

Evaluation of the Immunomodulatory Effect of Mesenchymal Stem Cells on Sepsis-Induced Acute Respiratory Distress Syndrome: A Systematic Review

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Abstract

Background: Sepsis and acute respiratory distress syndrome are the most important causes of death. Sepsis accounts for 20% of deaths worldwide and is one of the most common causes of acute respiratory distress syndrome (ARDS) with a prevalence of 23%. Sepsis-induced ARDS occurs among 10% of ICU patients. Today, mesenchymal stem cells (MSCs) therapy has been studied as a new treatment in the management of sepsis and as a promising treatment for ARDS. We aimed to systematically review studies on the use of MSCs for treatment of sepsis and ARDS.

Results: The results of the search strategy include eight studies: one meta-analysis, three systematic reviews, one clinical trial, one cohort study, one combined cohort study, and a double-blind clinical trial, and one case report with a sample size of animal models from two meta-analyses, and one systematic review of 1266 and 1326 animal models and 1,085 patients in human studies. The results of most studies indicated a significant relationship between mesenchymal stem cell (MSCs) therapy and reduced mortality of sepsis syndrome and ARDS. The results of systematic studies also supported the efficacy and health of MSCs in the treatment of sepsis and ARDS. Patients tolerated high doses of intravenous or intrathecal therapy.

Conclusion: Multi-potency MSCs have an extraordinary ability to respond and manage the immune system and have been studied in animal and human studies as an immune regulatory tool in improving acute disease conditions such as sepsis and respiratory distress syndrome. Results of studies showed that these stem cells can be used clinically, but the need for more extensive studies, especially human studies in the future, is still recommended.

Key Words: Acute respiratory distress syndrome, Mesenchymal stem Cells, Stem cells, Sepsis, Immunomodulation.

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1- INTRODUCTION

Sepsis is one of the causes of mortality and morbidity among inpatients, which can lead to death by suppressing the immune system. On the other hand, following sepsis, patients will be prone to acquired secondary infections, which will increase the chance of mortality (1). The sepsis pathogenesis is such that it causes erratic and unbalanced responses of the host immune system in the form of poor resistance to other infections, dysfunction of organs, and even permanent damage. Brain injuries and physical disabilities are among the adverse consequences of this disseminated and deadly infection; therefore, early and targeted treatment of sepsis is necessary (2). ICU patients are at high risk for sepsis. A total of 80% of these patients are at risk of respiratory, gastrointestinal and urinary tract infections 24 hours after admission, if the blood culture test in most of these patients is positive for the presence of acquired infections (3).

Prolonged hospital stays, the use of maintenance equipment, invasive monitoring, and vascular catheters have increased the risk of sepsis in ICUs, which has increased the chance of death by up to 40% (4). Numerous clinical trials have examined the effectiveness of various drugs and the management of sepsis treatment for more than a decade, since sepsis is the cause of 20% of deaths worldwide (5). In addition to sepsis, ARDS (Acute respiratory distress syndrome) occurs in 10% of ICU patients. Since these patients require mechanical ventilation in more than 23% of cases, sepsis is one of the most common causes of respiratory distress syndrome with a prevalence of 23%. The most common manifestations of this syndrome include inflammation and rupture of the alveolar-capillary membrane. This syndrome includes mild, moderate and severe forms of the disease. Most ARDS patients do not

survive. The risk of death increases with age and the severity of the disease, and some of survivors would recover completely; however, they suffer from permanent lung damage (6). The two sepsis and ARDS syndromes overlap and both of them are the most important causes of death. Although ARDS treatment includes supportive measures and sepsis treatment includes antibiotic regimens, they have not been effective and the need for specific treatments has been suggested (7). Over the past 50 years, many interventional therapies have failed and a specific treatment has always been considered for sepsis and ARDS.

Today, cell therapy is one of the new therapies that has been used under certain conditions. Many experimental studies have examined the effect of MSCs extracted from bone marrow cells. These cells have very attractive properties for treatment compared to other cells, for example, they are potentially less carcinogenic than embryonic stem cells, multiply rapidly in the laboratory, and are used in multi-dose or single-dose regimens. These cells have immunomodulatory properties without a requirement for host-recipient matching (8). So far, pre-clinical (animal models), and clinical (human) studies have been performed to evaluate the effect of MSCs treatment. Despite the high mortality and overlap of sepsis and ARDS despite being heterogeneous, cell therapy has been effective and healthy in this area, because the previous studies have proved a significant relationship in this regard with a reduction in mortality rate although it has no side effects for patients (9).

The aim of the present study was to systematically review studies where MSC therapy was used as a strategy for the treatment of sepsis and its associated ARDS. It was carried out individually and in several combinations during 2009-2019. Search results in these five databases were

merged and duplicates (with the same title, year of publication, and the author name) were removed. A total of 1,337 results were found. In the initial screening phase, 801 studies remained after removing the irrelevant and repetitive items. Finally, after the second screening phase, only English 8 human and animal studies were evaluated and entered the present systematic review. The articles were searched by one researcher, but another researcher checked the final list of articles to ensure the relevance of the studies with the aim of the present study. The reference of the articles and review articles on the subject of study were also carefully reviewed as the search process completed.

2- MATERIALS AND METHODS

2-1. Data Extraction

For each of the articles included in this study, the following data were extracted

and recorded in **Table.1**. Title, author name, year of publication, country, study population, study period, type and source of MSCs (Mesenchymal stem cells), first time of starting cell therapy, method of administration, and regimen dose are mentioned.

2-2. Quality of studies

In order to evaluate the quality of meta-analysis studies, AMSTAR 2, a critical appraisal tool for systematic reviews (12) was used and Newcastle-Ottawa Scale (13) quality control tool was also used for clinical trials. Finally, eight studies entered the final analysis phase after searching, screening, and evaluating the quality of the studies (**Figure.1**, and **Tables 2, 3**). Meta-analysis was not performed due to the existence of conflicting data, and the number of articles as well as each article dealing with a specific present topic.

Table-1: General characteristics of preclinical studies investigating the efficacy of Mesenchymal stem cells in models of sepsis, and acute respiratory distress syndrome.

Author/publication date/ reference/ country	Study design/information source	Population study/ Sample size	Search date/ included study	MSC source, Compatibility	Time of delivery post Sepsis-ARDS Dose	Results
SUN et al; (2020), 16, USA, Canada, Taiwan Spain, China	Meta-analysis, MEDLINE, EMBASE, Cochrane Library, and Web of Science	614, treated animal, 605, Control	25 RCTs, 2009–2019	Adipose, Bone marrow, Umbilical cord, Syngeneic, Allogeneic, Autologous, and Xenogenic	1h – 6h / IV 2.5×10 ⁶ - 10×10 ⁶	The results of this meta-analysis showed a significant relationship between treatment with mesenchymal cells and reduced mortality due to sepsis.
Walter et al; (2014), 17, USA, Canada, China	Review / Overview	667, treated animal, 659, Control	22 RCTs, 2007–2013	Bone marrow	30 min–24h IV intra broncheal	The results of most of the studies in this review study indicated a significant effect of mesenchymal cells therapy on lung improvement, sepsis and tissue regeneration
Byrnes et al; (2020), 8, California (USA) Galway, Ireland	Systematic Review	687 patients under treatment	18 RCTs, 2012–2019	Adipose, Bone marrow, Umbilical cord,	0.3 - 10 ×10 ⁶ cell/kg	The results of systematically reviewed studies supported the effect of mesenchymal cells in the simultaneous treatment of both acute sepsis and respiratory distress syndromes, with early and multi-shift injections being more effective.

Espinoza et al; (2016), 18, Spain, China	Systematic Review PubMed, PMC and Clinical Trials.gov	313 participants	14 RCTs, 1968–2015	Bone marrow	6h –48h / IV 5×10 ⁶ cell/kg	The results of systematic studies supported the efficacy and health of mesenchymal stem cells in the treatment of first and second phase renal and pulmonary injuries.
He et al; (2018), 19, China	Clinical trial	15 patients with severe sepsis, 10 male and 5 female	RCT, 2018	Allogeneic umbilical cord	1×10 ⁶ cells/kg 2×10 ⁶ cells/kg 3×10 ⁶ cells/kg single intravenous infusion	The results of this study supported the high dose efficiency of mesenchymal cells in severe sepsis. In patients, this dose was well tolerated.
Matthay et al; (2019), 20, USA	Prospective, double-blind, multicenter, randomized trial	60 patients with moderate to severe ARDS	RCT, 2014–2017	Allogeneic MSCs derived from human bone marrow	10×10 ⁶ MSC/kg	The results of this study supported the high efficiency of mesenchymal cells in the treatment of ARDS.
Chang et al; (2014), 21, Korea	Case Report	59-year-old man	Clinical case	Umbilical cord blood (UCB)	1 × 10 ⁶ /kg single intravenous infusion	The results of this study improved brain condition and pulmonary compliance immediately after mesenchymal stem cell injection in the treatment of ARDS.
Yip et al; (2020), 22, Taiwan	Cohort	9 patients with ARDS	Prospective phase I clinical trial 2017–2019	Human umbilical cord	1.0 × 10 ⁶ cells/kg 5.0 × 10 ⁶ cells/kg 1.0 × 10 ⁷ cells/kg single intravenous infusion	The results of this study showed an improvement in the immune system response by increasing the T- helper biomarkers of cell CD3+CD4+/ Cytotoxicity-T-cell CD3+CD8+/ Regulatory (P< 0.001).

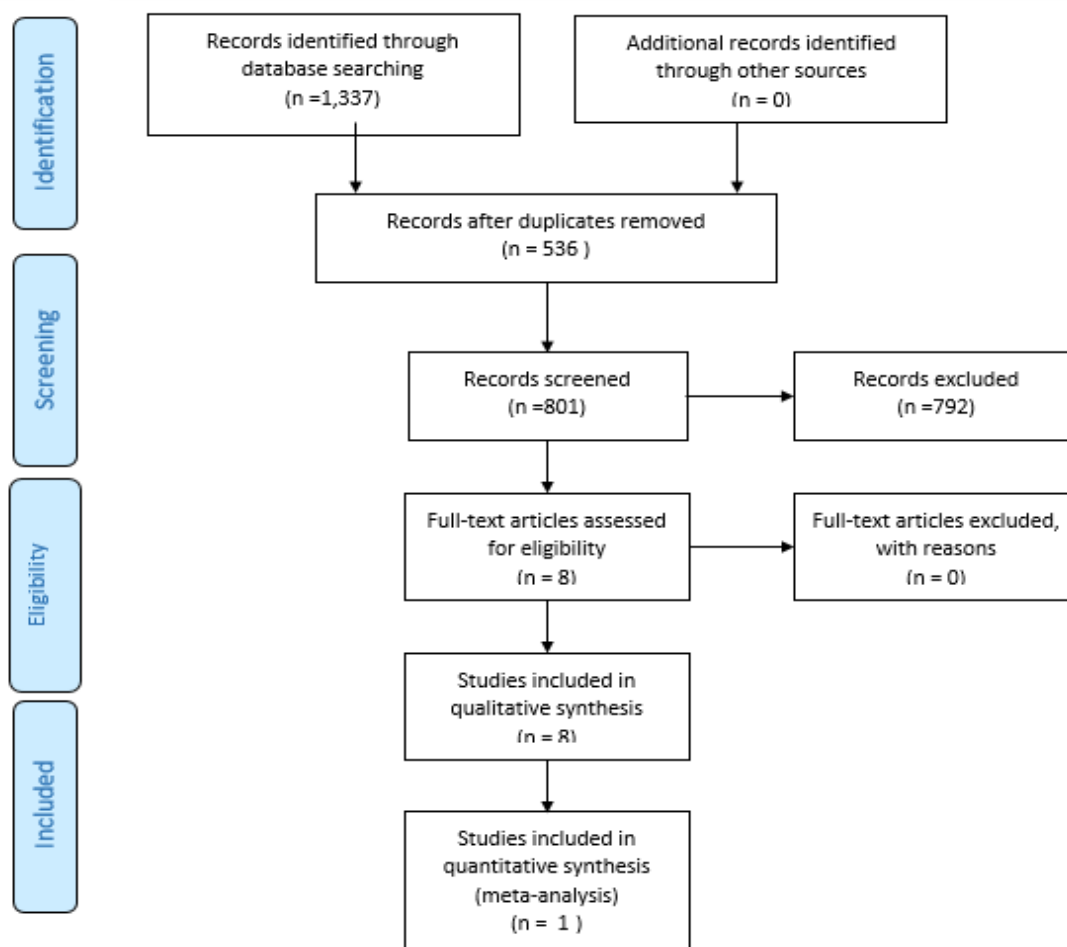
ARDS: Acute respiratory distress syndrome, RCT: Randomized Controlled Trial.

Table-2: Methodological quality assessment of meta-analysis/ Systematic Review (AMSTAR 2), (12).

Items	Study			
	SUN et al; (2020) ¹⁶	Walter et al; (2014) ¹⁷	Byrnes et al; (2020) ⁸	Espinoza et al; (2016) ¹⁸
1) Did the study address a clearly focused question?	Yes	Yes	Yes	Yes
2) Was a comprehensive literature search conducted using relevant research databases (i.e., ABI/INFORM, Business Source Premier, PsycINFO, Web of Science, etc.)?	Yes	Yes	Yes	No
3) Was the search systematic and reproducible (e.g., were searched information sources listed or search terms provided)?	Yes	No	No	Yes
4) Has publication bias been prevented as far as possible (e.g., were attempts made to collect unpublished data)?	Yes	Yes	Yes	Yes
5) Were the inclusion and exclusion criteria clearly defined (e.g., population, outcomes of interest, study design)?	Yes	No	No	No
6) Was the methodological quality of each study assessed using predetermined quality criteria?	Yes	No	No	Yes
7) Are the key features (population, sample size, study design, outcome measures, effect sizes, limitations) of the included studies described?	Yes	Yes	Yes	Yes
8) Was the meta-analysis conducted correctly?	Yes	No	No	No
9) Were the results similar from study to study?	Yes	Yes	Yes	Yes
10) Is the effect size practical relevant?	Yes	No	No	No
11) How precise is the estimate of the effect? Were confidence intervals given?	Yes	Yes	Yes	Yes
12) Can the results be applied to your organization?	Yes	Yes	Yes	Yes

Table-3: The results of Newcastle-Ottawa Scale (13).

Items	Study			
	He et al; (2018) ¹⁹	Matthay et al; (2019) ²⁰	Chang et al; (2014) ²¹	Yip et al; (2020) ²²
1. Was true randomization used for assignment of participants to treatment groups?	No	Yes	No	No
2. Was allocation to treatment groups concealed?	No	Yes	No	No
3. Were treatment groups similar at the baseline?	Yes	Yes	No	Yes
4. Were participants blind to treatment assignment?	No	Yes	No	No
5. Were those delivering treatment blind to treatment assignment?	No	Yes	No	No
6. Were outcomes assessors blind to treatment assignment?	No	Yes	No	No
7. Were treatment groups treated identically other than the intervention of interest?	Yes	Yes	Yes	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Yes	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes
11. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes
12. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	No	Yes	No	No

**Fig.1:** PRISMA flowchart.

3- RESULTS

After the final search, results of eight studies, two meta-analysis and systematic review with the sample size of 1266 and 1326 for animal models and 1,085 patients in human studies were mentioned: A meta-analysis reviewed 25 animal studies on the efficacy of MSCs in the treatment of sepsis, including sepsis and endotoxemia in both sexes by searching four databases: MEDLINE, EMBASE, Cochrane Library, and Web of Science during 2009-2019. All of these studies reported that MSC therapy significantly reduced mortality rate in animal models (CI 95%, OR 0.29 (0.22–0.38) $P < 0.001$). Eligible studies included MSCs from various tissues, including bone marrow, umbilical cord, and adipose tissue MSCs. Results showed that umbilical cord (UC) MSCs led to a significantly greater reduction in mortality among rats. The results of this meta-analysis supported the potential therapeutic effect of MSCs in the treatment of sepsis in the design of future clinical trials (14).

A review of 22 studies on the effectiveness of MSC therapy reported that the most important therapeutic effect of MSCs is their anti-inflammatory effects on the host body, which can improve sepsis and ARDS symptoms and promising survival rates. Besides, the antimicrobial effects of MSCs, especially in clearing the fluid inside the pulmonary alveoli, treating ARDS, and inhibiting the process of cell death, have been considered in the results of this review (15). There was another review study on the results of 12 clinical trials focusing on the MSCS administration for the treatment of ARDS and 6 clinical trials focusing the MSCS therapy for the treatment of sepsis. They reported that cell therapy led to a better tolerance of the treatment dose, reduced time on the ventilator, lack of serious reactions to treatment and ultimately reduced mortality rate following treatment. Although sepsis and ARDS are not

inherently homogeneous, MSC therapy improved both conditions (7). A systematic review of clinical trials obtained from the Pubmed Database between 1968 and 2015 revealed that MSCs could be extracted from bone marrow, adipose, and umbilical cord, and human placental tissue, cartilage tissue as sources of extraction. Laboratory studies have shown the extraordinary immunomodulatory properties of these cells, including anti-inflammatory and tissue regenerative properties, preventing cell death and antimicrobial properties. MSCs have been proposed as an effective treatment under critical conditions of patients such as ARDS, and septic shock syndrome in the first and second phases of clinical trials considering their special biology (16).

A single center clinical trial evaluated the effect of UC-MSCs on ICU patients over 18 years with a diagnosis of severe sepsis in a tertiary hospital in China from January 2015 to May 2016. In this study, 15 male and female patients with a mean age of 58 years were treated with low dose (1×10^6 cells / kg), medium dose (10^6 cells 2 cells / kg), and high dose cell therapy (3×10^6 cells / kg). Serious complications of MSC therapy were reported in none of the patients after 18 months of follow-up, and even high doses of cell therapy were tolerated by patients (17).

A double-blind multicenter clinical trial compared the effect of intravenous MSC therapy with placebo among 60 eligible patients in phase 2 of ARDS at five university medical centers in the United States from March 24, 2014 to 9 February, 2017. In this study, intravenous MSC injection performed at a dose of 10×10^6 / kg after random allocation. No adverse side effects were reported in any of the treated patients, except in one case of death that was not related to medication. The results of this study supported the efficacy and health of MSC therapy (18).

A case-report study was carried out on a 58-year-old man with a history of pulmonary tuberculosis who was suddenly hospitalized with symptoms of progressive pneumonia in ARDS. The patient underwent UC-MSC treatment after a long period of mechanical ventilation on day 114. Lung compliance and brain condition were observed immediately after a single-dose treatment and, after three days, improvement were also seen on chest radiography. The patient eventually died. However, the results of the study suggested MSC-based cell therapy for the treatment of ARDS (19). Another clinical trial evaluated the effect of UC-MSC in the treatment of 9 patients with moderate to severe ARDS admitted to a hospital in Taiwan. The results showed a reduction in mortality rate. In this study, a single-dose administration of MSCs did not cause any side effects (20). A single-center double-blind randomized clinical trial evaluated the effect of MSC therapy in patients with ARDS from January to April 2013. Twelve patients with a diagnosis of ARDS with a PaO₂ / FiO₂ ratio < 200 mmHg were randomly divided into cell therapy and control groups. The intervention group underwent a single dose of adipose-derived mesenchymal stem cell (AD-MSC) therapy and results showed no adverse side effects. Also, the length of hospital stay, days of hospitalization outside the ICU, and no ventilator use were the same in the two cell therapy and placebo groups. There was no significant difference between the two groups in terms of changes in the SP-D, IL-6, and IL-8 levels. However, overall, the administration of allogeneic MSCs was recognized as a healthy treatment for ARDS, although it was recommended that the optimal treatment level be tested in future studies (21).

4- DISCUSSION

The aim of the present study was to review pre-clinical studies (animal studies)

and clinical studies (human studies) to evaluate the effect of MSC therapy on the improvement of sepsis and ARDS with the aim of reducing mortality rate in these two acute conditions. Findings from the studies included in this study showed the importance of the applicability of cell therapy in animal model studies and in human studies. New cell-based therapies have attracted a great deal of attention after bone marrow cell transplantation. The basic concepts of cell therapy include easy replacement of damaged tissues due to their immunomodulatory and regenerative properties. Stem cells are multipotent progenitor cells, originating from mesoderm tissue during blastocyst development. Mesenchymal stromal cells have extraordinary properties, especially their unique therapeutic properties in the treatment of sepsis and ARDS (7, 22). