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Original Research Paper

Pathology

TRALI AND ITS ASSOCIATED RISKS TO COVID-19 PATIENTS ADMINISTERED WITH CONVALESCENT PLASMA THERAPY: A REVIEW

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ABSTRACT As the months progress, the world still seems lacking behind the definitive treatment or vaccine options against COVID-19. The numbers of patients suffering from active COVID-19 infections are rising drastically across the world, scientists are close to deciding on some promising drug, vaccine candidates and clinical trials are on at multiple centers to test the safety and efficacy of these options. Amongst the many scientific approaches following up the term that seem to have entered common parlance with COVID-19 is Convalescent Plasma Therapy (CPT) a treatment which involves injecting the COVID-19 patient with convalescent sera of person who has recovered from the infection recently has been the subject of increasing attention. With researchers hoping that CPT can be given to people with severe COVID-19 to boost their ability to fight the virus, Studies are underway to evaluate the efficiency of CPT as a treatment for those with serious life threatening COVID-19. Its efficiency depends on whether the disease produced a lot of antibodies in the affected patient. The current article explains a vivid picture as to how the therapy has many hidden disadvantages and associated risks like Transfusion-related acute lung injury (TRALI), which is a fatal adverse effect of transfusion characterized by sudden acute respiratory distress. Drastic changes are seen causing complement activation which results in influx of neutrophils into the lungs and leads to the damaging of the pulmonary microvasculature with marked hypoxemia, hypotension, fever, and severe bilateral pulmonary edema. This serious pulmonary syndrome having a mortality rate of 47% should not be taken for granted, the recommendations mentioned in this article are necessary to follow so that the sample used can be tested to prevent TRALI in the affected/other COVID-19 recipients who are severely ill and can be subjected to death from TRALI rather than combating the novel COVID-19.

KEYWORDS : Convalescent Plasma Therapy, Transfusion-related acute lung injury (TRALI), COVID-19

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named as coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) currently, has no approved specific antiviral agents targeting the novel virus, while some drugs are still under investigation, no official drug of choice has been approved. [1] Since the effective vaccine and specific antiviral medicines are unavailable, it is an urgent need to look for an alternative strategy for COVID-19 treatment, especially among severe patients. [2]Since a regulatory approach rather than solely a medical practice using convalescent plasma or serum in the treatment of MERS-CoV has shown advantages in promoting patient safeguards it is expected same for the treatment of COVID-19. [3] Convalescent Plasma Transfusion (CPT) treatment which involves injecting the COVID-19 patient with convalescent sera of people who has recovered from the infection recently has been the subject of increasing attention. [4] With a very long history of use in the treatment of infectious disease, CPT has been accounted to be used during the outbreak of many diseases such as in the case of Influenza A (H1N1) pdm09 and Spanish Influenza A (H1N1) in 1915-1917 but to every advantage this plasma therapy brings there are associated disadvantages the most common being Transfusion-related acute lung injury (TRALI) [5-7]

The third leading cause of transfusion related death in the United States, Transfusion-related acute lung injury (TRALI) is a life-threatening adverse effect of transfusion characterized by sudden acute respiratory distress.[8] With the majority of deaths associated with fresh frozen plasma transfusions, on a clinical basis TRALI is well-marked by symptoms including dyspnea, fever, hypotension and hypoxemia of SpO2 less than 90% on room air with a ratio of partial pressure of oxygen to a fractional inspired oxygen concentration of less than 300 mmHg. [9-12] Not only diagnosed clinically, diagnosis can be made clear with radiographic findings, the radiological picture is of bilateral pulmonary infiltrates without evidence of cardiac compromise or fluid overload. [13] Symptoms typically begin 1-2 hours after transfusion and are fully manifested within 1-6 hours. [14] Diagnostic criteria for TRALI are when the symptoms develop during or within 6 hours of transfusion without any risk factors for developing acute lung injuries such as sepsis from pneumonia, aspiration, and shock. [15, 16]

Convalescent Plasma Therapy

Most people who recover from COVID-19 develop antibodies (proteins that the immune system produces in response to infection) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). [17-19] Antibodies are found in plasma, the yellow plasma is collected from donors who have recovered from COVID-19 through a process called apheresis, which uses a special machine to separate the blood into different components. [20] The plasma is removed, while the rest of the blood components are returned into the donor's body. As with all blood products, convalescent plasma is thoroughly tested before use. [21] All donated blood is screened for blood type compatibility as well as infections like hepatitis B and C, HIV, and many other less common infections. SARS-CoV-2 is not spread by blood, and there is no risk of transmission from recovered donors. [22]

