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Convalescent Plasma Therapy for COVID-19 is a Challenging Option: Review

Maged Naser[1], Mohamed M.Nasr[2].and Lamia H. Shehata[3]

[1]Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of ob/gyn,

[2]King Fahd Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of Surgery,

[3]Care National hospital. Department of Radiology.

Abstract – The guiding principle of plasma therapy can be utilized for prophylaxis and treatment reasons, taking into account non-availability of suitable vaccination for prevention or no settled conclusive cure for SARS-CoV-2, plasma therapy is obtaining importance in a current pandemic as one of the treatment options of COVID-19. Despite the fact that, it has been said to be a useful approach in exceptional preliminary studies, convalescent plasma (CP) treatment has various limitations. In this review, an attempt has been made to audit positive viewpoints, negative views and specific limitations of the CP therapy for COVID-19 cases. The outcomes of various studies show that CP treatment would possibly be considered one of the alternatives but while questioning about it as a therapeutic approach, thinking about beneficial aspects, the negative aspects and barriers are to be considered before its administration as a therapeutic agent.

Keywords – COVID-19, Convalescent plasma, Positive aspects, Negative aspects, Limitations.

I. INTRODUCTION

The recent COVID-19 pandemic delivered about by way of severe acute respiratory syndrome Covid 2 (SARS-CoV-2) [1] has proven the fragility of our health systems in managing crisis circumstances identified with the unfold of new infectious agents that require the fast development of high quality care strategies. Tragically, there are a several potentially pandemic infections, for example, flavi viruses (e.g., West Nile infection [WNV], dengue infection, and Zika infection [2], chikungunya infection [3], influenza infections A [e.g., A(H1N1) and A(H5N1)] [4], Ebola virus (EBOV) [5], and respiratory beta coronaviruses (SARS-CoV and Middle East respiratory disorder CoV [MERS-CoV]), which could put us in circumstances essentially identical as the circumstance with the present day pandemic and which requires the development of unique intervention protocols. .

While vaccination method is without a doubt a suitable objective, development of a vaccine requires a time period not compatible with a crisis circumstance. It is moreover a prophylactic method that has no utilization in the therapeutic setting. Then again, the utilization of antivirals is presently available [6,7]. For the constrained wide variety of antiviral agents at currently available, unless if provided free of cost to developing countries, monetary fee is an issue. Also, manufacturing is challenging to scale up in short intervals of time.

In occasions in which the new pathogen can induce an immune reaction with the production of neutralizing antibodies, passive transfusion of convalescent blood products (CBPs), specifically, convalescent plasma (CP), has validated to be a wining and logistically attainable therapeutic strategy [8]. CBPs can be made through collecting entire blood or apheresis plasma from a convalescent donor. This methodology has been utilized since 1900 [9].

Corresponding Author: Maged Naser

The crucial mentioned issue of action for CBP treatment is clearance of viremia, which typically occurs 10 to 14 days after infection [10]. So, CBP has been generally administered; after the presence of early symptoms to maximize efficacy. Convalescent whole blood (CWB), notwithstanding antibodies, provides control of hemorrhagic events, as in Ebola infection disease, if transfusion occurs within 24 h to preserve viable platelets and clotting factors.

CP best fits settings where only antibodies are required.

We have described currently applied sciences for CP collection, manufacturing, pathogen inactivation, and banking of CP, then, we have summarized historic settings of CBP application, with a unique highlight on applications for COVID-19 and other future pandemics.

II. CP DONOR RECRUITMENT STRATEGIES

Convalescent donor checking out for neutralizing antibodies is obligatory in upstream donor selection. Donor selection is structured on neutralizing antibody titer, as assessed by way of a plaque reduction neutralizing test (PRNT) [11], which requires a viable isolate, replication-competent cell lines, and skilled personnel. Since PRNT sets aside effort to be set up and requires expensive facilities, in resource-poor settings or in time-sensitive situations, collection based on a retrospective PRNT or, alternatively, on enzyme linked immunosorbent assay(ELISA) focusing on the recombinant binding domains (RBDs) of the viral antireceptor has frequently been implemented; underneath these conditions, research have proposed that ELISA ratios/indexes have properly relationships with PRNT titers; e.g., the Euroimmun ELISA IgG score detected 60% of tests with PRNT titers of >1:100, with 100% specificity utilizing a signal/cutoff reactivity index of 9.1 [12]. The current understanding of neutralization proposes that the virus blocking off impact is identified with the amount of antibodies against different epitopes covering the virion, whose stoichiometry is in turn influenced via antibody concentration and affinity.

The donor need to ideally live in a similar location as the predicted recipient(s) to allow consideration of mutations of the target viral antigens. SARS-CoV-2 S protein has as of now mutated after a few months of viral circulation [13], with one mutation outside the receptor-binding motif (23403A→G single nucleotide polymorphism, comparing to a D614G amino acid change) currently defining a predominant clade [14]described through diminished S1 shedding and accelerated infectivity [15]. It ought to be viewed that preferring indigos donors ought to represent drawbacks in areas with pandemics of other infectious diseases (e.g., malaria).

Three approaches are hypothetically available to recruit CP donors, with every having advantages and disadvantages. The least coast effective approach is evaluating the general regular blood donor's populations for the presence of anti SARS-CoV-2 antibodies. In areas of endemicity, such an approach approves many fit donors with the extra benefits of seroprevalence learn about in general population (80% of instances being asymptomatic) but requires a large budget. On the other hand, recruitment of hospital discharged patients is highly cost-effective (patients can be easily tested before discharge and tracked), however patients who have required hospitalization are almost positive to be elderly with comorbidities and, thus, unfit to donate.

The intermediate approach, accepted by way of privacy regulations, is settling on choices to positive cases under home-based quarantine to request donations; given the large numbers of such cases, some of them are probably to be everyday donors, and home-based convalescents advocate that they are fit enough to donate. Lessons from MERS [16] and preliminary proof with COVID-19 [17-19] propose that patients with mild symptoms would possibly enhance low-titer antibodies, making antibody titration appreciably more essential in the population extensive and home-based approaches. Plasma samples collected an average of 30 days after the beginning of symptoms, had undetectable half-maximal neutralizing titers in 18% of donors [20].

Under emergency settings, it has routinely occurred that donors are no longer screened for high-titer neutralizing antibodies or that low-titer donations are collected; regardless, when the urgent requests are fulfilled and a buffer stock has been made, repeat donations ought to focus on donors with high titers [21].

As of late proposed, plasmapheresis could furthermore assist the convalescent COVID-19 donor through lessening the prothrombotic state via the citrate-based anticoagulants administered during donation and by removal of high-molecular weight viscous components [22].In the United States a few preliminaries have been started to make registries (e.g., ClinicalTrials.gov registration no. NCT04359602) or acquire plasma with titers of >1:64 from immune donors for banking purposes, besides quick reinfusion (e.g., preliminary NCT04360278, NCT04344977, or NCT04344015). These methodologies ought to be urged to better face the subsequent waves of the COVID-19 pandemic.

III. Convalescent plasma and pathogen inactivation

CP ought to be collected via apheresis to ensure lager volumes than available with whole blood donations and extra normal donations and to strive no longer to reason pointless anemia in the convalescent donor. Double filtration plasmapheresis (DFPP) utilizing fractionation filter 2A20 is under investigation as an approach to amplify IgG three to four times.

i. Pathogen Inactivation:

Albeit neither the U.S. Food and Drug Administration (FDA) [23] nor the European Center for Disease Control (ECDC) is suggesting pathogen reducing technologies (PRT) for CP [24], several authors assume about that, underneath emergency settings, donor screening and traditional viral nucleic acid testing (NAT) (i.e., HIV, hepatitis C infection [HCV], and hepatitis B infection [HBV] NAT) would not be enough to assurance CP protection [11]. Under this situation, more virological trying out and PRT double the expenses of the therapeutic dose. Several technologies for PRT have been permitted and are presently marketed.

