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Blood Safety in SARS-CoV-2 Infection

Mozhgan Hashemieh [1, *]

[1]Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Associated Professor of Pediatric Hematology and Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: mozhganhashemieh@gmail.com

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Abstract

SARS-CoV-2 is a novel infectious agent that rapidly spread from a single city in China to all parts of the world. Right now, the world is facing a major pandemic crisis and every infected patient can infect the other two to three persons. The non-specific symptoms at the early stages of coronavirus 2019 (Covid-19) and also the presence of infected asymptomatic patients result in the absence of accurate estimation of infected patients. Although coronaviruses often affect the upper or lower respiratory tract, viral shedding in plasma or serum can occur and therefore, there is a theoretical risk regarding the transmission of these viruses by transfusion. Experience with other viruses from the corona family group (SARS-CoV and MERS-CoV) tells us that Covid-19 might have a significant impact on blood supply. Until now, SARS-CoV-2 has not been identified as a transfusion transmissible virus and viremia has only been diagnosed in serious patients who would not be allowed for blood donation. In this review article, the safety of blood products during the Covid-19 outbreak is discussed.

Keywords: Covid-19, Blood, Transfusion, SARS-CoV-2

1. Context

The outbreak of coronavirus 2019 (Covid-19) in Wuhan city, China, was announced for the first time, on January 31, 2020, by the world health organization (WHO) (1). The source of the majority of initial cases was from a seafood market, but this virus quickly spread in other parts of China and then disseminated worldwide (2). Similarly, in February 2003, severe acute respiratory syndrome (SARS) was reported as a new public health problem. The clinical presentation of SARS included fever, dry cough, dyspnea, malaise, headache, and hypoxemia. More than 8,000 patients were affected and 9% - 10% of SARS patients died (3). Also, in September 2012, 2,494 cases of infection with Middle East Respiratory Syndrome coronavirus (MERS-CoV) were identified and WHO reported 858 deaths due to this virus. These three infections are all caused by coronaviruses (1). Coronaviruses are large RNA viruses that have been divided into four subtypes: alpha, beta, gamma, and delta. Alpha and beta subtypes can infect mammals (4, 5). The Covid-19 is a life-threatening emergency for public health worldwide (6). The most important symptom is fever, which was identified in 3.8% of patients at first presentation, but 88.7% of patients became febrile at the time of hospitalization. Cough is another principal symptom of the disease (6). Gastrointestinal symptoms are not common, which differs from SARS-CoV and MERS-CoV, and it shows that SARS-CoV-2 has different tropism in comparison with two previous coronaviruses (7, 8). The absence of fever is also more common in Covid-19 compared with SARS-CoV and MERS-CoV (6). Another major dominant symptom is lymphocytopenia that may sometimes be severe (9, 10). The other common symptoms include sputum production, dyspnea, sore throat, headache, myalgia, and arthralgia (11). Approximately 80% of the reported patients in China had mild to moderate form of the disease and 13.8% had severe disease. In 6.1% of cases, the disease was so critical that conditions such as septic shock, respiratory failure, and multiorgan damage were developed (12). As mentioned before, this virus can be transmitted from person to person via respiratory droplets and by touching droplet-contaminated surfaces of objects and then touching the mouth or nose or eyes (13). Multiple published articles have reported that many cases of Covid-19 are asymptomatic and only some of them would develop a clinical disease (14-17). Population groups, which have more severe disease and also a higher mortality rate, include age over 60 years, male patients and cases with an underlying condition such as diabetes mellitus, cancer, immunodeficiency, hypertension, cardiovascular disease, and chronic respiratory disorders (18). Children and neonates could be infected with Covid-19, but it seems that the course of dis-

ease in children is milder than adults (12). The median incubation period of this virus is 5 to 6 days, with a range of 1 - 14 days (19, 20). The RNA of SARS-CoV-2 has been isolated from respiratory tract specimens, whole blood, serum, urine, feces, saliva, and even tears (12). In a study by Chen et al. on 57 Chinese patients, six out of them had viremia and in these patients, more severe disease developed (21). Although many researchers have detected viral RNA from plasma or serum of infected cases with three types of coronaviruses during different periods of infection, identification of viral RNA by polymerase chain reaction (PCR) does not mean the detection of intact infectious virus (1). So far, no transmission of SARS-CoV-2 by transfusion has been reported (22), but the detection of asymptomatic patients and their probable role in transmission by transfusion is worthy of consideration (1).

