Original Article

Autologous Activated Platelet-Rich Plasma Therapy for Pregnant COVID-19 Patients: A Case Series

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Abstract

As pregnant women are more susceptible to COVID-19 and have higher mortality rate, it is crucial to find a more efficacious and safer therapy for them. Among the various therapies available, intravenous autologous activated Platelet-Rich Plasma (aaPRP) is a potential candidate due to its well-known anti-inflammatory effect and autologous property. To the best of our knowledge, this is the first study which reported the aaPRP therapy in pregnant COVID-19 patients. Among these patients, two had severe to critical symptoms and two had mild to moderate symptoms. The analysis revealed that intravenous aaPRP was able to ameliorate the hyper-inflammatory and hypercoagulability state of the patients without any adverse events observed.

Keywords: coronavirus disease 2019, pregnancy, platelet-rich plasma

Introduction

The Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a global pandemic that threatens not only the world economy but also the lives of many patients around the world.[1] Since its first case in Wuhan, China on December 2019, it rapidly progressed and infected over 93 million people leading to over 2 million deaths worldwide just within a month.[2] Furthermore, individuals of different age groups with various comorbid conditions are susceptible to being infected by this virus.[3] However, some conditions, such as pregnancy, make females more susceptible to this viral infection.[4] Physiological and immunological changes in pregnant women is the reason behind this susceptibility.

Among the various hormonal changes in pregnant women, the change in estrogen and progesterone levels during the first trimester causes a reversible thymus degeneration which reduces the number and the activity of $CD4^+$ and $CD8^+$ T cells. Furthermore, the upregulation of angiotensin converting enzyme 2 (ACE-2) receptor and the change in progesterone level affects the nasal mucosa to facilitate adhesion and prevent its elimination which increases the risk of pregnant women to get infected by SARS-CoV-2. Moreover, the decrease in functional residual capacity and increase in oxygen consumption due to vascular congestion makes pregnant women more susceptible to severe and even critical forms of respiratory infections including COVID-19.[5]

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Thus, these physiological and immunological changes have made pregnant women likelier to be hospitalized, intubated, mechanically ventilated and admitted to the intensive care unit (ICU) than nonpregnant women.[6] In addition, pregnant women with COVID-19 have a 22 times higher mortality rate than nonpregnant women. These deaths are mostly attributed to the severe inflammatory state in pregnant women.[7] As the main cause of death is mostly due to the severe inflammatory state, therefore, an agent to control the inflammation is required.

Among the various anti-inflammatory agents, autologous activated Platelet-Rich Plasma (aaPRP) is a potential safe candidate. The aaPRP induces no adverse events due to the autologous property and activation which removes platelets and leukocytes.[8] Moreover, aaPRP is rich in various growth factors which exert anti-inflammatory effects and various studies have reported its efficacy and safety aaPRP in COVID-19 patients as well.[9-11] However, to the best of our knowledge, no such studies have been reported in pregnant COVID-19 patients. Therefore, this case series would like to report the efficacy of aaPRP in four different cases of pregnant women suffering from COVID-19.

Case Report

Case 1

A 41-year old woman with 24 weeks of pregnancy got admitted to the Koja Regional Public Hospital (Jakarta, Indonesia) in the early morning of June 6, 2021. Her major complaints were 4-day cough and dyspnea and a 3-day fever. Her medical history showed presence of two comorbidities i.e. hypertension and diabetes mellitus. Upon the onset of symptoms, she underwent a rapid antibody IgM and IgG test for SARS-CoV-2 and was found positive for SARS-CoV-2. Thereafter, nasopharyngeal swab RT-PCR test also confirmed this result. She was then admitted to COVID-19 care unit of Koja Regional Public Hospital.

After admission,the woman was further evaluated with hematological and radiological tests. The hematological test showed increased White Blood Cells (WBCs) with domination of neutrophils. In addition, rise in D-dimer level, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and in the levels of liver enzymes Aspartate Transaminase (AST) and Alanine Transaminase (ALT) was also observed. Moreover, decreased Prothrombin Time (PT) and hypokalemia i.e. low potassium level, was also noted. On the other hand, radiological test showed bilateral infiltrates which indicated bilateral pneumonia and Acute Respiratory Distress Syndrome (ARDS).

