Short Communication:
Autologous Placenta-derived Mesenchymal Stem Cell Transplantation for Labored Pregnant Patients With COVID-19

Nazanin Ashtar Nakhaei[1], **Amir Hossein Norooznezhad**[2*]

1. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
2. Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.

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Citation Ashtar Nakhaei N, Norooznezhad AH. Autologous Placenta-derived Mesenchymal Stem Cell Transplantation for Labored Pregnant Patients With COVID-19. Immunoregulation. 2021; 4(1):17-20. http://dx.doi.org/10.32598/Immunoregulation.4.1.5

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Article info:
Received: 13 May 2021
Accepted: 23 May 2021
Available Online: 01 Jul 2021

Keywords:
Coronavirus Disease 2019 (COVID-19), Inflammation, Cytokine storm, Mesenchymal stem cells, Cell therapy

ABSTRACT

Coronavirus Disease 2019 (COVID-19) is one of the most critical health issues in the world. According to the findings, systemic proinflammatory cytokine release is associated with the pathogenesis of cytokine storm, contributing to morbidities and even mortality in patients diagnosed with COVID-19. Among pregnant patients diagnosed with COVID-19, preterm labor is one of the most crucial side effects, with a prevalence of up to 63.8% in some studies. As well as cytokine storm, proinflammatory cytokines are involved in preterm labor. Mesenchymal Stem Cells (MSCs) transplantation has been used in different trials to suppress inflammation in many inflammatory diseases. MSCs have also been successfully applied to treat patients diagnosed with COVID-19, considering the cytokine storm in these patients. So, it is possible to use the transplantation of MSCs derived from the maternal side of the placenta as an autologous product to suppress cytokine storm in critically ill patients diagnosed with COVID-19. The autologous transplantation of MSCs helps to suppress cytokine storm and systemic inflammation. Inhibition of systemic cytokine release could prevent poor outcomes, especially mortality and morbidities in the mentioned patients.

1. Introduction

According to The World Health Organization, coronavirus disease 2019 (COVID-19) has become an international emergency [1]. One of the most important causes of death in the patients is cytokine storm caused by the excess release of proinflammatory cytokines. Thus, alleviating the systemic inflammation following this cytokine storm has been suggested as an essential treatment strategy for critically ill patients with COVID-19 [2, 3].

As well as other sub-populations, COVID-19 has been studied in pregnant women. Similar to the normal population, SARS-CoV-2 infection in pregnant women

* **Corresponding Author:**
Amir Hossein Norooznezhad, MD.
Address: *Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.*
Phone: *+98 (918) 8564304*
E-mail: *norooznezhad@gmail.com*

could present with various clinical manifestations from asymptomatic to severe symptoms [4]. The severity of COVID-19 is associated with the level of some of the proinflammatory cytokines [5]. Other than non-pregnancy-related morbidities, which could be found in all populations, preterm labor is an essential complication in pregnant women with COVID-19. According to the studies, the rate of preterm labor in women diagnosed with SARS-CoV-2 infection is up to 21.2% of total deliveries [6]. However, systematic reviews have mentioned other rates from 39% [7] to 63.8% [8]—all of them are notable rates. From the pathophysiological aspects, inflammation (sterile and or non-sterile types) is one of the most important causes of preterm labor. Thus, considering the association between proinflammatory cytokines release and preterm labor [9], it seems that the cytokine storm is responsible for some of the non-pregnancy-related morbidities/outcomes, including preterm labor. When preterm labor occurs due to the cytokine storm in a pregnant woman with COVID-19, the anti-inflammatory treatment is necessary to prevent other inflammatory dependent outcomes (such as septic shock) and to decrease mortality and morbidities in the patient.

Hypothesis

Autologous Mesenchymal Stem Cells (MSCs) derived from the maternal side of placental from critically ill pregnant women with preterm labor could help suppress cytokine storm and systemic inflammation. Inhibition of systemic cytokine release could prevent poor outcomes, especially mortality and morbidities in the mentioned patients.

Evaluation of hypothesis

Human-derived MSCs are among the most powerful immunomodulatory agents widely used in cell-based therapies [10]. So, due to their immunomodulatory effect, these cells are suggested for preventing or attenuating the cytokine storm. MSCs' safety and effectiveness have been demonstrated in many clinical trials, especially in immune-mediated inflammatory diseases, such as graft-versus-host disease [11] and systemic lupus erythematosus [12]. The immunomodulation effect of the MSCs is achieved through paracrine secretion of cytokines or direct interaction with immune cells and their toll-like receptors activation by double-stranded RNA from a virus such as coronaviruses [13, 14]. MSCs promote the survival of monocytes and induce differentiation toward macrophage M2 anti-inflammatory phenotype that expressed CD206 and CD163. In addition, activated MSCs secrete Prostaglandin E2 (PGE2) that drives resident macrophages with an M1 proinflammatory phenotype toward an M2 anti-inflammatory phenotype. Also, MSCs exert their immune suppressive potential through cell-cell contact and by secretion of immune regulatory molecules. MSCs display broad immunomodulatory properties, including inhibiting the proliferation and function of T cells, natural killer T cells, T regulatory cells, B cells, and dendritic cells. However, several soluble factors play a significant role in the immunosuppressive effects of MSCs. These compounds include PGE2, Ttransforming Growth Factor (TGF)-β1, indoleamine 2,3-dioxygenase, nitric oxide, hepatocyte growth factor, and interleukin-10 [15, 16]. Also, the antimicrobial role of MSCs has been reported [17], which could be effective for those COVID-19 patients with secondary bacterial infections such as hospital-acquired infections, especially in intubated patients.

MSCs, as well as other stem cells, could be used in two forms of autologous and allogenic considering their source. After years of trials, a 2020-systematic review and meta-analysis have shown a "favorable safety" of MSCs transplantation (both autologous and allogenic) according to the performed studies [18]. However, some studies have raised concerns regarding the use of allogenic MSCs transplantation. Some studies have shown that proinflammatory cytokines could affect MSCs to express Major Histocompatibility Complex (MHC) class I and a possible de novo expression of MHC class II [19].

Recently, the successful use of allogenic MSCs has been reported in critically ill patients diagnosed with COVID-19 [20-22]. The origin of the cells was Wharton jelly [22] and the human umbilical cord [20, 21]. So far, infusion of mesenchymal stem/stromal cells has been successfully and safely tried for the treatment of idiopathic pulmonary fibrosis [23], pulmonary sarcoidosis [24], multiple sclerosis [23], and Crohn disease [25].

2. Conclusion

In patients with COVID-19, proinflammatory cytokines are the key players of cytokine storm, leading to serious morbidities and even mortality. Thus, one of the helpful treatments could be the suppression of cytokine storm. Considering the notable ratio of preterm labor in critically ill pregnant patients with COVID-19 (due to elevated proinflammatory cytokines level), transplantation of autologous placental-derived mesenchymal stem/stromal cells following delivery could be an effective treatment for this condition which also could avoid any possible and unknown allogenic adverse effect. The au-

thors believe that complementary studies are helpful for the investigation of this treatment method in the clinic.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Both authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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