 (66.6)	9 (60)
(1) Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg,	21(70)	11(73.3)	10 (66.6)
(1) pulmonary infiltrates occupying more than 50% of both lungs.	21(70)	11(73.3)	10 (66.6)
Days from onset of illness to hospitalization – no. (%)	17(56.6)	9 (60.6)	8 (53.3))
Days from hospitalization to randomization Median (IQR)	13 (11–16)	13 (11–17)	13 (10–16)
Treatment during study period – no. (%)			
Anti-viral	29(96.6)	15(100)	14(93.3)
Anti-bacterial	25(83.3)	13(86.6)	12(73.8)
Inotropes	7 (23.3)	4(26.6)	3(8.8)
Interferon	12(40)	5(33.3)	6(40)
Renal replacement therapy	0	0	0
Oxygen therapy	30(100)	15(100)	15(100)
Invasive mechanical ventilation	0	0	0
ECMO	0	0	0
Glucocorticoid therapy	23(76.6)	12 (80)	11(73.3)
Days from illness onset to steroid therapy – median (IQR)	13 (11–17)	13 (12–19)	13 (9–17)
Days of steroid therapy – median (IQR)	6 (3–11)	7 (3–11)	6 (2–12)

P value was significant at <0.05.
Values as shown as absolute number.
IQR: interquartile range.

Table 2. Illness severity scale during the 5 days study period (original).

Study milestones		Respiratory rate > 24/ min	Blood oxygen saturation ≤ 93% on room air	Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg	Pulmonary infiltrates occupying more than 50% of both lungs.
Baseline	RCP	11 (73.33)	9 (60)	10(66.33)	10(66.33)
	Control	12 (80)	10 (66.6)	11(73.3)	11(73.3)
PTD 1	RCP	7(46.3) *	6(40) *	7 (46.6) *	6 (40) *
	Control	12(80)	8(53)	10 (66.33)	10(66.33)
PTD 2	RCP	5 (33.3) *	3 (20) *	5(33.3) *	No CT was done
	Control	10 (66.3)	9(60)	10(66.34)	
PTD 3	RCP	5 (33.3) *	3(20) *	4 (26.4) *	5(33) *
	Control	8(53.3)	7(46.3)	9(60)	10(66.3)
PTD 4	RCP	6(44) *	4 (26.4%) *	3(20%) *	No CT was done
	Control	10(66.3)	8 (53.3)	8(53.8)	
PTD 5	RCP	4(26) *	3(20) *	4 (26.4) *	5(33) %*
	Control	8(53)	8(53.3)	9 (60)	10(66.3)

* p value of < 0.05 is considered significant. Numbers are compared to control group.
Value are shown as absolute numbers or percentage.
PTD (post-transfusion day).
Baseline data: after randomization.