2. Comparison of SARS-CoV-2 with Older Generations

In SARS infection, the incubation period was short, and the patients were not infectious in this period. Moreover, the majority of infected cases with SARS-CoV had severe symptoms and only few asymptomatic patients have been detected. The viral load of patients with SARS infection is low and until now no transfusion-transmitted case has been reported. Moreover, the American Association of Blood Bank (AABB) has reported that researchers failed to isolate MERS-CoV from MERS patients. In other words, the viral load of MERS is reported to be low. Therefore, FDA declares that the deferral criteria for donors are similar between SARS-CoV and MERS-CoV infections, so donors can donate blood 14 days after the last exposure or 28 days after complete resolution of symptoms and cessation of the treatment. However, patients who are infected with Covid-19 might be infectious during the incubation period and viral RNA could be isolated from plasma or serum in the first two to three days after the beginning of the symptoms. The rate of infectivity during the incubation period is uncertain. Also, the viral load of Covid-19 in the plasma or serum of patients is not clear so far (1). In January 2020, the European Center for Disease Prevention and Control announced that individuals could not donate blood for 21 days after possible exposure to a confirmed patient with Covid-19. Meanwhile, documented Covid-19 patients should be deferred for blood donation for at least 28 days after the resolution of symptoms or discontinuation of the treatment (23).

3. Inactivation of Covid-19 in Blood Products

After the outbreak of SARS and MERS, a few studies evaluated the pathogen inactivation/reduction technologies (PRTs). Some blood products could be damaged by PRT; therefore, a single PRT is not advised for all blood products (24, 25). Two principal methods for the inactivation of viruses are heat and solvent/detergent (S/D). Darnell et al. have reported that heating 60°C for 15 to 30 minutes is sufficient for diminishing the SARS-CoV from plasma without cells (26). Also, Yunoki et al. have shown that virus inactivation for plasma products could be performed by 60 0C of heat for 10 hours (27). However, heating results in denaturation of proteins in blood components, so it could be used only in manufactured plasma-derived products. Solvent detergents such as TNBP/Triton X-100, TNB/Tween 80, and sodium cholate could inactive SARS-CoV (26). Moreover, illumination with various wavelengths could inactivate SARS and MERS viruses. Ultraviolet A and B with amotosalen or riboflavin could affect the virus nucleic acid, and UV-C light alone could inactivate the virus. Furthermore, visible light plus methylene blue could influence the virus and inactivate it (28-30). The use of PRT for whole blood is doubtful, and so there are no studies about inactivation of coronavirus in whole blood. However, PRT methods are expensive and therefore, the introduction of PRT for Covid-19 would not be cost-effective and is not recommended. Another risk of PRT is damage to some blood products, especially platelets, which may lead to a higher dose requirement in patients (31). Moreover, the lack of PRT methods for red blood cells is another problem for the inactivation of the virus for safety of blood products (31). Transmission of SARS-CoV-2 via blood and blood products is only theoretical. Covid-19 is an enveloped virus, and the current production process for plasma derivatives could inactivate this virus. It seems that there is no risk for transmission via plasma derivatives (32). The main concern in this time is the reduction of blood supply during the Covid-19 pandemic due to blood donor reluctance or the danger of infectivity of the donors (32, 33).

4. Strategies for Reduction of Risk of Transmission Via Blood or Blood Products

Respiratory viruses such as coronaviruses have never been reported to be transmitted via blood or blood products and the risk of transmission is only theoretical (33). However, it seems that the possibility of transmission of these viruses through blood transfusion during the incubation period or from asymptomatic individuals needs further investigation (31). There are strategies proposed to diminish the risk of transmission of SARS-CoV-2 via blood and blood products. Donors with signs and symptoms of fever, cough or shortness of breath are avoided to donate blood and potential donors should be educated to inform in case of developing a respiratory disease within 28 days

of blood donation. Also, individuals who have recently recovered from confirmed Covid-19 and those with a history of direct exposure to a confirmed case should avoid blood donation for 28 days. In situations with widespread illness, an option for reducing the risk of transmission via transfusion is the quarantine of blood components with delayed-release into the blood bank pool. This strategy may be problematic for platelet concentrates due to the short half-life of this component. The staff working in blood bank centers should be educated about signs and symptoms of Covid-19 and refrain from working if they feel unwell (32). Donors with a history of Covid-19 could donate blood 28 days after complete recovery. Moreover, the collection of convalescent plasma is possible from these donors for the treatment of patients with Covid-19 (34, 35).

