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Convalescent Plasma Therapy: A Review

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ABSTRACT: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also called as Novel corona virus (2019-nCoV) is responsible for the corona virus disease 2019 (COVID-19) pandemic which was found firstly in Hubei province ,Wuhan, China in December 2019. This caused death of lakhs of people around the world .For the treatment of the same the therapeutic options including antimalarials, antivirals, and vaccines etc. are under study and development. Meanwhile the current pandemic has brought the concern of whole world over the old therapeutic tools to treat infectious diseases which is Convalescent Plasma (CP) therapy, a classical adaptive immunotherapy treatment ,which has been applied to the prevent and treat many infectious diseases for more than one century.

Key words: SARS-CoV -2 , convalescent plasma therapy (CPT), COVID-19 , neutralizing antibodies (nabs) , immunoglobulins ,

I. INTRODUCTION:

In December 2019, a new member of the Coronaviridae family associated with severe pneumonia was detected in Hubei province of Wuhan, China [1]. Patients showed similar symptoms and findings to SARS-CoV and MERS-CoV detected by high fever, dyspnea, and chest radiographs revealing invasive multilobed lesions in the patient's body [2,3]. The virus was initially termed as 2019 novel corona virus (2019-nCoV) by world health organization in February 2020 [1], and it is currently known as SARS-CoV-2 producing the corona virus disease 2019 (COVID19). The origin of the virus is unknown, but structurally the virus shares 88% identity with bat-derived SARS-like corona viruses named bat-SL-CoVZC45 and bat-SL-CoVZXC21, suggesting that bats are the most likely the origin of this virus [4].This corona virus disease 2019 (COVID 19) epidemic developed into an unprecedented global public health crisis with significant humanitarian consequences[5,6]. Viruses of the Coronaviridae family have a positive-sense, single strand, RNA structure with 26 to 32 kilobases length [7,8].

The current treatment for COVID-19, has been limited to general supportive care, with provision of critical care as no approved therapies or vaccines are available. [9]Over the last two decades, CP therapy was successfully used in the treatment of SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome), and in H1N1(Swine Flu) 2009 pandemic with satisfactory effects and safety . And now these evidences drive all the hopes of fighting this pandemic of COVID-19 with help of convalescent plasma therapy in treatment. This classical and historical interventions have remerged as options for the control of the disease, the convalescent plasma (CP)[10].The CP therapy uses an individual who is sick with infectious diseases and has recovered , with blood drawn and screened for particular microorganism neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, convalescent plasma containing these neutralizing antibodies can be administered in individuals with specified clinical disease to reduce symptoms and mortality. Thus , convalescent plasma transfusion (CPT) has been the subject of increasing attention, especially in the wake of large- scale epidemics [11] .It has recently been suggested by Food and Drug Administration that administration and study of investigational CPT can provide a clinical effect for treatment of COVID-19 during this public health emergency. [12]

II. WHAT IS CONVALESCENT PLASMA THERAPY?

Convalescent plasma (CP) is a strategy of passive immunization which is used in prevention and management of infectious diseases since early 20th century [13]. The CP is obtained using aphaeresis in survivors with prior infections caused by various pathogens in whom antibodies against the causal agent of disease are developed. The

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major target is to neutralize the pathogen for its eradication [14].

Immunized plasma acts by binding to a given pathogen including virus (eg-SARS-2) directly and causing its denaturisation, primarily, also eradicating virus from the peripheral blood stream while other antibody mediated pathways including compliment system, antibody dependent cell-mediated cytotoxicity or phagocytosis might, also, contribute towards the therapeutic effects achieved [15]. In the absence of any proven drugs or therapy, convalescent plasma has been used previously in outbreaks of Machupo virus, Junin virus, Lassa fever and few others to name.[15] The CP has been considered as an emergency intervention in several pandemics, including the Spanish flu, SARS-CoV, West Nile virus, and more recently, Ebola virus previously [16]. The CP early administered after symptoms onset, showed reduction in mortality compared with placebo or no therapy in severe acute respiratory infections of viral etiology like influenza and SARS-CoV, also a similar response in Ebola virus disease was not observed [16, 17].

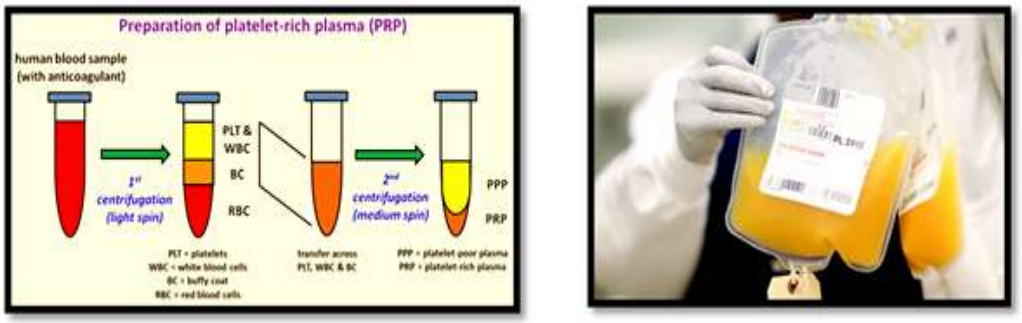

Fig- [1.1], [1.2] PRP-protein rich plasma used to infuse in patients' blood

III. HISTORICAL EVIDENCE FOR PLASMA THERAPY:

In as early as the 1918–1925 Spanish influenza pandemic, Studies evaluated convalescent blood products to treat pneumonia due to Spanish influenza in hospitals, A meta-analysis conducted in 2006 showed a sizable reduction in overall fatality rate, from 37% among controls to 16% among patients treated with convalescent plasma. Benefit was broadened among patients receiving the treatment early, importantly within the first four days of pneumonia complications [18]

Although these early epidemiological studies had been rather rudimentary in their design , they underlined the beneficial role of convalescent plasma that indicated modern researchers to support the role of this regimen in a possible future H5N1 influenza pandemic treatment. Also Convalescent serum had been used during the first half of the 20th century for measles,[19]poliomyelitis,[20] and mumps.[21]

Decades later, in the pandemic influenza A (H1N1) 2009 virus infection, convalescent plasma treatment was able to significantly reduce respiratory tract viral load, serum cytokine response (interleukin-6, interleukin-19, tumor necrosis factor-alpha), and mortality in a comparative study recruiting 99 patients. In that study, the decrease in mortality was rather impressive, as the odds of death decreased by 80%.[22]

A systematic review and meta-analysis gave 32 studies of severe acute respiratory syndrome (SARS) coronavirus infection and severe influenza and highlighting the consistent evidence for the reduction in mortality, in case of early administration of convalescent plasma and hyper immune immunoglobulin after symptom onset. The meta-analysis confirmed the sizable reduction in number of mortality, pointing to a decrease by 75% in the odds of death.[23]

Moreover , transfusion of convalescent plasma collected from patients that recovered from Ebola virus has been recommended by the World Health Organization as an empirical treatment for the Ebola outbreaks, with provision of guidance , about the selection of donors, screening, and handling of blood and plasma units.[24]

IV. CONVALSCENT PLASMA THERAPY TREATMENT – MECHANISM OF ACTION (ELABORATE)

A] Steps involved in the acquaintance process:

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1. The convalescent donors must undergo standard pre-donation assessment to ensure competence with current regulations regarding plasma donation process [25] Current convalescent donors between 18 and 65 are considered as subjects without infectious symptomatology and a negative test for COVID-19 after 14 days of recovery.[26]
2. Donors from endemic areas for tropical diseases (e.g., malaria) should be excluded from the process of plasma donation.
3. In addition to molecular tests, it is more critical to recognize the emotional situations, to find out susceptibilities, and guarantee not exploitation of donors [27]
4. Apheresis process is the recommended procedure to obtain plasma. This procedure is based on a continuous centrifugation of blood from donor to allow a selective collection plasma. For efficiency of this technique ,around 400–800 mLis collected from a single apheresis donation. This amount of plasma could be stored in units of 200 or 250 mL, and frozen within 24 hrs of collection to be used in further transfusions [28].
5. As CP production requires very high quality standards, it is must to be free from any infection, so tests for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, syphilis, human T-cell lymphotropic virus 1 and 2, and Trypanosoma cruzi should be carried out before further process. [25,29].

6. In this sense, the nucleic acid test for HIV and hepatitis viruses is mandatory to guarantee the safety of recipients health and other possibilities of carrying diseases[30].
7. Other protocols suggest the inactivation of pathogens with riboflavin or psoralen plus exposure to ultraviolet light to improve safety of CP which will be used for transfusion in patients. [31]

8.. In the different studies for corona viruses the administration of CP ranges between 200 and 500 mL in single or double scheme dosages. Presently, the recommendation of dose is to administrate 3 mL/kg per dose in two days[28]. This strategy also facilitates the distribution of plasma units (250 mL per unit) and provide a standard option of delivery in public health strategy.

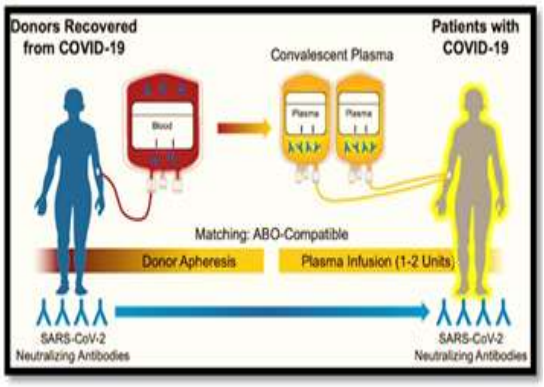

Fig.1.3. The steps involved in the convalescent plasma therapy .

B] Composition of CP :

1. Composition of CP is variable and includes a wide variety of blood derived components like proteins, WBCs etc.
2. Plasma contains a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins like albumin, immunoglobulin, complement, coagulation and antithrombotic factors responsible for blood clotting process. [32] .
3. Interestingly, it's known that plasma from healthy donors provides immunomodulatory effects via the plasma infusion of anti-inflammatory cytokines and antibodies that blockade complement, inflammatory cytokines and auto antibodies[33]
4. These factors may influence the immunomodulatory effect of CP in patients with COVID-19 (see below for details).

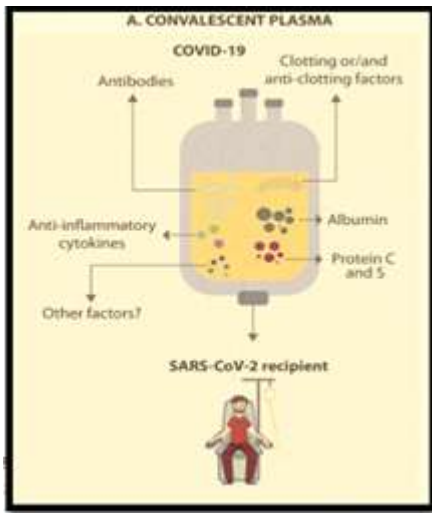

Fig-1.4- Different components present in plasma(plasma –rich -protein)

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V. EFFECTIVENESS OF CP IN COVID-19 PATIENTS:

Convalescent plasma (CP) therapy, is a classic adaptive immunotherapy, which was successfully used in the treatment of SARS, MERS, and 2009 H1N1 pandemic with satisfactory efficacy and safety [34]

A analysis from 32 studies of SARS corona virus infections and severe influenza intended a statistic reduction in the pooled odds of mortality following CP therapy, compared with placebo or no therapy (odds ratio, 0.25; 95% confidence interval, 0.14–0.45) [35]. However, this therapy was unable to significantly improve the survival of patients in the Ebola virus disease, due to the absence of data of neutralizing antibody titration for stratified analysis [36]. Since the virological and clinical characteristics share similarity among SARS, Middle East Respiratory Syndrome (MERS), and COVID-19 [37], CP therapy might be a promising treatment option for COVID-19 treatment . [38]

COVID-19 patient's reports intended that critically ill patients exhibited positivity for anti-cardiolipin IgA antibodies as well as for anti–β2-glycoprotein I IgA and IgG antibodies when given CP [39]. This evidence may suggest that CP-COVID-19 may neutralize this type of auto antibodies reducing the odds of suffering from thrombotic events (i.e., antiphospholipid syndrome). Moreover, a recent report of patient suffering from Sjögren's syndrome and COVID-19 has successfully treated with CP.This suggests that CP strategy is effective and safe in autoimmune conditions [40].

In addition, some antibodies inhibit the complement cascade (i.e. C3a & C5a), and may restrict the formation of immune complexes [41,42]. Complement-deficient mice with induced SARS-CoV-2 infection indicated high viral titers with secretion of inflammatory cytokines and chemokines, and immune cell infiltration in the respiratory tract and lungs. These results suggest that complement activation largely contribute to the systemic inflammation and migration of neutrophils to the lungs, perpetuating damage to tissues[43]. Further studies have shown that IgG transferred from convalescent plasma neutralize cytokines such as IL-1β and TNFα [44]. In this concern passive immunity by infusion of plasma for COVID-19 may limit the inflammatory cascade driven by pathogenic antibodies, as well as the cellular damage induced by the complement cascade activation in excessive inflammatory environments.

Antibody-dependent enhancement (ADE) is a mechanism in which the intensity of virus increases in the presence of pre-existing poorly NAbs, helping the replication of virus into macrophages and other cells via interaction with Fc and complement receptors [45]. This mechanism is used by novel corona viruses, HIV and dengue viruses to take advantage of prior anti-viral humoral immune response to effectively infect host target cells increasing to death [46,47].

In vitro assays with human promonocyte cell lines explained that SARS-CoV ADE was initially mediated by antibodies against spike proteins, specifically increasing the rate of apoptosis in these cells [47]. Vaccine development must consider this phenomenon in patients with COVID-19, and treatment of CP-COVID-19 in these areas should be conducted with caution [48].

One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia -An in-vivo trial also showed that the effects of this antibody were not only limited to free viral clearance and blocking new infection, but also included acceleration of infected cell clearance.[49]

Viraemia peaks in the first week of infection in most viral illnesses. The patient usually develops a primary immune response by days 10–14, which is followed by virus clearance.[50]Therefore, theoretically, it should be more effective to administer the convalescent plasma at the early stage of disease.[50] However, other treatments might have an effect on the relationship between convalescent plasma and antibody level, including antiviral drugs, steroids, and intravenous immunoglobulin.[51]

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Sr no. of Patient	Plasma transfusion date	Before Convalscent plasma transfusion			After Convalscent plasma transfusion		
		DateDate	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)	DateDate	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)
1	February 9	February 8	1:160	37.25	February 10	1:640	Negative
2	February 9	February 8	1:640	38.19	February 14	Unavailable	Negative
3	February 13	February 12	1:320	38.07	February 14	1:640	Negative
4	February 13	February 12	1:160	37.68	February 14	1:640	Negative
5	February 12	February 11	1:320	34.64	February 14	1:640	Negative
6	February 12	February 11	1:640	Negative	February 14	1:640	Negative
7	February 12	February 11	1:640	35.45	February 14	1:640	Negative
8	February 12	February 11	1:160	Negative	February 14	1:640	Negative

Table -1 – SARS-CoV -2 and Serum neutralizing antibody titers in patients receiving CPT(convalescent plasma therapy)

Sr.no of Patient	Antiviral Drugs for treatment.	Other treatment (antifungal) drugs	Corticosteroids drugs	Before CP treatment (O2 support)	After CP treatment (O2 support)
1	Arbidol 0.2 g q8h	Moxifloxacin i.v.	Methylprednisolone i.v	High Flow Nasal cannula , mechanical ventilation	High –flow nasal cannula
2	Arbidol 0.2 q8h po.	Cefoperazone Sodium i.v	None	None	None
3	Arbidol 0.2 g q8h po. Ribavirin 0.5 qd i.v	Cefoperazone sodium i.v	None	High flow nasal cannula, mechanical ventilation	Mechanical ventilation
4	Ribavirin 0.5 g qd i.v	Linezolid i.v Imipenemsitastin Sodium i.v	Methylprednisolone i. v	Mechanical ventilation	High –flow nasal cannula
5.a)	Arbidol 0.2 g q8h po.	Moxifloxacin i.v	Methylprednisolone i.v	Low –flow nasal cannula	Low –flow nasal cannula
b)	Remdesivir 0.2 g qd I.v	Cefoperagone Sodium and Tazobactam Sodium i.v	None	None	None

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6.	Arbidol 0.2 g q8h po.	None	None	None	None
7.	Arbidol 0.2 g q8h po. IFN-a 500 MIU qd inh.	Cefoperagone Sodium Caspofungin i.v	Methylpred nisolone i. v	High flow nasal cannula,	High flow nasal cannula
8.	Arbidol 0.2 g q8h po.	Cefoperagone Sodium i.v Levofloxacin i.v	Methylpred nisolone i. v	High flow nasal cannula,	High flow nasal cannula,
9.	Arbidol 0.2 g q8h po. Oseltamivir 75. Mg q12 po.	None	None	Low flow nasal Cannula	Low flow Nasal Cannula (Intermittent)
	Peramivir 0.3 g qd i.v	none	None	None	None
10.	Arbidol 0.2 g q8h po.	Cefoperagone Sodium i.v and Tazobactam Sodium i.v	Methylpred nisolone i.v	High –flow nasal cannula	None

Table -2 – Effect of plasma therapy on patients suffering from COVID 19

VI. STEPS IN CONVALESCENT PLASMA COLLECTION:

The regulations of every single step of CP collections are very important. Starting from the assessment of donor to the administration of CP to the patients, all of the steps should be organized carefully and should be performed by experienced health workers.

6.1Donors Eligibility

The criteria for eligibility of CP donors may vary between countries. According to the FDA, individuals who meet the following criteria can be a CP donor:

1. The individuals who are recovered from COVID-19, blood donor tests were done and suitable for donation;
2. Evidence of COVID-19 documented by a laboratory tests either by a diagnostic tests (eg, nasopharyngeal swab) at the time of illness, or a positive serological test for SARS- CoV- 2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID- 19 was suspected.
3. Individual's complete resolution of symptoms at least 14 days prior to donation.
4. Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
5. When measurement of neutralizing antibody titers is available, neutralizing antibody titers of at least 1:160 is recommended. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available

6.2. Pre-Donation Evaluation Of Donors :

1] Real time reverse transcriptase PCR (RTPCR) is currently a favored assay for the detection of coronavirus.. In this concern , corona virus pre donation screening tests should be supported by antibody detecting tests too. [52]

2] Female donors with a history of pregnancy should be screened for HLA antibodies in order to minimize the risk of transfusion- related acute lung injury (TRALI). Moreover, a blood sample should be obtained for antibody testing before referring the donor to an apheresis procedure.

3] There is uncertainty in the total antibodies or subclasses (eg, IgM, IgG, or IgA) are the optimal measures, and which antigen is most informative. [49] ,[50]

4] Current situation stated that CPs that are collected ≥14 days after resolution of symptoms contain high titers of antibodies. [50] , [52].According to FDA if testing can be conducted, neutralizing antibody titers should be at least 1:160 but a titer of 1:80 may be considered acceptable if an alternative matched unit is not available. [48]

6.3.Donor Recruitment

Blood centers may play a role in recruitment of donors in collaboration with partner

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hospitals. In Turkey, therapeutic apheresis centers licensed by the Ministry of Health and Turkish Red Crescent carry out activities for obtaining CP from donors.

VII. PATIENT SELECTION

There are several clinical trials that are ongoing which have very different eligibility criteria from the severely affected to post exposure individuals suffering from COVID 19.[53] The patient selection may vary between countries. The FDA allowed the use of CP to patients who met the criterias such as[48]:

A. Immediately life- threatening COVID- 19.
B. Laboratory confirmed COVID- 19.
a. Severe disease is defined as one or more of the following-
i. Dyspnea,
ii. Tachypnea ≥ hypnea
iii. Blood oxygen saturation ≤ 93%,
iv. $PaO_2/FiO_2 < 300$,
v. Respiratory failure,
vi. Lung infiltrates >50% within 24- 48 hours
vii. Multiple organ dysfunction.
viii. Septic shock,

VIII. DOSE OF CONVALSCENT PLASMA THERAPY:

In clinical trials, one unit of plasma (200 mL) is planned for use for prophylaxis and 1-2 units have been planned for treatment. The antibodies' duration of efficacy is unknown but is estimated to last in weeks to a few months since the dose received.[54], [55]

In the previous use of CP therapy in SARS, 5 mL/kg of plasma at a titer of 1:160 was used. [56] According to the linear proportionality, 3.125 mL/kg of plasma with the titer of >1:64 may provide an equivalent immunoglobulin level to one- quarter of 5 mL/kg plasma with a titer of 1:160. [57]

In pediatric transfusions, dose selected by body weight should be used. Covid-19 is rarely symptomatic in the pediatric age group. Therefore, every procedure and treatment in this age group should be performed within the scope of clinical research in cooperation with national and international health authorities.[57]

IX. ADAVANTAGES OF CONVALSCENT PLASMA THERAPY:

1] Plasma is also likely to contain antibodies against other common betacoronaviruses associated with the common cold, which have been shown to cross-react with SARS-CoV-2 antigens in intravenous immunoglobulin (IVIg) preparations [58], likely stemming from recent infection with another human betacoronavirus [59]

2] After demonstration that blood group O health care workers were less likely to become infected with SARS-CoV [60], a research group proved that anti-A blood group natural isoagglutinins (which can also be found in CP plasma from blood group O and B donors) inhibit SARS-CoV entry into competent cells [61]. Such binding could opsonize virions and induce complement-mediated neutralization [62]

3]Since SARS-CoV-2 uses the same receptor as SARS-CoV, anti-A isoagglutinins are expected to have similar effects against SARS-CoV-2 [63]; accordingly, clusters of glycosylation sites exist proximal to the receptor-binding motif of the S protein from both SARS-CoV [64] and SARS-CoV-2 [65]

X. LIMITATIONS OF CONVALSCENT PLASMA THERAPY:

The risks of CP administration are similar to those of standard plasma:

1] Infection with another infectious disease agent (viral transmission or bacterial contamination), immunological reactions such as serum disease, non- hemolytic transfusion reactions (tremors, fever, urticaria), transfusion- associated circulatory overload and full formcan be observed. [66]

2] The risk of TRALI is generally less than one for every 5000 transfused units, but in COVID- 19, the risk of TRALI is one of the major concerns about CP because most of the critically ill patients have ARDS and disseminated intravascular coagulation.

3] Specific risk about AntiSARSCoV2 CP is transfusion- transmitted SARS- CoV- 2. This remains theoretical because there has been no report of SARS- CoV- 2 transmission by blood transfusion. This risk is particularly important in prophylactic use since critically ill patients are already infected.

4] The other theoretical risk of CP is an antibodydependent enhancement (ADE). Antibodies that developed during a previous infectious disease caused by a different viral serotype may exacerbate clinical severity[67]. Previous infection with other types of corona virus may arise the concern about the risk of ADE in COVID- 19 and the geographic variation in disease severity may be attributed to this mechanism. [68]

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5] The other theoretical risk of CP is the attenuation of the development of a natural immune response, especially when administered for prophylaxis. CP treatment is recommended only in academic or comprehensive centers that can manage potential treatmentrelated complications, such as TRALI.[69]

No serious adverse events have been reported in any study of CP. In developed countries, for HIV, hepatitis B and hepatitis C viruses, the risk of transfusion- transmissible infection is less than one infection per two million donations. [70]

XI. FUTURE SCOPE OF CONVALSCENT PLASMA THERAPY:

Plasma Science and Technology offer their valuable contribution to human health since more than 50 years, after decades of experiences in the field of biomaterials; and more than a decade in using plasmas for therapeutic uses in medicine.

Plasma Science and Technology is blessed with a wealth of opportunities and potential applications exploitable in Biology and Medicine for human health.[70]The intrinsic motivation of cold plasma-related research in PlasmaMedicine, Sterilization/Decontamination, and Biomedical Materials is to see its translation into Health Science.