As CP production requires high quality standards, it must be free of any infection, so tests for human immunodeficiency virus (HIV), syphilis, hepatitis C, hepatitis B, human T-cell lymphotropic virus 1 and 2, should be performed There is not a standard transfusion dose of CP. [21] In different studies for corona viruses the administration of CP ranges between 200 and 500 mL in single or double scheme dosages. Composition of CP is variable and includes a wide variety of blood derived components. [21] Plasma contains a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins. These factors may influence the immunomodulatory effect of CP in patients with COVID-19 [22]

Multiple published and unpublished studies have now reported on the use of convalescent plasma to treat severely or

critically ill COVID-19 patients, without unexpected or serious adverse events. [23] Many patients improved clinically and cleared the virus, however the role of the convalescent plasma treatment in these patients is unclear, because all patients received at least one additional therapy, including antivirals, antibiotics or antifungals, and corticosteroids. [24] In the sole randomized controlled trial reported to date, patients with severe disease, but not incubated patients with critical disease, receiving convalescent plasma showed more frequent and faster clinical improvement compared to controls, however the trials was terminated early due to lack of eligible patients at the study sites and because of the provided associated risks.[25]

ASSOCIATED RISKS

The risk of contracting COVID-19 infection from receiving convalescent plasma therapy hasn't been tested yet. Concerns include potential worsening of immune-mediated tissue damage via the poorly understood phenomenon of antibody-dependent enhancement (ADE), and blunting of endogenous immunity to the virus. [25] Known risks of plasma transfusion include allergic reactions, transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI) as with any plasma or blood transfusion are expected. [26] From the past researches it has been observed that Convalescent plasma therapy carries the risk of:

- Allergic reactions
- Lung damage and difficulty breathing
- Transmission of infections, including HIV and hepatitis B and C

TRALI

It appears that unlike allergic or anaphylactic immune-mediated transfusion reactions, antibodies implicated in TRALI are usually of donor origin. [27] TRALI is caused by damage to pulmonary vasculature from neutrophil-mediated in forms of human neutrophil antigen (HNA) or human leukocyte antigen (HLA) antibodies in donor blood which bind to antigens of a recipient. [28] Once transferred to the recipient, these antibodies may cause complement activation resulting in neutrophilic influx into the lungs and damage to the pulmonary microvasculature. [29] The antigen-antibody reaction activates neutrophils in the lung microcirculation, releasing oxidases and proteases that damage blood vessels and make them leak.[30] The clinical result may be subtle or significant. In either case, there is typically a marked hypoxemia, hypotension, fever, and severe bilateral pulmonary edema. Respiratory support should be as intensive as dictated by the clinical picture. [30]

TRALI can happen in healthy patients who are transfused with plasma that have high amounts of antibodies whose neutrophil has already activated. Higher TRALI incidence was reported with plasma from female donors because the literature found parous female donors with multiple HLA antibodies. [31] Female donor plasma has larger quantities of anti-HLA class II and HNA positive antibodies. The diagnosis of TRALI is particularly challenging in complex inpatients such as those encountered in the intensive care unit setting, given that such patients often have multiple medical problems and may exhibit some symptoms of TRALI even before transfusion.[32]

Pathophysiology

The exact mechanism of TRALI is quite uncertain so far, a "two-hit" process has been proposed for the same. [33] According to the hypothesis, the first "hit" is induced by an underlying condition, such as trauma or sepsis, in this case patients dealing with COVID-19 which primes granulocytes and/or activates endothelial cells, thereby causing neutrophils to become sequestered in the pulmonary vasculature. [33] The second "hit" results from passive infusion of donor antibodies in the blood product that is the Convalescent plasma therapy that recognize either human leukocyte antigens (HLA) on recipient endothelial cells or human neutrophil antigens (HNA) on recipient neutrophils. [34] Alternatively (or in addition), infusion of biologic response modifiers (e.g., CD40 ligand) in the plasma portion of the donor product could induce the second hit. [35] Together, these processes induce capillary endothelial damage, resulting in vascular permeability and pulmonary edema and eventually causing Transfusion related acquired lung injury (TRALI) [36, 37](Fig1 and 2)