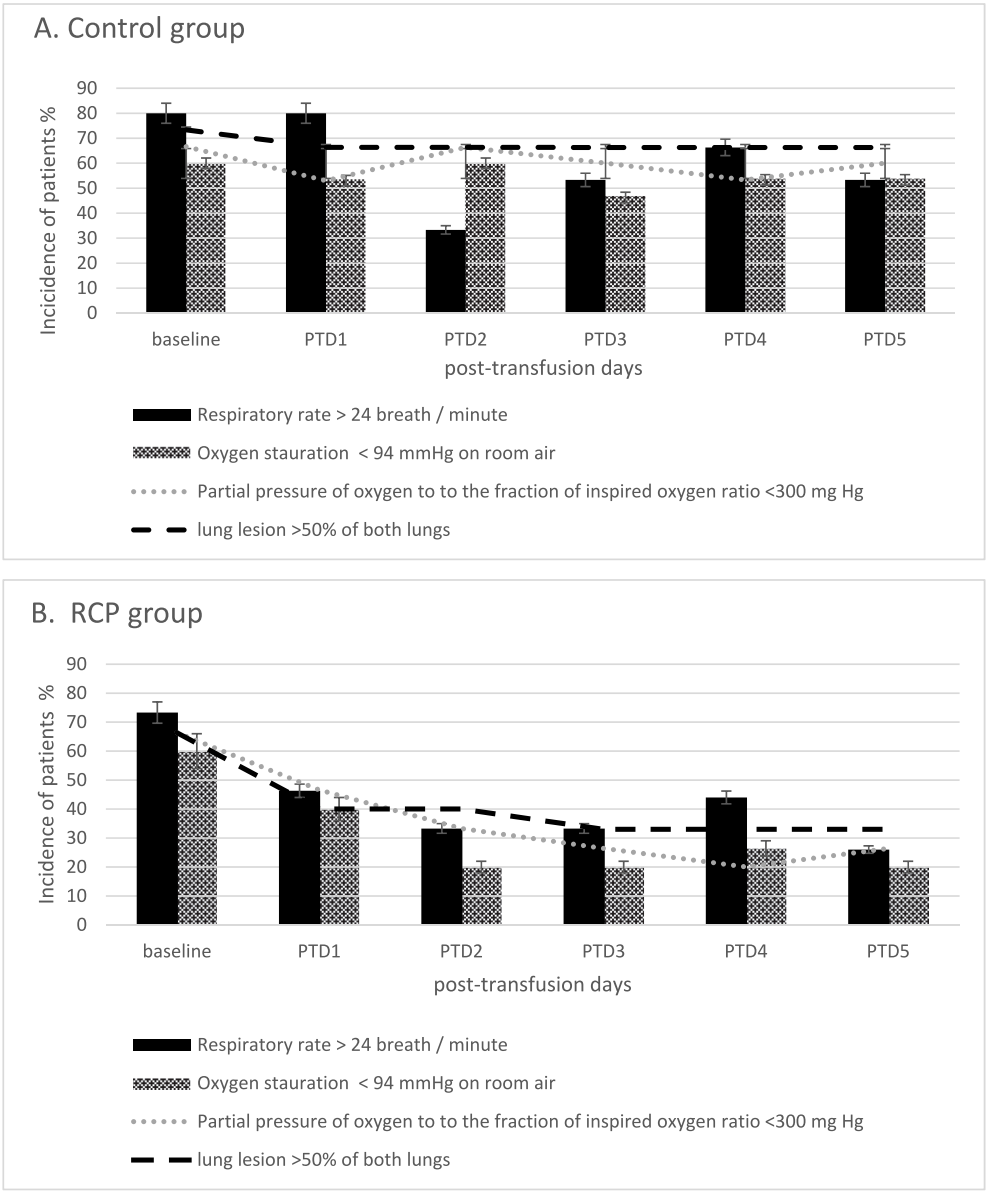

Figure 2. Illness severity scale during the 5 days study period **Abbreviation**: PTD, post-transfusion day; recovered COVID-19 plasma. **Notes**: Our primary end point was improvement of two points of the 4-points illness severity skill during the first 5 days after plasma transfusion; Error bars represent ± 5% deviation from real values.

Table 3. Biomarkers of severe COVID-19 infection during the course of the study (original).

Severe COVID 19 infection biomarkers	Study group	Baseline values	PTD 1	PTD 2	PTD 3	PTD4	PTD5
S. ferritin>500 mcg/L	RCP	712 ± 12	212 ± 14*	216 ± 13*	201 ± 12*	190 ± 12*	156 ± 76*
	Control	712 ± 12	612 ± 54	523 ± 14	401 ± 15	496 ± 12	609 ± 76
S. D dimer>1000 ng/ml	RCP	2203 ± 65	1062 ± 32*	999 ± 23*	812 ± 12*	790 ± 56*	876 ± 32*
	Control	1989 ± 65	1502 ± 34	999 ± 23	918 ± 13	1890 ± 56	2012 ± 32
S. troponin > 30 ng/L)	RCP	22 ± 12	28 ± 12	22 ± 92	26 ± 42	20 ± 62	21 ± 92
	Control	21 ± 12	27 ± 12	24 ± 42	23 ± 52	19 ± 82	61 ± 72
S. L.D > 245 units/L	RCP	98 ± 41	114 ± 56	108 ± 21	78 ± 81	88 ± 41	97 ± 27
	Control	93 ± 61	104 ± 26	105 ± 51	88 ± 61	87 ± 31	87 ± 17
S. CPK >300 units/L	RCP	176 ± 83 u/L	176 ± 93 u/L	197 ± 98 u/L	165 ± 74 u/L	187 ± 43 u/L	169 ± 53 u/L
	Control	166 ± 53 u/L	156 ± 63 u/L	147 ± 58 u/L	165 ± 64 u/L	177 ± 43 u/L	199 ± 54 u/L
<800 lymphocytes in 1 microliter (μL) of blood	RCP	767 ± 87/μL	908 ± 77/μL*	1098 ± 87/μL*	980 ± 47/μL*	1098 ± 76/μL*	1098 ± 43/μL*
	Control	767 ± 87/μL	798 ± 77/μL	987 ± 87/μL	997 ± 47/μL	1098* ±76/μL	1098 ± 43/μL
S. CRP >100 mg/L	RCP	314 ± 65	65 ± 85*	56 ± 94*	98 ± 43*	87 ± 56*	65 ± 45*
	Control	278 ± 65	243 ± 85	246 ± 94	265 ± 33	257 ± 56	243 ± 45

