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ANALISIS *HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS* SEBAGAI TERAPI YANG MENJANJIKAN DALAM MENGATASI BADAI SITOKIN PADA PASIEN COVID-19

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ABSTRAK

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Pendahuluan: Covid-19 merupakan penyakit menular yang disebabkan oleh *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2) yang menyebabkan terjadinya pandemi. Salah satu komplikasi dari penyakit ini adalah *Acute Respiratory Distress Syndrome* (ARDS) yang disebabkan oleh badai sitokin. Saat ini, perawatan untuk pasien Covid-19 dengan ARDS hanya bersifat simtomatik dan memiliki banyak kelemahan. Oleh karena itu, agen terapeutik yang baru untuk mengatasi Covid-19 masih dibutuhkan. Tinjauan literatur ini dibuat untuk mengetahui potensi *human umbilical cord mesenchymal stem cells* (hUC-MSCs) sebagai agen terapi baru bagi pasien Covid-19.
Metode: Tinjauan literatur ini dibuat berdasarkan artikel dari beberapa *database* medis seperti NCBI Pubmed, Elsevier, dan Google Scholar, dengan pencarian kata kunci “ARDS”, “Covid-19”, “Badai Sitokin”, “hUC-MSCs”, dan “Sel Punca”.
Pembahasan: Didapatkan 5 jurnal utama yang berkorelasi dengan tujuan pembuatan tinjauan literatur ini yang kemudian dianalisis secara sistematis. Badai sitokin merupakan respon imun yang berlebihan disebabkan oleh peningkatan sitokin proinflamasi yang dapat menyebabkan kerusakan pada organ terutama pada paru-paru. Di sisi lain, hUC-MSCs merupakan sel punca mesenkimal yang berasal dari tali pusat manusia yang dapat mengatasi badai sitokin pada pasien Covid-19 dengan mengurangi sitokin proinflamasi, meningkatkan konsolidasi inflamasi paru, meningkatkan indeks oksigenasi, dan meningkatkan waktu pemulihan.
Simpulan: hUC-MSCs berpotensi menjadi agen terapeutik yang menjanjikan untuk mengatasi infeksi Covid-19.

Kata Kunci: ARDS, Badai Sitokin, COVID-19, hUC-MSCs, dan Sel Punca

THE ANALYSIS OF HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS AS A PROMISING THERAPY IN OVERCOMING CYTOKINE STORM IN COVID-19 PATIENTS

ABSTRACT

Background: *COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that was recently characterized as a pandemic. One of the complications of this disease is Acute Respiratory Distress Syndrome (ARDS) which is caused by cytokine storm. Current treatments for COVID-19 with ARDS are only symptomatic and have many weaknesses. Therefore, new therapeutic agent for COVID-19 is still needed. This literature review is made to determine the potential of human umbilical cord mesenchymal stem cells (hUC-MSCs) as a novel therapeutic agent in COVID-19 patients.*

Methods: *This literature review is based on articles from several medical databases such as NCBI Pubmed, Elsevier, and Google Scholar, with the keywords used are "ARDS", "COVID-19", "Cytokine Storm", "hUC-MSCs", and "Stem cell".*

Discussion: *There are 5 major studies that correlate with the aim of this literature which were analyzed systematically. Cytokine storm is an excessive immune response caused by the increase of proinflammatory cytokines that can cause organ injury, especially in the lung. On the other hand, hUC-MSCs, a mesenchymal stem cell derived from human umbilical cord, can overcome the cytokine storm in COVID-19 patients by reducing the proinflammatory cytokine, improving lung inflammatory consolidation, increase oxygenation index and increasing the recovery time.*

Conclusion *hUC-MSCs have the potential to become a promising therapeutic agent to overcome the COVID-19 infection.*