Solvent/Detergent (S/D)- filtered plasma offers rapid inactivation of >4 logs of most enveloped viruses; albeit the technological was developed and is widely used for large plasma pools, small scale reduction has been reported. The technology relies upon on a several stages, addition of 1% tri(n-butyl) phosphate–1% Triton X-45, removing of solvent and detergent through skill of oil extraction and filtration, lastly sterile filtration [25]. Filtration across 75-to 35-nm-pore-size hollow fibers could remove viruses, (for example, beta coronaviruses) while saving IgG [26], but this has not been applied yet.

Recently, photo inactivation inside the presence of a photosensitizer has grown to be the widespread for single-unit inactivation; accredited technologies encompass mixtures of methylene blue and visible light [27] (Theraflex), amotosalen (S-59) and UV A [28] (Intercept), riboflavin and UV B [29] (Mirasol). These methods do not affect immunoglobulin activity. Fatty acids are additionally an alternative. In 2002, it used to be accounted for that caprylic acid [30] and octanoic acid [31] were positive as S/D at inactivating enveloped viruses. Heat remedy of plasma has been utilized beforehand [32,33] but comes with a hazard of aggregation of immunoglobulins [34,35].

IV. Convalescent plasma for covid-19

When the COVID-19 pandemic seemed [36,37], several authors proposed CP as a possible therapeutic agent [38,39]. Of interest, the most critically ill patients exhibit extended viremia (strongly corresponded with serum interleukin-6 [IL-6] levels) (10), which makes feasible therapeutic intervention with antiviral agents and immunoglobulins even at late stages. Viral shedding in survivors can hold going as long as 37 days [36], mandating SARS-CoV-2 RNA screening CP donors. Serum IgM and IgA antibodies seemed in COVID-19, patients as early as 5 days after signs onset [40], whilst IgG can be recognized at day 14 [41]. IgGs are for the typically diagnosed after 20 days [42,43]. Seriously ill female patients generate IgG earlier and at higher titers [44,45]; the greatest phase of the neutralizing antibody response has been tested to be associated with the IgG1 and IgG3 subclasses [46,47]. Duration of anti- SARS-CoV-2 antibodies in plasma is currently unknown; whilst the overall antibody responses for other beta coronaviruses typically decreases after 6 to 12 months [48], SARS-specific neutralizing antibodies usually proceed for 2 years [49]. In this way, by using a long way most of the countries, a suitable donor should donate 600 ml of plasma (equivalent to three therapeutic doses underneath most present day preliminaries) every 14 days for a minimal of 6 months. Up to 7 plasma donations have been validated now not to limit antibody titers in convalescent donors [17]. In contrast, to SARS and MERS patients, most COVID-19 patients show few or no symptoms and don't need hospitalization; this should advocate that most of convalescent donors are best sought in general population even though specific studies on antibody titers in mildly symptomatic patients suggest low titers. [17,19]

SARS-CoV-2 is diminished by >3.4 logs with the aid of Mirasol [50] (and probably by using different PRTs); in any case, SARS-CoV-2 viral RNA (vRNA) is detectable at low viral load in a minority of serum samples collected in acute infection but isn't associated with infectious SARS-CoV-2 [51]. Intercept remedy has been demonstrated not to lessen SARS-CoV-2 neutralizing antibodies titers [52]. The crucial contraindications to CP therapy are sensitivity to plasma protein or sodium citrate, selective IgA deficiency (< 70 mg/dl in patients 4 years old or older), leading to anaphylaxis from IgA-containing CP [53], or therapy with immunoglobulins in the final 30 days (as a result of a hazard of developing serum sickness). As in several different preliminary settings, concurrent viral or bacterial infections, thrombosis, poor compliance, short life expectancy (e.g., multi-organ failure), and being pregnant or breastfeeding are also contraindications [54].