On the first day of admission, the patient was administered favipiravir 1,600mg twice (b.i.d.) for a day followed by favipiravir 600mg b.i.d. for the next five days. In addition, parenteral dexamethasone 6mg was given to her once a day (q.d.) for 5 days and intravenous ceftriaxone 2gfor only 1 day. Moreover, she was also given high flow nasal cannula until intubation. Besides these medications, she also received IV aaPRP on the third, fifth and seventh day of admission. Further hematological evaluation was done on the sixth day of admission after receiving two aaPRP therapies. The reports revealed that the levels of WBC, PT and CRP came to their normal range. Next hematological and radiological evaluation was done on the ninth day of admission which further showed improvement in patient's profile. Although patient's D-dimer levels were further decreased yet they were still above the normal range. Also, patient's bilateral infiltrate became less prominent as observed by the chest x-ray. Further improvement with only small infiltrates left on the pericardial region was noticed on the eleventh day. Thereafter, the patient was discharged on the same day with no complaints left.

Case 2

A 34-year old woman with 32 weeks of pregnancy was shifted from Mitra Keluarga Hospital to the Koja Regional Public Hospital on June 3, 2021. Her major complaints were 4-day cough, sore throat, dyspnea and 3-day constipation. Shehad been tested positive for SARS-CoV-2 with nasopharyngeal RT-PCR swab test. She had no remarkable medical history but had experienced Disseminated Intravascular Coagulation (DIC) before she was admitted to Koja Regional Public Hospital. Thereafter, she was shifted to the COVID-19 care unit of Koja Regional Public Hospital where her hematological tests and chest x-ray were performed. The rise in D-dimer level, AST, ESR, CRP level and respiratory alkalosis was noticed. The chest x-ray showed infiltrates covering large parts of both lungs which indicated bilateral pneumonia and ARDS. Because of these symptoms, the patient was diagnosed as a critical case of COVID-19.

On the first day of admission, the patient was given favipiravir 1,600mg b.i.d. for a day followed by favipiravir 600mg b.i.d. and parenteral dexamethasone 6mg q.d. for the next five days. In addition, 1g of meropenem thrice daily (t.i.d.) was also administered. Being in critical condition, the patient was ventilated mechanically and given vasopressor as well. Furthermore, she also

received IV aaPRP on the first, third and fifth day of admission. The hematological evaluation on the sixth day of admission showed certain improvements including the decrease of AST to its normal range and of pH from 7.523 to 7.485. Next day, further hematological evaluation showed an increase in WBC count with neutrophil dominance. With no more symptoms left, the patient was finally discharged on the twelfth day of admission. Thereafter, the woman delivered the baby through cesarean section and both the patient and the baby were healthy.

Case 3

A 25-year old woman in her 33rd week of pregnancy got admitted to the Koja Regional Public Hospital on May 22, 2021. Her major complaints were 3-day stomach cramps, fever, cough and 2-day anosmia and ageusia. She was declared SARS-CoV-2 positive through nasopharyngeal RT-PCR swab test. Later on, increase in ESR, D-dimer and CRP whereas decrease in sodium level was observed through hematological assessment. Moreover, Disseminated Intravascular Coagulation (DIC) was also noticed through these tests. Furthermore, the chest x-ray report showed that the patient was suffering from ARDS.

After clinical examination, the patent was administered favipiravir 1,600mg b.i.d. for a day followed by favipiravir 600mg b.i.d. for the next five days. Additionally, parenteral dexamethasone 6mg q.d. for 5 days and ceftriaxone 2g daily for seven days were also prescribed. She was also given non-rebreather mask (NRM) of 15 LPM oxygen, ringer's lactate every 12 hours and ammonium chloride as an expectorant to ameliorate her symptoms. The patient then consented to receive IV aaPRP therapy on the seventh, ninth and eleventh day of admission. The patient was then evaluated after each aaPRP therapy. Interestingly, the patient showed improvement following the second IV aaPRP therapy showing a decrease in CRP level to its normal range. Moreover, the chest x-ray report showed less infiltrates on both lungs. With further improvements in patient's health, she was finally discharged on June 5th, 2021. The patient was also followed-up regarding her pregnancy and delivery. The patient delivered healthy baby through cesarean section without any complications.

Case 4

A 26-year old woman with 30 weeks of pregnancy was admitted to the Koja Regional Public Hospital on March 11, 2021 with chief complaint of 3-day cough and dyspnea. The patient was tested positive for SARS-CoV-2 through nasopharyngeal swab RT-PCR. On hematological evaluation, the patient was found to have an increase in WBC count with neutrophil dominance, increase in D-dimer level, AST, ALT and CRP level. In addition, metabolic alkalosis and low O_2 saturation were also noticed. The radiological evaluation showed that the patient had bilateral infiltrates in both lungs and was diagnosed with ARDS.