Keywords: *ARDS, COVID-19, Cytokine Storm, hUC-MSCs, and Stem cell*

1. INTRODUCTION

Corona Virus Disease (COVID-19) is an infectious disease caused by the newly discovered corona virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This virus's transmission is human-to-human contamination by droplets from coughing and sneezing. The World Health Organization (WHO) on April 27, 2021 reported 147 million confirmed cases and 3 million deaths due to COVID-19. In Indonesia, 1.6 million confirmed cases were reported and 44 thousand deaths due to COVID-19 with a Case Fatality Rate (CFR) of 2.72%. COVID-19 has been declared as a pandemic since March 12, 2020 and has received special attention, especially in preventing transmission and developing better therapies for COVID-19 patients.[1]

Current therapy for COVID-19 patients, especially with life-threatening acute respiratory distress syndrome (ARDS), can only be treated supportively with oxygen, sepsis, and infection therapy. The available antiviral agents only target the viral replication cycle such as camostat mesylate, favipiravir and remdesivir.[2,3] The current therapy is not yet optimal, have many side effects, and still require research to find therapeutic innovations in COVID-19 management, especially in cases of ARDS. ARDS is caused by a cytokine storm, an excessive immune response which is marked by the increase of inflammatory cytokine and chemical mediators production, due to viral infection. This condition can cause dysfunction and destructions in the lungs resulting in systemic disturbances that can lead to death if not treated promptly.[4]

Recently, many studies have investigated the use of mesenchymal stem cells (MSCs), a non-hematopoietic multifunction stem cell which can be isolated from bone marrow, adipose tissue, placental tissue, the umbilical cord, etc., as an immunomodulatory

therapy for COVID-19. It works by reducing the inflammatory responses of COVID-19 cytokine storm.[5,6] One of the MSCs that is most clinically tested in COVID-19 patients is human umbilical cord mesenchymal stem cells (hUC-MSCs). Therefore, this literature review is made to analyze the potential of hUC-MSCs as a promising immunomodulatory treatment to reduce the risk of morbidities and mortalities of COVID-19 disease.

2. METHODS

This literature review is made by literature study method by collecting various valid references about the potential of human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs) as a therapeutic agent for COVID-19 infection. The keywords that are used are ARDS, COVID-19, cytokine storm, hUC-MSCs, novel therapy, and stem cell. The studies used as references for this literature review are from valid scientific databases such as NCBI pubmed, Elsevier, and Google Scholar. All references that are used were published within the last 10 years. Studies that are used in this literature review are studies that meet the following inclusion criteria: 1) Contain the keywords used in this literature review; 2); Can be accessed; and 3) Published within the last 10 years. The information collected is analyzed systematically with the method of approach to the problems related with the topic of the study. The reference method used in this literature review is in the Vancouver reference style method.

3. DISCUSSION

3.1 Cytokine Storm

Cytokine storm is an exessive immune condition resulting from significant elevation of serum proinflammatory cytokines level such as interleukin (IL) 6, IL-8, tumor necrosis factor α (TNF-α), and interferon γ (IFN- γ) , as an innate immune response of viral infection.[7-10] Cytokine storm not only eliminate pathogen microorganism, but could also cause lung tissue injury, multiple organ failure, and could aggravate the prognosis of COVID-19 patient.[8] The mechanism of cytokine storm in COVID-19 infection begins with the release of Damage-Associated Molecular Patterns (DAMPs) and Pathogen-associated molecular patterns (PAMPs) from infected body cells. It then triggers the activation of antiviral response through the activation of innate and adaptive immune system, such as the activation of macrophages, neutrophils, natural killer (NK) cells, and T cells. These cells then produce cytokines such as TNF-α and IL-6, which plays a role in increasing the body's inflammatory response and inducing the formation of nitric oxide (NO) synthetase.[9,10]

The activated T cells will also induce the secretion of TNF-α and IFN-γ, that acts as a positive feedback in increasing the body's inflammatory response. Neutrophils will also produce Reactive Oxidative Species (ROS) which played a role in killing the COVID-19 pathogen. The elevated circulating proinflammatory cytokines and the highly aggressive immune response to this cytokine storm can cause excessive infiltration of the inflammatory cells and cause lung injury to ARDS. This can lead to a decrease in body oxygen saturation and cause the increase of mortality and morbidity in COVID-19 patients.[8-10] The illustration of how cytokine storm happens can be seen in figure 1.