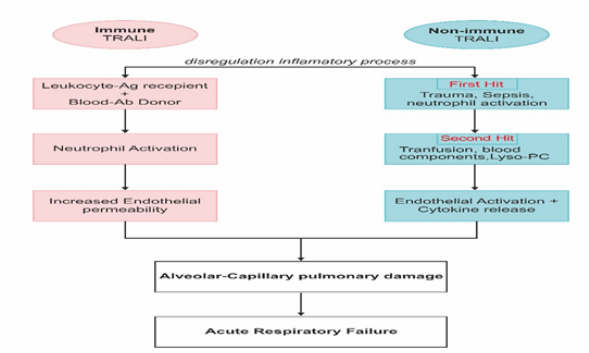

Fig 1. Pathophysiology Of Immune And Non-immune TRALI

First Hit (Patient factors)	Second Hit (Transfusion factors)
- Sepsis	**RBC (Erythrocyte)**
- Hematologic malignancy	- HLA/HNA
- Heart surgery	- Bio-active lipids
- Mechanical ventilation	- sCD40L
- Age of patients	- Aged erythrocyte
- Massive blood transfusion	**Fresh Frozen Plasma**
- Chronic alcohol abuses	- HLA/HNA
- Shock	**Platelets**
- Severe liver disease	- HLA/HNA
- Spine Surgery	- Bio-active lipids
- Liver Surgery	- sCD40L
- Acute renal failure	

Fig2. Factors Associated With 'first Hit" And "second Hit"

Since COVID-19 is a serious issue to combat it with the convalescent plasma therapy every associated risk should be properly diagnosed especially TRALI, It is unlikely that TRALI can ever be entirely prevented, but its frequency may be reduced by diagnosing TRALI correctly and consistently. [38] Few necessary things required include, Timing of transfusion with respect to symptom onset. Presence of other risk factors for acute lung injury like severe sepsis, Shock, Multiple traumas should be kept in mind before making a complete prognosis. [39]

Recommendations

The diagnosis and management of TRALI is not simple and is best done with an inter-professional team that includes a hematologist, cardiologist, pulmonologist, internist, and a specialty trained nurse experienced with the care of these patients. [40] Despite suspected various hypotheses; it could certainly be prevented with the careful approach in blood transfusions, especially in those who are more vulnerable to acquire TRALI [40]

1. Be alert that any respiratory distress occurring during or following blood or blood component(s) transfusion could potentially be TRALI. Discontinue the transfusion

immediately begin oxygen and supportive therapy.
2. Administer supplemental oxygen and employ ventilation as necessary. If left untreated this might become a medical emergency; support blood pressure and maintain an open airway.
3. Notify the Blood Center that supplied the blood component and return remaining product to be tested for anti-HLA and/or anti-granulocyte antibodies in the donor.
4. Supportive measures must be taken to improve oxygenation. Although there is no specific treatment for TRALI, low tidal volume application is feasible in this case.
5. Despite suspected various hypotheses; it could certainly be prevented with the careful approach in blood transfusions, especially in those who are more vulnerable to acquire TRALI. Due to no definitive treatment, prevention is the best key to keep TRALI from occurring by treating underlying diseases first. [41]

The above recommendations are necessary to follow so that the sample used can be quarantined and test related components from the same donor to prevent TRALI in other COVID-19 recipients who are severely ill and can be subjected to death from TRALI rather than combating the novel COVID-19.

CONCLUSION

The diagnosis and management of TRALI is not simple and is best done with an inter-professional team that includes a hematologist, cardiologist, pulmonologist, internist, and a specialty trained nurse experienced with the care of these patients. [42] Researchers hope that convalescent plasma can be given to patients with severe COVID-19 to boost their ability to fight the virus. Studies are underway to evaluate use of convalescent plasma as treatment for patients with severe COVID-19 and to prevent infection (prophylaxis) in certain high-risk patients exposed to COVID-19. Convalescent plasma might provide immunity by giving patients neutralizing antibodies for SARS-CoV-2. [43] Although there is a lot that is unknown, convalescent plasma may work best for patients earlier in the disease course. Currently, convalescent plasma is being given to small numbers of hospitalized patients with severe or life-threatening COVID-19 illness. [44] Several case reports suggest treatment is helpful while others still discard it because of the disadvantages provided therefore larger studies are still needed for a large scale use of this therapy at such a drastic pandemic without providing any associated risks.

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