Despite the beauty and uniqueness of plasma technologies at low (LP) and atmospheric (AP) pressure, they actually show many challenges at the same time in many fields, most of all in Biology and Medicine, sometimes also beyond Science and Technology, as in the case of Ethic issues.

XII. CONCLUSION:

The exact treatment of COVID19 disease is currently unknown. Even though limited published studies are not prospective or randomized, until the development of vaccines or therapeutics, CP seems to be a safe and probably effective treatment for critically ill patients with COVID19. At least preliminary results of multi-centre randomized controlled clinical trials should be waited. Meanwhile, in this pandemic, scientists should be encouraged to collaborate on common research protocols, rather than conducting independent researches. International multicenter randomized controlled trials are needed. full form use should be encouraged to be made within the scope of clinical trials in cooperation with national and international health authorities.

REFERENCES:

[1]. N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang , J. Song, et al.A novel coronavirus from patients with pneumonia in China, 2019 N Engl J Med, 382 (2020), pp. 727-733,

[2]. J.F.-W. Chan, S. Yuan, K.-H. Kok, K.K.-W. To, H. Chu, J. Yang, et al. Lancet, 395 (2020), pp. 514-523,

[3]. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al.Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China Lancet, 395 (2020), pp. 497-506,

[4]. 4]
R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. W u, et al.Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding Lancet, 395 (2020), pp. 565-574

[5]. D. CavanaghCoronavirus avian infectious bronchitis virus Vet Res, 38 (2007), pp. 281-297

[6]. M.M. Ismail, A.Y. Tang, Y.M. SaifPathogen icity of turkey coronavirus in turkeys and chickens Avian Dis, 47 (2003), pp. 515-522

[7]. S. Su, G. Wong, W. Shi, J. Liu, A.C.K. Lai, J. Zhou, et al.Epidemiology, genetic recombination, and pathogenesis of coronaviruses Trends Microbiol, 24 (2016), pp. 490-502

[8]. World Health Organization . Coronavirus disease 2019 (COVID- 19) - Situation Report - 90 (April 19, 2020). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed April 19, 2020.

[9]. D. Cavanagh Coronavirus avian infectious bronchitis virus Vet Res, 38 (2007), pp. 281-297

[10]. G. Marano, S. Vaglio, S. Pupella, G. Facco, L. Catalano, G.M. Liumbruno, et al.Convalescent plasma: New evidence for an old therapeutic tool? Blood Transfus, 14 (2016), pp. 152-157

[11]. M.M. Ismail, A.Y. Tang, Y.M. SaifPathogen icity of turkey coronavirus in turkeys and chickens Avian Dis, 47 (2003), pp. 515-522

[12]. R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. W u, et al.Genomic characterisation and epidemiology of 2019 novel coronavirus:

Implications for virus origins and receptor binding Lancet, 395 (2020), pp. 565-574

[13]. G.Marano, S Vaglio, S Pupella , G Facco,L Catalano, G.M.L Liumbruno,et al Convalscent plasma : New evidence for an old therapeutic tool? Blood Transfus, 14(2016) , pp.152-157

[14]. T.Burnouf, J.Seghatchian Ebola virus convalescent blood products : Where we are now and where we may need to go Transfus Apher Sci 51(2014) pp.120-125

[15]. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, et al. (2016) Convalescent plasma: New evidence for an old therapeutic tool? Blood Transfus 14:152-157

[16]. J. Mair-Jenkins, M. Saavedra-Campos, J.K. Baillie, P. Cleary, F.-M. Khaw, W.S. Lim, et al.The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis J Infect Dis, 211 (2015), pp. 80-90

[17]. J.Van Griensven, T. Edwards, X. de Lamballerie, M.G. Semple, P. Gallian, S. Ba ize, et al.Evaluation of convalescent plasma for Ebola virus disease in Guinea N Engl J Med, 374 (2016), pp. 33-42

[18]. Luke TC, Kilbane EM, Jackson JL, et al. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006;145:599–609

[19]. Park WH, Freeman RG. The prophylactic use of measles convalescent serum. JAMA. 1926;87:556–558

[20]. Park WH. Therapeutic use of antipoliomyelitis serum in preparalytic cases of poliomyelitis. JAMA. 1932;99:1050–1053.

[21]. Rambar AC. Mumps: use of convalescent serum in the treatment and prophylaxis of orchitis. Am J Dis Child. 1946;71:1–13.

[22]. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52:447–456

[23]. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211:80–90.

[24]. Health Organization. Use of convalescent whole blood or plasma collected from patients recovered from Ebolavirusdisease.2014; https://www.who.int/csr/resources/publications/ebola/convalescenttreatment/en/. Accessed April 08, 2020.

[25]. P. Tiberghien, X. de Lambalerie, P. Morel, P. Gallian, K. Lacomb e, Y. YazdanpanahCollecting and evaluating convalescent plasma for COVID-19 treatment: Why and how Vox Sang (2020)

[26]. K. Duan, B. Liu, C. Li, H. Zhang, T. Yu, J. Qu, et al.Effectiveness of convalescent plasma therapy in severe COVID-19 patients Proc Natl Acad Sci U S A (2020)

[27]. J.-D. Tissot, O. GarraudEthics and blood donation: A marriage of convenience Press Medicale, 45 (2016), pp. e247-e252

[28]. E.M. Bloch, S. Shoham, A. Casadevall, B.S. Sachais, B. Shaz, J.L. Winters, et al.Deployment of convalescent plasma for the prevention and treatment of COVID-19 J Clin Invest (2020),

[29]. R.Y. Dodd, L.A. Crowder, J.M. Haynes, E.P . Notari, S.L. Stramer, W.R. SteeleScreening blood donors for HIV, HCV, and HBV at the American Red Cross: 10-year trends in prevalence, incidence, and residual risk, 2007 to 2016 Transfus Med Rev (2020)

[30]. S.K. Niazi, F.A. Bhatti, N. Salamat, E. Ghan i, M. TayyabImpact of nucleic acid amplification test on screening of blood donors in Northern PakistanTransfusion, 55 (2015), pp. 1803-1811

[31]. J.M. Bello-López, L. Delgado-Balbuena, D. Rojas-Huidobro, J. Rojo-MedinaTreatment of platelet concentrates and plasma with riboflavin and UV light: Impact in bacterial reduction Transfus Clin Biol, 25 (2018), pp. 197-203

[32]. R.J. Benjamin, L.S. McLaughlinPlasma components: Properties, differences, and uses Transfusion, 52 (Suppl. 1) (2012), pp. 9S-19S.

[33]. J.D. Lünemann, F. Nimmerjahn, M.C. Dalak asIntravenous immunoglobulin in neurology--mode of action and clinical efficacy Nat Rev Neurol, 11 (2015), pp. 80-89.

[34]. J. H. Ko et al Challenges of convalescent plasma infusion therapy in Middle East

respiratory coronavirus infection: A single centre experience. Antivir. Ther. 23, 617–622 (2018).

[35]. Convalescent Plasma Study Group J. Mair-Jenkins et al :Convalescent Plasma Study Group, The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. J. Infect. Dis. 211, 80–90 (2015).

[36]. Ebola-Tx Consortium , J. van Griensven et al .; Ebola-Tx Consortium, Evaluation of convalescent plasma for Ebola virus disease in Guinea. N. Engl. J. Med. 374, 33–42 (2016).

[37]. P. I. Lee, P. R. Hsueh, Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV. J. Microbiol. Immunol. Infect., in press.

[38]. L. Chen, J. Xiong, L. Bao, Y. Shi , Convalescent plasma as a potential therapy for COVID-19. Lancet Infect. Dis. 20, 398–400 (2020).

[39]. Y. Zhang, M. Xiao, S. Zhang, P. Xia, W. Ca o, W. Jiang, et al.Coagulopathy and antiphospholipid antibodies in patients with Covid-19 N Engl J Med, 382 (17) (2020), p. e38.

[40]. M. Ye, D. Fu, Y. Ren, F. Wang, D. Wang, F. Zhang, et al.Treatment with convalescent plasma for COVID-19 patients in Wuhan, China J Med Virol (2020)

[41]. H.U. Lutz, P.J. SpäthAnti-inflammatory effect of intravenous immunoglobulin mediated through modulation of complement activation Clin Rev Allergy Immunol, 29 (2005), pp. 207-212

[42]. M. Basta, F. Van Goor, S. Luccioli, E.M. Billings, A.O. Vort meyer, L. Baranyi, et al.F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins Nat Med, 9 (2003), pp. 431-438

[43]. L.E. Gralinski, T.P. Sheahan, T.E. Morrison, V.D. Menachery, K. Jensen, S.R. Leist, et al.Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis MBio, 9 (2018)

[44]. Y. Abe, A. Horiuchi, M. Miyake, S. Kimura Anti-cytokine nature of natural human immunoglobulin: one possible mechanism of the clinical effect of intravenous immunoglobulin therapy Immunol Rev, 139 (1994), pp. 5-19.

[45]. R. Kulkarni Antibody-dependent enhancement of viral infections BT - Dynamics of immune activation in viral diseases editor P.V. Bramhachari (Ed.), Dyn. Immune Act. Viral Dis, Springer Singapore, Singapore (2020), pp. 9-41,

[46]. A. Vatti, D.M. Monsalve, Y. Pacheco, C. Ch ang, J.-M. Anaya, M.E. GershwinOriginal antigenic sin: A comprehensive review J Autoimmun, 83 (2017), pp. 12-21

[47]. S.-F. Wang, S.-P. Tseng, C.-H. Yen, J.-Y. Yang, C.-H. Tsao, C.-W. Shen, et al.Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins Biochem Biophys Res Commun, 451 (2014), pp. 208-214.