Injury to the alveolar epithelial cells was the main cause of ARDS COVID-19 patients.[11] ARDS prevents lung from filling up with air and then causes hypoxemia. Hypoxemia will end up become hypoxia, a main cause of mortality in patients with severe COVID-19 infections. Hypoxia will affect human body systemically and could cause multiple organs destruction.[12] So, it is necessary to increase patient's oxygenation index faster to prevent further damage to other body organs.

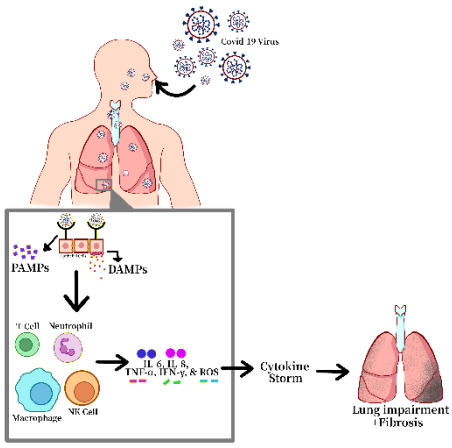


Figure 1. The mechanism of cytokine storm.

3.2 Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) are multipotential stem cells obtained from several parts of the body, such as the umbilical cord, infrapatellar or abdominal fat pat, amniotic fluid, wharton's jelly stem cells, and etc. [13] One of the MSCs that have been widely tested clinically in COVID-19 patients is human umbilical cord mesenchymal stem cells (hUC-MSCs).

Various studies have found that MSCs have an effect on autoimmune diseases to inflammatory diseases and fibrosis of the lungs. Research on the anti-inflammatory and lung antifibrosis effects of MSCs has attracted attention especially in its use as an intervention for cytokine storm therapy in COVID-19 patients, especially those with ARDS.[14] After the MSC's are administrated, these stem cell will move to the organs that experience inflammation (homing), by binding to stromal derived factor 1 (SDF-1), a cytokine that are released by inflammatory organs. SDF-1 will bind the CXCR4 receptor in the MSCs.[15] MSC is a type of stem cell that can evade the body's immune system because it does not express major histocompatibility complex class 2 (MHC-2) on its surface, and it doesn't have co-stimulator factor such as CD40, CD60, and CD86.[16] The effect of MSCs in overcoming cytokine storm involves various mechanisms like suppression of the immune system by increasing anti-inflammatory cytokines such as tumor growth factor (TGFβ) and IL-10, lower the level of pro-inflammatory cytokines such as IFN-γ, IL-6, and TNF-α, and protects the alveolar epithelium.[14]

A study conducted by Shu *et al* in 2020 shows improvement in COVID-19 patients CT lung image marked by the decrease in lung lesions after MSC intervention. The mechanism of MSC in improving lung function involve the process of repairing the microenvironment of lung, repairing pulmonary epithelial cells, and preventing the occurrence of pulmonary fibrosis.[14,17] The illustration of how hUC-MSCs work can be seen in figure 2.

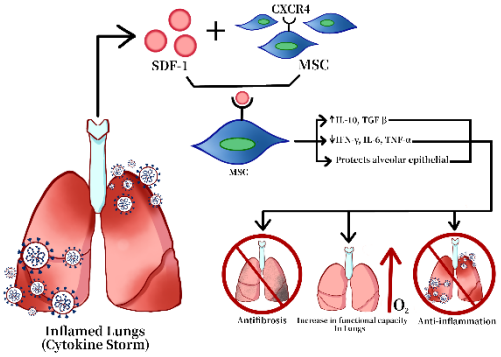


Figure 2. How hUC-MSCs work.