significant p value of ≤ 0.05, compared to control group.
RCP group (recovered COVID- 19 plasma) baseline (after randomization), COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase. Ferritin: serum ferritin, S. troponin: serum troponin, S D dimer: serum D dimer; PTD: post-transfusion day.
Values are show as absolute numbers or mean ± standard deviation.

not apparent in the control group, Figure 2(b), compared to their baseline values, P > 0.05.

9.3. Secondary end-points

Table 3 shows that in RCP group, both serum ferritin and serum d dimer showed statistically significant improvement on the 5 days study period compared to the control group (p value = 0.0002). Blood serum levels of troponin, lactic dehydrogenase, and creatinine phosphokinase, had normal baseline ranges and did not show noticeable change over the 5 days study period in comparison to the control group levels. Serum lymphocytic count showed statistically significant higher values than control ones, on every day during the study. While, serum c- reactive protein showed statistically significant lower values than control ones, on every day during the study. However, in control group, table 3 shows that there was no significant statistical difference as regard blood serum levels of troponin, lactic dehydrogenase, and creatinine phosphokinase over 5 days of the study period, compared to their baseline values. Nevertheless, a statistically significant improvement could be detected in both lymphocytic count on the last two days of the period of the study, PTD4 and PTD 5. CRP showed insignificant change during the 5 days study time, compared to its baseline parameters. Table 4, shows that COVID- 19 neutralizing antibodies were not detected in either studied group before plasma transfusion (baseline values). However, in the RCP group, the incidence of patient who developed positive neutralizing antibodies was significantly higher than the baseline (P < 0.001). In the control group, neutralizing antibodies were undetected throughout the entire study period (p = 0.05). Moreover, no viral negative seroconversion was detected by Nasopharyngeal/oropharyngeal SARSCoV-2 RNA, assayed RT-PCR, and serums remained positive in all patients in RCP and control group, throughout the 5 days study period. There were no transfusion related complications.

10. Discussion

This clinical trial investigated the efficacy and safety of recovered plasma, collected from eligible donors who had recovered from COVID-19 to treat patients with severe SARS- Co 2 infection. Recovered plasma has not been yet proven to be effective in COVID-19. The FDA recommends that it is crucial to understands its safety and efficacy via clinical researches before routinely giving recovered plasma to patients with COVID-19. FDA also is internationally collaborating with scientists and medical societies to develop a master protocol for recovered plasma, aiming at reducing duplicative works[16]. The results of this research showed that plasma of recovered COVID-19 individuals was safe

and effective therapeutic modality in severe COVID-19 infections.

The longer the COVID −19 symptoms persist, the riskier it gets[17]. An interesting observation in our study, was the ability of RCP to improve clinical picture, within a day of plasma transfusion. This rapid onset of symptoms alleviation was in accordance with other publications suggesting that RCP ameliorated dyspnea and improved oxygen saturation within days of transfusion. [17,18] Thus, RCP could be used as salvage therapy in patients with persistent symptoms or severe form of the disease. [18] Published data from other publications and WHO based programs, suggesting that recovered plasma may decrease the severity or shorten the course of COVID-19 infection [19,20].

To date, there is no widely accepted clinical classification of COVID-19. The diagnosis of severe COVD-19 relies upon diverse clinical, laboratory, and radiological parameters. Due to the wide range of clinical pictures, image findings, and serological derangement, along with the unpredictability of the COVIS-19 outcome, compounded with fluctuating reported mortality rates, different medical authorities have different classifications of the severity of the disease. As our primary end point was the time to clinical improvement, we designed a four-category severity illness scale to use as indicators of severe infection and to measure patients` clinical progress, they included: Dyspnea, oxygen saturation level, partial pressure of arterial oxygen to fraction of inspired oxygen ratio and CT chest lesions. Although fever is the first common reported symptoms among COVID-19 patients (88.6%) followed by cough (57%)[19], we did not include them, though, in our four-category scale as they do not distinguish between mild and severe infection nor they predict the prognosis. [20] A key element in the efficacy of RCP treatment is attributed to neutralizing antibodies. High plasma levels of neutralizing antibody should enhance the efficacy, thorough viral deactivation or/and collateral immune response. [21] indeed, due to constraints of cost and availability, we measured neutralizing antibodies in donors and recipients' blood, quantitively (detectable vs undetectable). RCP is mixture of immunoglobulins, albumin, coagulation factors, complement proteins, anti-thrombotic proteins among hundreds of proteins of different molecular weights and cellular interactions. These proteins may influence the modulatory immune effect of RCP in patients with COVID-19 in many ways[22]. Indeed, plasma with low neutralizing antibodies titer could, enhance clinical recovery, through immune modulatory mechanism rather than viral neutralization pathway that leads to downregulation of inflammatory cytokines, and reduction of the severity of symptoms. [23] This agrees with our findings, as we observed improvement in clinical, laboratory, and radiological parameters in RCP patients, while, nasal/oral swabs remained positive during the whole study period.

Several studies have classified COVID-19 CT lesions into stages depending upon the onset of the disease, the pathological morphological characteristic and the areas affected in the lungs. The majority of patients (56%) have no CT findings in early stage, while in the remaining 46% have unilateral lung lesions with peripheral distribution. In advanced stages, CT findings expand to involve both lungs, and central zones with typical radiological patterns. [24] Lung lesions have both diagnostic and prognostic importance, as persistent pulmonary infiltrates on CT during COVID-19 pneumonia, were related to high mortality rate[25]. A characteristic feature of this experiment was the rapid regression of pulmonary lesions on chest CT. Classically, COVID-19 pneumonia manifests as ground-glass opacities (GGO), in the peripheral lung zones, with foci of consolidations. Up to 88 and 60% of patients with severe COVID-19, have GGO and consolidation, respectively. This was in line with the results of the current trial, as 66% and 73% of RCP and Control group, respectively, showed pulmonary infiltrates occupying more than 50% of both lungs. However, after RCP transfusion, the time to regression of lung infiltrates on chest CT was 3 days, notably shorter than the average 10 days reported in community-acquired pneumonia (CAP) cases[26]. This accelerated pulmonary infiltrates regression noted in our study could be attributed to the definition of “regression” of lung infiltrates. In our protocol, regression was defined as lung infiltrates occupying less than 50% of both lungs, whereas, in their study protocol regression was defined as complete absence of infection-related lung infiltrates. Moreover, our patients were already on steroid therapy during the study period which could have accelerated the process of lung lesions regression.

Table 4. Qualitative Serum neutralizing antibody and nasopharyngeal/oropharyngeal swab (RT-PCR), SARS-CoV-2 RNA during the 5 days study period..

COVID 19 infection indices	donors	Recipient (Study groups) no-%	Baseline values	PTD 1	PTD 2	PTD 3	PTD4	PTD5
Neutralizing antibody	+	RCP	0	9 (60)	11(73.3)	12(80)	9(60)	11(73.3)
		Control	0	0	0	0	0	0
nasopharyngeal/oropharyngeal swab	-	RCP	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)
		Control	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)

Values are presented as absolute numbers or percentage
No-%: number of patients, percentage.

We measured a number of laboratory indicators associated with severe infection and worse outcomes. These biomarkers included Serum levels of ferritin, D dimer, troponin, lactic dehydrogenase, creatine phosphokinase and lymphocytes. [26] C-reactive protein (CRP), a cardinal inflammatory marker, Lymphocytic count, a key player for diagnosis and prognosis in COVID19 disease, and ferritin, a main marker for immune dysfunction showed statistically significant improvement after RCP transfusion in line with clinical picture improvement and appearance of neutralizing antibodies in RCP group. High ferritin was found in autopsies of COVID-19 victims, and was linked to proinflammatory and immune dysregulation leading to cytokine storm, a fatal outcome of COVID-19 patients[27].

Our clinical trial has limitations. First, we did not measure quantitively the neutralizing antibodies titer either in donor or recipient blood. This was due to unavailability of the measuring kits and the financial burden. Second, both groups were receiving standard therapy during the time of trial. The reported results could be at least in part due to the one or more of the standard medications. Third, only one dose of plasma was studied, different doses would have yielded different results. Fourth, this was a preliminary trial done on 30 patients that will be followed by another trial on a larger sample of patients.

In conclusion, a single dose of 250 ml of RCP to severely ill COVID-19 patients, mitigated the severity of symptoms, endured by all patients with reliable safety and improved radiological findings and laboratory parameters,

Declaration

The Author declares that there is no conflict of interest.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280. .

[2] Tang F, Quan Y, Xin ZT, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. J Immunol. 2011;186:7264–7268.

[3] Hui DS, Lee N. Adjunctive therapies and immunomodulating agents for severe influenza. Influenza Other Resp Viruses. 2013;7(Suppl 3):52–59.

[4] Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348 (20):1967- 1976. .

[5] Bonafè M, Prattichizzo F, Giuliani A, et al. Inflammaging: why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev. 2020 May 3;S1359-6101 (20):30084–30088.

[6] Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med. 2020;382:1787–1799.

[7] Hu CJ, Zhang Z, Jiang S, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. 2020. DOI:10.1101/2020.03.22.20040758.

[8] Gautret J-C, Parola LP, Hoang VT, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56 (1):105949 10.1016. doi:10.1016/j.ijantimicag.2020.105949.

[9] Soo YOY, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect. 2004;10(7):676- 678. .

[10] Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2020;7:CD013600.

[11] Zingher A, Mortimer P. Convalescent whole blood, plasma and serum in the prophylaxis of measles. JAMA. 1926 April 12;1180–1187:Rev Med Virol. 2005; 15:407–421.

[12] Luke TC, Casadevall A, Watowich SJ, et al. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med. 2010;38:e66–73.

[13] Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial JAMA Netw Open, (2020), 3 Article e208857, 10.1001.

[14] Cheng Y, Wong R, Soo YOY, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24:44–46.

[15] Olivares-Gazca JC, Priesca-Marín JM, Ojeda-Laguna M, et al. Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with covid-19: a pilot studY. Rev Invest Clin. 2020;72 (3):159–164. DOI:10.1073/pnas.2004168117. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020;117(17):9490-9496.

[16] FDA issues emergency use authorization for convalescent plasma as potential promising COVID–19 treatment, another achievement in administration's fight against pandemic. August 23, 2020. Avilable from: https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment.

[17] Kong Y, Cai C, Ling L, et al. Successful treatment of a centenarian with coronavirus disease 2019 (COVID-19) using convalescent plasma [published online ahead of print, 2020 May 21. Transfus Apher Sci. 2020;102820. DOI:10.1016/j.transci.2020.102820.

[18] Kong Yujie MLA, Cai C, Ling L, et al. Successful treatment of a centenarian with coronavirus disease 2019 (COVID-19) using convalescent plasma. Transfus

Apheresis Sci. 2020 May 21;102820. DOI:10.1016/j.transci.2020.102820.

[19] Kong APA, Cai Y, Ling C, et al. Successful treatment of a centenarian with coronavirus disease 2019 (COVID-19) using convalescent plasma. Transfus Apheresis Sci. 2020;102820. Advance online publication. DOI:10.1016/j.transci.2020.102820

[20] Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020;130(6):2757–2765.

[21] Eckhardt CM, Cummings MJ, Rajagopalan KN, et al. Evaluating the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma in severely ill adults with COVID-19: A structured summary of a study protocol for a randomized controlled trial [published correction appears in Trials. 2020 Jun 16;21(1):536. Trials. 2020;21-(1):499.Published 2020 Jun 8. DOI:10.1186/s13063-020-04422-y

[22] Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020 May 22:m1966. PubMed. DOI:10.1136/bmj.m1966

[23] Van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016;374:33–42.

[24] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020 Apr 22;323(20):2052–2059.

[25] Yoon SH. Chest radiographic and CT findings of the 2019 novel coronavirus disease (Covid-19): analysis of nine patients treated in korea. Korean J Radiol. 2020;21:498–504.

[26] El Homsi M, Chung M, Bernheim A, et al. Review of chest CT manifestations of COVID-19 infection. Eur J Radiol Open. 2020 7. 100239. DOI: 10.1016/jejro.2020.100239

[27] Bruns AH, Oosterheert JJ, El Moussaoui R, et al. Pneumonia recovery: discrepancies in perspectives of the radiologist, physician and patient. J Gen Intern Med. 2010;25(3):203–206.