[48]. FDA . Investigational covid- 19 convalescent plasma—emergency INDs. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ideprocess-cber/investigational-covid-19-convalescent-plasma-emergency-inds. Accessed May 11, 2020.

[49]. Lu CL Murakowski DK Bournazos S et al. Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 in vivo.Science. 2016; 352: 1001-1004

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

[51]. Luke TC Kilbane EM Jackson JL Hoffman SL Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment?.Ann Intern Med. 2006; 145: 599-609

[52]. Schoofs T Klein F Braunschweig M et al. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1.Science. 2016; 352: 997-1001

[53]. https://clinicaltrials.gov/ct2/results?cond=co nvalescent+plasma. Accessed May 11, 2020.

[54]. Casadevall A, Scharff MD. Return to the past: the case for antibody- basedtherapies in infectious diseases. Clin Infect Dis. 1995;21:150- 161.

[55]. Casadevall A. Passive antibody administration (immediate immunity) as aspecific defense against biological

weapons. Emerg Infect Dis. 2002;8:833- 841.

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

[57]. Bloch EM, Shoham S, Casadevall A, et al. Deployment ofconvalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020;130:2757-2765. 10.1172/JCI138745.

[58]. Díez J-M, Romero C, Gajardo R. 2020. Currently available intravenous immunoglobulin (Gamunex©-C and Flebogamma© DIF) contains antibodies reacting against SARS-CoV-2 antigens.

[59]. Ng K, Faulkner N, Cornish G, Rosa A, Earl C, Wrobel A, Benton D, Roustan C, Bolland W, Thompson R, AguaDoce A, Hobson P, Heaney J, Rickman H, Paraskevopoulou S, Houlihan CF, Thomson K, Sanchez E, Shin GY, Spyer MJ, Walker PA, Kjaer S, Riddell A, Beale R, Swanton C, Gandhi S, Stocking er B, Gamblin S, McCoy LE, Cherepanov P, Nastouli E, Kassiotis G. 2020. Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans.

[60]. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PKS, Ng MHL, Sung JJY, Wong R. 2005. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 293:1450–1451. doi:10.1001/jama.293.12.1450-c.

[61]. Guillon P, Clément M, Sébille V, Rivain J-G, Chou C-F, Ruvoën-Clouet N, Le Pendu J. 2008. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 18:1085–1093. doi:10.1093/glycob/cwn093.

[62]. Neil SJ, McKnight A, Gustafsson K, Weiss RA. 2005. HIV-1 incorporates ABO histo-blood group antigens that sensitize virions to complement-mediated inactivation. Blood 105:4693–4699. doi:10.1182/blood-2004-11-4267.

[63]. Breiman A, Ruvën-Clouet N, Le Pendu J. 2020. Harnessing the natural anti-glycan immune response to limit the transmission of enveloped viruses such as SARS-CoV-2. PLoS Pathog 16:e1008556. doi:10.1371/journal.ppat.1008556.

[64]. Han DP, Lohani M, Cho MW. 2007. Specific asparagine-linked glycosylation sites are critical for DC-SIGN- and L-SIGN-mediated severe acute respiratory syndrome coronavirus entry. J Virol 81:12029–12039. doi:10.1128/JVI.00315-07.

[65]. Kumar S, Maurya VK, Prasad AK, Bhatt M LB, Saxena SK. 2020. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). Virusdisease 31:13–21. doi:10.1007/s13337-020-00571-5.

[66]. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg. 2009;108:759- 769.

[67]. Katzelnick LC, Gresh L, Halloran ME, et al. Antibody- dependent enhancement of severe dengue disease in humans. Science. 2017;358:929 Tetro JA. Is COVID- 19 receiving ADE from other oronaviruses? Microbes Infect. 2020;22:72-73.

[68]. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schroder AS, Burdelski C, deHeer G, Nierhaus A, Frings D, Pfefferle S, Becker H, BrederekeWiedling H, deWeerth A, Paschen HR, SheikhzadehEggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Puschel K, Kluge S. 6 May 2020. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med doi:10.7326/ m20-2003.

[69]. I. Adamovich, S. D. Baalrud, A. Bogaerts, P. J. Bruggeman, M. Cappelli, V. Colombo, U. Czarnetzki, U. Ebert, J. G. Eden, P.Favia, D. B. Graves, S. Hamaguchi, G. Hieftje, M. Hori, I. D. Kaganovich, U. Kortshagen, M. J. Kushner, N. J. Mason, S. Mazouffre, S. M. Thagard, H. R. Metelmann, A. Mizuno, E. Moreau, A. B. Murphy, B. A. Niemira, G. S. Oehrlein, Z. L. Petrovic, L. C. Pitchford, Y. K. Pu, S. Rauf, O. Sakai, S. Samukawa, S. Starikovskaia, J. Tennyson, K. Terashima, M. M. Turner, M. C. M. van de Sanden, A. Vardelle, J. Phys. D Appl. Phys. 2017, 50, 323001.