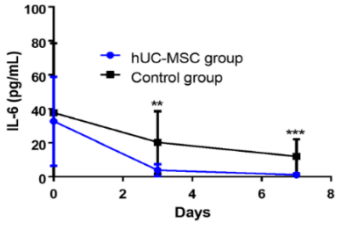
Ethical use of MSCs has been granted permission by various ethical institutions such as the Western Institutional Review Board, UHS/JHS Human Subject Research Office/Institutional Review Board and is free of ethical issues.[18] There also have been many studies that found the use of MSCs can increase the recovery time of COVID-19 patients which then increase the survival rate of these patients.[14]

The various mechanisms by MSCs in overcoming cytokine storms and free of ethical issues showed that hUC-MSCs as one of the MSCs are promising innovative therapeutic agent in the treatment of COVID-19 patients.

3.3 The Effect of human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs) in Laboratory Profiles (Pro- And Anti- Inflamatory Cytokines)

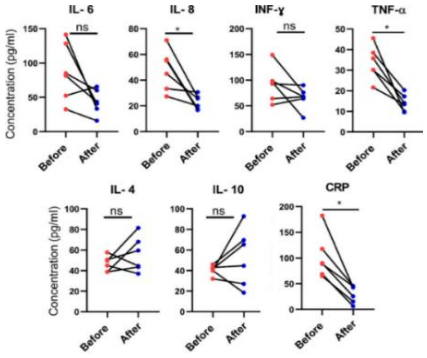
In 2020, Shu *et al* did a research to observe the effect of human umbilical cord mesenchymal stem cells (hUC-MSCs) on the level of IL-6 in severe COVID-19 patients with ARDS. The patients were randomly divided into two groups. Twelve patients were divided into

intervention group and 29 patients were divided into control group. The intervention group from this research was given the stem cells intravenously 2x10^6 cells/Kg, antiviral drugs, and glucocorticoids, while the control grup was only given antiviral drugs and glucocorticoid. The hUC-MSCs were given in one hour (35 drops/ minute) for 14 days. The patients were evaluated gradually. This research shows significant reduction of IL-6 levels after 7 days of therapy in the intervention group compared with the control group as we can see in graphic 1.[17]



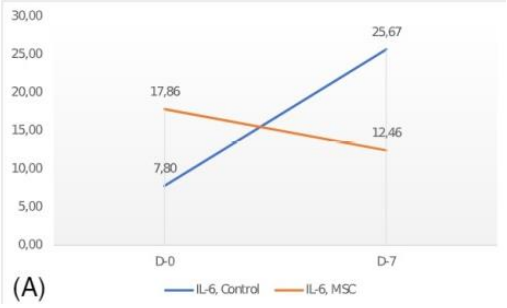
Graphic 1. The Effect of hUC-MSCs on IL-6 Profile.[17]