The patient was given favipiravir 1,600mg b.i.d. for a day followed by favipiravir 600mg b.i.d., parenteral dexamethasone 6mg q.d. for next 5 days and ceftriaxone 2g daily for seven days. Additionally, NRM of 15 LPM, ringer's lactate every 12 hours and ammonium chloride as an expectorant was also administered to the patient to improve her symptoms. Moreover, IV aaPRP therapy was also given to the patient on the third, fifth and seventh day of admission. As observed in case 3, the improvement in this patient was also noticed after the 2nd aaPRP therapy. Notable improvements include the decrease of WBC count to its normal range, a slight decrease in CRP level and return of alkaline pH to its normal range. Moreover, increase of patient's O_2 saturation to its normal range was also observed. Further improvements were observed after the 3rd IV aaPRP therapy with more decrease of CRP level almost to its normal range and of D-dimer level. Upon radiological evaluation, the patient showed improvements with less bilateral infiltrates on the lungs. Following these clinical improvements, the patient was finally discharged on March 25th, 2021. Later on, the patient follow-up regarding her pregnancy showed that the woman without any complication delivered a normal baby.

Discussion

This report described the progression of two severe-critical and two mild-moderate pregnant COVID-19 patients who underwent the therapy of intravenous autologous activated Platelet-Rich Plasma (aaPRP). Other than this, these patients were also given favipiravir as an antiviral medication, dexamethasone, and meropenem or ceftriaxone according to the standard guidelines in Indonesia established by the Indonesian Society of Respirology.[11] To the best of our knowledge, this is the first report regarding the use of IV aaPRP therapy on pregnant women suffering from COVID-19. Because of obtaining patient's informed consent in different times, the aaPRP administration day for each patient was not uniform in this case series.

As far as the outcome is concerned, similar hematological results were observed in each case i.e. decrease in

the level of CRP, WBC count, D-dimer level and the ESR to their normal range. These findings indicated that V aaPRP was able to ameliorate the hyper-inflammatory and hypercoagulability state of the patients. Similar findings were reported by other studies as well.[9,10] The aaPRP is known for its anti-inflammatory effect which is exerted through the release of more than 1,000 kinds of bioactive factors and cytokines including Interleukin-1 Receptor Antagonist (IL-1RA) and Interleukin-2 Receptor Antagonist (IL-2RA).[12–14] As the hyper-inflammatory state is reduced because of these cytokines, the hypercoagulability state is also reduced due to less inhibition of natural anticoagulant pathways and fibrinolytic activity.[15] Moreover, the decrease in lung infiltrates is also attributed to this anti-inflammatory effect of IV aaPRP therapy.[16]

Regarding its safety, in accordance with the findings of other studies, no adverse event was observed clinically due to IV aaPRP use in any case reported in this case series. This is safe because aaPRP are activated platelets which leaves almost no platelet upon administration which may cause thrombosis.[8] Thus, our finding adds up to the current knowledge regarding the safe use of IV aaPRP in pregnant women affected with COVID-19.

Because of the requirement of patient's own blood and simple processing, overall this therapy is beneficial for the treatment of pregnant COVID-19 patients. However, as this case series reported only four cases, more studies with larger population and control group and a clinical trial is still required to further confirm our findings.

Conclusion

To sum up, the use of IV aaPRP shows beneficial effects in ameliorating the hyper-inflammatory and hypercoagulability state of pregnant women suffering with COVID-19. Additionally, this therapy further reduces the damage caused in the lungs due to this viral disease.

Declaration of Consent

Written informed consent was obtained from all the patients for publication of this case report.

List of Abbreviations

aaPRP: autologous activated platelet-rich plasma
ACE-2: angiotensin-converting enzyme-2
ALT: alanine transaminase
ARDS: acute respiratory distress syndrome
AST: aspartate transaminase
CD: cluster of differentiation
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
DIC: disseminated intravascular coagulation
ESR: erythrocyte sedimentation rate
IgG: immunoglobulin G
IgM: immunoglobulin M
IL-1RA: interleukin-1 receptor antagonist
IL-2RA: interleukin-2 receptor antagonist
IV: intravenous
Lpm: liter per minute
NRM: non-rebreather mask
PT: prothrombin time
SARS-CoV-2: severe acute respiratory syndrome coronavirus02
WBC: white blood cell

Competing Interests

The authors declare that they have no competing interests.

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