In an early case sequence from China, 5 patients under mechanical ventilation (4 of 5 with no preexisting medical condition) received transfusions of CP with an ELISA IgG titer of >1: 1,000 and a PRNT titer of > 40 at days 10 to 22 after admission. Four

patients recovered from acute respiratory disease syndrome (ARDS), and three have been weaned from mechanical ventilation within 2 weeks of therapy, with remaining patients being stable [55]. Another Chinese pilot find out about (ChiCTR2000030046) of 10 critically ill patients showed that one dose, of 200 ml of CP with a neutralizing titer of >1:640 resulted in an undetectable viral load in 7 patients, with radiological and clinical improvement [56].

A third collection of 6 cases with COVID-19 pneumonia in Wuhan confirmed that a single 200-ml dose of CP (with titers of anti S antibodies decided with the aid of chemiluminescent immunoassay [CLIA] just) administered at a late stage lead to viral clearance in two patients and radiological resolution in 5 patients [57]. Pei et al. pronounced successful therapy of 2 out of 3 patients with 200-to 500-ml dosages of CP [58]. Recovery from mechanical ventilation was likewise announced with the aid of Zhang et al. in a single affected person after antibodies in CP had been titrated with an anti N protein ELISA [59]. No improvement in mortality in spite of viral clearance used to be suggested in a retrospective observational learn about selecting 6 late-stage, seriously ill sufferers treated with gold-immunochromatography-titrated CP, compared to results in thirteen untreated controls (85). One case of recovery in a centenarian patient who got 2 CP units (S-RBD-specific IgG titer of > 1:640) was once additionally reported [60]. One case of recovery in a centenarian patient who got 2 CP units (S-RBD-explicit IgG titer of >1:640) was also reported [61].

Effective cure used to be accounted for in 3 cases with ARDS and mechanical ventilation making use of two 250-ml CP doses (titrated with ELISA only) in South Korea [62], in 2 cases from Iraq [63], in 8 out 10 serious cases from Mexico [64], in 20 out of 26 extreme cases from Turkey [65], in a kidney transplant recipient from China [66], for a case with severe aplastic anemia in Poland [67],for a case with X-linked a agammaglobulinemic in Spain [68], and in 1 patient with marginal zone lymphoma handled with bendamustine and rituximab in the United Kingdom [69]. Facilities in the United States mentioned successful remedy with CP in 18 out of 20 patients in a sequence [70], in 27 out of 31 patients with severe to life threatening in any other series [71], in one case with myelodysplastic syndrome [72], in a critically ill obstetric patient (in a mix with remdesivir) [73], and in an allogeneic stem cell transplant recipient [74].In a large case series from Wuhan, 138 patients had been transfused with 200 to 1,200 ml of CP at a median of 45 days after symptoms' onset and experienced a 50% lower intensive care unit admission rate and mortality than the group dealt with best supportive care.

Responders had greater lymphocyte counts, decrease neutrophil counts, and lower lactate dehydrogenase (LDH), type B natriuretic peptide (BNP), urea nitrogen, procalcitonin, glucose, and C-receptive protein (CRP) levels. Complete data on neutralizing antibodies titers in COVID-19 convalescent plasma (CCP) units have been no longer available, but responders tended to have received CP units with greater neutralizer tiers [75].

Randomized preliminary study, 39 patients in New York with severe COVID-19 were transfused with 2 units of ABO-type matched with CP with anti- Spike antibody titers of ≥1:320 (measured through a two-step Spike protein-directed ELISA). CP recipients had been nearly certain than control patients to not increase their supplemental oxygen necessities via post transfusion day 14 (odd ratio [OR], 0.86), but survival improved only for nonintubated patients (hazard ratio [HR], 0.19) [76]. Another planned, multicenter randomized controlled preliminary from China (ChiCTR2000029757) enlisted 103 patients with severe to life-threatening COVID-19. The study used to be underpowered as a result of earlier than expected (200 cases) terminated. CP (9 to 13 ml/kg from donors with S-RBD IgG titer of ≥1:640) used to be associated with a bad SARS-CoV-2 PCR test at 72 h in 87.2% of the CP group versus 37.5% of the BSC group, yet clinical improvement at 28 days was statistically different only in patients with severe, but now not in life-threatening disease [77].