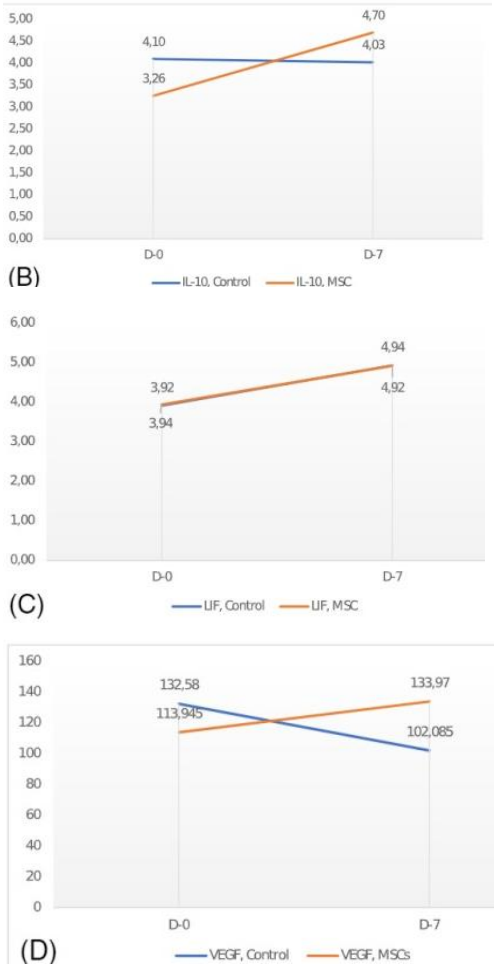
A study by Hashemian *et al* in 2021, also discovered that the administration of hUC-MSCs could also reduce several proinflammatory cytokine, such as IL-6, IL-8, INF-γ, TNF-□, increase multiple anti-inflammatory cytokines, such as IL-4 and IL-10, and also reduce C-Reactive Peptide (CRP) that acts as an acute phase reactants significantly which contribute to the cytokine storm on COVID-19 patient. This research was done in 11 severe COVID-19 patients with ARDS. Each patients received the hUC-MSCs at a dose of 600 x 10^6 which were divided into three doses and standard medication based on their individual condition. The stem cells were administered intravenously every day for 30-45 minutes (50 drops/ minute) The result of the research can be seen in graphic 2.[7]



Graphic 2. The Effect of hUC-MSCs on Another Lab Profiles.[7]

Another study conducted by Dilogo et al., used hUC-MSCs given to the experimental group (critically ill patients who were confirmed positive for RT-PCR) with a single intravenous infusion dose of 1 x 10^6 /kilogram body weight in 100 mL of 0.9% saline solution. The results of laboratory biomarker measurements showed a significant decrease in the trend of the pro-inflammatory cytokine IL-6 (graphic 3A) and an increase of the anti-inflammatory cytokine IL-10 (graphic 3B) in the intervention group after hUC-MSCs administration was given. In addition, there is an increase in leukemia inhibitory factor (LIF) (graphic 3C) which has a repair and regeneration effect on type 2 alveolar epithelium, and inhibits the effect of T-lymphocytes CXCR3+CD4+, CXCR3+CD8+, and CXCR3+CD56 cells that play a role in the occurrence of cytokine storms. Another effect of hUC-MSCs administration in the experimental group was a decrease in CD8-CXCR3 and CD56-CXCR56 cells and an increase in vascular endothelial growth factor (VEGF) (graphic 3D), an angiogenic factor which plays role in recovery from lung damage.[19]





Graphic 3. The Effect of hUC-MSCs on IL-6 profile (A), IL-10 profile (B), LIF profile (C), and VEGF profile (D).[19]

3.4 The Effect of human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs) in Clinical Aspects

3.4.1 The Effect of hUC-MSCs on Inflamatory Consolidation Computed Tomography Imaging and Oxygenation Index in COVID-19 Patients

The research that Shu *et al* conducted in 2020 also showed better inflammatory consolidation reduction 2 weeks after treatment shown on computed tomography lung images in hUC-MSCs group patients compared with the control group as we can see in figure 1.[17]

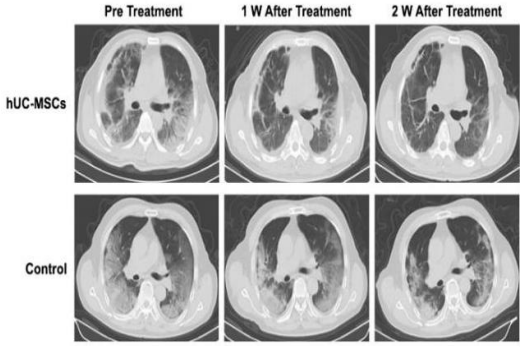
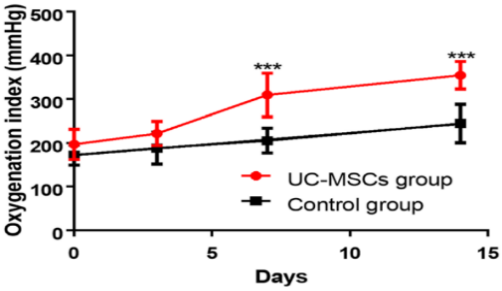


Figure 3. The comparison of inflammatory consolidation reduction showed on Computed Tomography Image in hUC-MSCs and control group.[17]

This research also showed that the time for patients' oxygenation index, assessed by arterial blood gas analysis, that is needed to return to the normal range was faster in the intervention group compared to the control group after fifteen days of treatment as we can seen in graphic 3.[17]

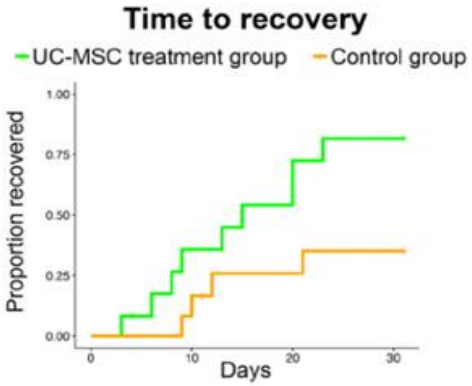


Graphic 4. The increase of oxygenation Index in hUC-MSCs group.[17]

3.4.2 The Effect of hUC-MSCs on Recovery Time in COVID-19 Patients

According to a study conducted by Lanzoni et al in 2020 with a total of 24 severe COVID-19 with ARDS patients. The patients were divided into two groups, twelve for intervention group and twelve for control group. The intervention group were given hUC-MSCs with standard treatment and the control group only get standard treatment. This research used a total cell dose of $100 \pm 20 \times 10^6$ hUC-MSCs per infusion in two dose that are infused intravenously to the intervention group. The therapeutic use of hUC-MSCs in this study shows an increase the recovery time of the intervention group faster than the control

group which was only given a placebo (P=0,307). The comparison of the recovery time from the intervention group and control group can be seen in graphic 4.[14]



Graphic 5. The increase of recovery time in hUC-MSCs treatment group.[14]

3.5 The Effect of human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCss) on Patient Mortality and Survival Rate.

A study conducted by Dilogo et al, with a single intravenous infusion dose of 1 x 10^6/kilograms body weight in 100 mL of 0.9% saline solution to 40 critically-ill patients who were confirmed positive of RT-PCR test without comorbidities showed a mortality rate of 65% (26 patients) and survival rate of 35% (14 patients). Of the 14 patients who experienced recovery, 10 patients came from the hUC-MSCs intervention group, and only 4 patients came from the control group. This shows that the administration of hUC-MSCs gives a 2.5 times higher survival rate. The hUC-MSCs test in patients with comorbidities showed a 4.5x increase in survival rate in the intervention group (9 patients) compared to the control group (2 patients).[19]

4. CONCLUSION

Based on 4 studies about hUC-MSCs, it is concluded that this stem cell is one of the many stem cells that have potential to reduce the inflammatory response in cytokine storm condition of COVID-19 patients. Many studies have proved that hUC-MSCs can decrease many proinflammatory cytokine, such as IL-6, IL-8, TNF-□, INF-γ, increase anti-inflammatory cytokines like IL-4 and IL-10, decrease acute phase reactan, CRP, improve lung inflammatory consolidation, increase oxygenation index and recovery time. It can also increase survival rate in COVID-19 patients. Therefore, by looking every hUC-MSCs clinical trial, it can be concluded that hUC-MSCs have the potential to become a therapy agent in COVID-19 patiens and can decrease the mortality and morbidity of COVID-19 infection.

As an additional suggestion, further clinical studies should be carried out to see the effect of administering hUC-MSCs on other inflammatory profiles accompanied by a more varied study sample so that the effectiveness of using hUC-MSCs can be further improved.

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