5. Organizing the Demand for Blood

The outbreak of Covid-19 has an unfavorable impact on blood supply; hence, the management of demand for blood and blood products is a critical decision. During the pandemic of Covid-19, the health care system shifts toward patients who have been infected. In this phase, the cancellation of all elective surgeries and also non-urgent medical interventions has been strongly recommended. However, in emergency situations such as trauma, post-partum hemorrhage and urgent surgeries, blood transfusion is necessary and lifesaving (32). Also, in hemoglobinopathies such as thalassemia and sickle cell disease, patients are transfusion-dependent and need repeated blood transfusions in order to survive. Therefore, decision making about indications of blood transfusions within outbreaks of Covid-19 is an important topic (36, 37).

6. Discussion

Covid-19 is a newly emerging virus that has affected almost all countries worldwide. This virus is now spreading around the world and has animal to person as well as person to person transmission. According to Chinese authors, each infected case could infect two to three additional people. The virus RNA has been detected in the blood of 15% of the patients. However, there is no clear evidence for blood-borne transmission of this virus (38). One of the most controversial topics is the potential of virus transmission via blood and blood products. In many blood bank centers, the measurement of body temperature before blood donation is suggested. Also, blood donors are provided with questionnaires regarding symptoms of fever, cough, and dyspnea. Furthermore, donors should be educated to inform in case of developing any symptoms of Covid-19 after blood donation (1).

There are a number of key questions about the transmission of this novel virus via the transfusion of blood products. It is not yet clear if there is viremia before the affected person is symptomatic or there would be enough quantity to result in clinical infection in blood recipient. In other words, it is unclear that viremic period would have a potential risk to the recipient of blood products (39).

Except for adenoviruses, all respiratory viruses attach to the receptors of the respiratory tract (40). Huang et al. in a study on patients with Covid-19, evaluated the results of PCR testing of serum samples and showed a very low viral load in these patients (9). One of the most effective strategies to reduce the risk of transmission through blood products is the exclusion of at-risk donors. As it was mentioned before, any individual with possible exposure to a confirmed case of Covid-19 should avoid blood donation. Recovering patients are also not eligible for blood donation until 28 days after symptom resolution.

Another issue is that if any additional procedure is necessary during the procedure of blood collection (31). To know more precisely whether the risk of transmission of SARS-CoV-2 by transfusion is higher than the other coronaviruses, further investigation is required (1). The routine use of PRT methods in transfusion medicine for all blood products is controversial since some blood components are damaged by this method and these methods impose a high cost on blood banking services (24, 25). Therefore, whether these PRTs should be applied depends on the severity and prevalence of SARS-COV-2 in various parts of the world.

The actual risk of transmission of Covid-19 by transfusion is another issue that could affect this decision (1). Nucleic acid testing (NAT) is a reliable method for the detection of transfusion-transmitted viruses; hence this method could prevent the spread of the emerging infection via blood products (3). For the first time, NAT-based methods detected SARS-CoV during the outbreak of this virus in 2003. Antibodies of SARS could be measured in patients on day 16 (41-43). Therefore, NAT is the sole method for the detection of SARS-COV in the early phase of the disease or persons with mild symptoms (44). SARS-CoV-2 is a novel agent and there is not sufficient information about the validity of any test as a screening test for asymptomatic blood donors. In fact, NAT is probably the most reliable test but is expensive; additionally, there is not enough experience in its usage.

7. Conclusion

SARS-CoV-2 is an infectious agent that has become a global health threat. The Covid-19 outbreak is transmitted mainly by the respiratory route and the probability

of transmission by transfusion is just a matter of theory. According to the current knowledge, there is no evidence that this virus may be transmitted by blood or blood products; however, Covid-19 is a novel viral agent and the risk of transmission of SARS-CoV-2 by transfusion of blood products cannot be excluded with confidence.

On the other hand, decreased availability of blood donors could result in the shortage of blood supply, which could be a significant hazard for blood services in every country. It seems that a lot of time is necessary to answer key questions regarding blood safety in the field of Covid-19.

Footnotes

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