V. Monitoring response to CP treatment:

CP is considered as an experimental therapy, and, thusly, phase three randomized controlled preliminaries ought to be encouraged. Notwithstanding this suggestion, in emergency settings stage two preliminaries are commonly begun, hampering efficacy analysis. Reaction in distributed preliminaries is generally measured clinically by way of (PaO2/FiO2 ratio) or radiologically according to target organs. Alternative endpoints can incorporate anti SARS-CoV-2 antibody titer or absolute lymphocyte be counted increases in recipients, SARS-CoV-2 viral load or IL-6 levels. Whenever quantitative PCR is not available, cycle threshold (CT) value increases in qualitative PCR after transfusion may be a proxy for reduced viral load.

VI. Beneficial effects of other plasma components:

Plasma is a combination of organic compounds, inorganic salts and water. It has been proven to contain more than 1000 proteins including albumin, immunoglobulins, coagulation and antithrombotic factors, complement components, and so forth [78]. These

plasma factors may exert really beneficial effects, e.g., replenishing coagulation elements are useful in patients with hemorrhagic fevers.

As in Ebola viral ailment [79,80]. Plasma proteins, especially albumins add to maintain up with colloidal osmotic pressure of body fluid compartments.

It has been likewise proven that plasma from healthy donors has immunomodulatory influences through anti-inflammatory cytokines and antibodies by means of blocking complement activation, inflammatory cytokines and autoantibodies [81].

VII. TOLERANCE TO CP THERAPY:

Taking everything into account, the CP therapy is concerned, CP transfusion is well-tolerated with the aid of all patients and may doubtlessly improve the clinical outcomes in extreme COVID-19 cases in spite of the truth that related for sure adverse effects [82,83].

VIII. NEGATIVE FACTORS OF PLASMA THERAPY:

i. Adverse reactions

Adverse reactions ranging from mild fever to allergic reactions to life-threatening bronchospasm, transfusion related acute lung injury and circulatory over-load in patients with cardiorespiratory disorders, renal impairment and aged individuals have been stated [84,85,286,87,88].

a) Risk of transfusion related infections:

Although very rare, administration of CP incorporates the chance of transmission of potential pathogen, for instance, every other infectious disease like hepatitis B infection (HBV), hepatitis C contamination (HCV), Human Immunodeficiency contamination (HIV), Treponema pallidum just as SARS-CoV-2 itself. Thus, evaluating for presence of these pathogens is obligatory to avoid from the chance of transfusion related infections [84,83,87].

b) Risk of reinfection:

Administration of CP, for example passive antibodies may suppress/attenuate the humoral immune response of recipient therapy inhibiting the synthesis of particular antbodies' towards SARS-CoV-2 (pathogen particular antibodies). This may make an individual prone to reinfection by SARS-CoV-2 [85,83,89].

c) Other antagonistic responses:

CP therapy has been mentioned to purpose a transitory facial red spot in one patient beneath study [82]. Phlebitis and generalized jaundice have moreover been stated to appear in some patients [84].

d) Immunizer dependent enhancement (ADE):

There is a remote possibility of antibody dependent enhancement of disease process. ADE is an interplay whereby antibodies existing in the donor's plasma may exacerbate disease by way of improving passage of virus into the cell and multiplication of virus [83,84].

e) Important limitations of plasma therapy:

In spite of the reality that CP transfusion has been discovered effective in fighting infected cases of COVID-19, it is associated with quite a several limits. The important limitations of plasma therapy are as follows:

f) lack of neutralizing antibodies in affected person plasma:

The patients lately recovered from the SARS-CoV-2 infection can be effective donors for preparation of plasma for treating COVID-19 cases. The most important for preparation of plasma for treating COVID19 cases. The most essential requirement for this donor need to have a high titer of neutralizing antibodies in their plasma. The studies show that not all patients recovered from SARSCoV-2 infection have desired levels of antibodies in convalescent stage. Around 30% of sufferers recovered from SARS-CoV-2 produced low titer of antibodies. Another difficulty is that these antibodies last only for a short duration which is to be measured in weeks or months [83,84,90,91].

g) Large infusion volumes:

Another important limitation of CP treatment is the necessity of large infusion volumes. Different studies show that transfusion of 200 ml–2400 ml CP is required for treatment reason [82]. There is no standardization of transfusion dose of CP and various dosages have been utilized in different studies. Depending on the patient, a dose of 200 ml–2400 ml used to be utilized by means of Zhang et al. [92]. Notwithstanding, Duan et al. infused one unit of 200 ml of CP [82].

IX. Timing of administration:

Another essential drawback is time of administrations of CP to infected patients. It is predicted to be more effective, each time administrated earlier than the development of humoral immune response to SARS-CoV-2. Thus, testing recipient(patient) for neutralizing antibodies would be beneficial in identifying the best recipient for treatment purpose [87].

X. Waning of plasma antibodies:

As, mutations are frequent in SARS-CoV-2 there is possibility of waning of plasma antibodies [87]. Bridging the gap between COVID 19 positive and recovered cases. There is an addition of a large number of COVID 19 positive cases each day in almost all countries; nonetheless, the quantity of cases being recovered from SARS-CoV-2 infection is comparatively less. Consequently, it is very challenging to meet the prerequisite of large amount of plasma expected to treat large number of cases being added every day. The bridging over of this gap between recovered cases and new cases has being truly challenging, due to which this treatment option might also no longer be feasible as a long way as availability of large volume of convalescent plasma.

XI. Basic administrative and logistic therapy:

The necessary barriers include identified, consenting, collecting and testing donors. Identifying/finding donors with robust humoral response (donors with high levels of desired antibodies) is an important obstacle. Absence of assay method for detection of neutralizing antibodies would possibly impede the identification of suitable/ideal donors. written knowledgeable consent for donations related to plasma through patients recently recovered from COVID-19 infection would possibly be an another important hurdle [83,84].

XII. Donors eligibility criteria:

Donors consenting for donation of plasma ought to meet the eligibility standards for standard blood donation. Donors should be negative for SARS-CoV-2 test and need to be free from COVID-19 symptoms. Donor dependent variability in antibodies. Specificities and titer of antibodies in CP is another problem associated with different individuals [83,87]. Donated plasma ought to be compatible with the A-B-O blood type of the recipient [84].

XIII. What are the obstacles to early treatment?

There are a few calculated boundaries to CP treatment. To commence with, at some point of a pandemic, there is immense gathering of severely ill patients to emergency rooms, and in collapsed health systems, the turnaround time between emergency room admission and admission to a ward can be relevant. Furthermore, except fast (antigenic or molecular) checks for SARS-CoV-2, the turnaround time for conclusive affirmation of dedication with polymerase chain response tests, as a rule run in batches, takes from 5 to 10 h. Then, at that point, paperwork additionally sets aside opportunity with regards to putting up the papers for deciding on an affected person internal a scientific preliminary, and there are difficulties related with outpatient transfusion of regarded infectious individuals. At long last, ABO- like minded CP units may no longer be at once available at the local blood donation center, and enlisted patients are thusly left on the holding up list. This load of elements is likely going to influence the efficacy of CP treatment. We advocate large deployment of rapid assessments within emergency departments, where CP should be safely managed even earlier than the patient arrives at the remaining ward.

As counseled by means of these days revised European Commission hints on CCP, ‘evidence suggests that research should focus on early transfusion of convalescent plasma with high neutralizing antibody titers’. [93]. In conclusion, CP is emerging as a new time-sensitive, life-saving treatment.

XIV. Conclusion

The assessment of a number previously research exhibit that CP remedy is really useful in the management of a number of viral infections, together with COVID-19. It ought to be regarded one of the other options, particularly for the cure of viral infections for which no appropriate antibody or set up antiviral therapy is accessible. Nonetheless, whilst thinking about it for therapeutic approach, considering recommended outcomes the negative aspects and boundaries are to be taken into consideration before its administration as a therapeutic agent.

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

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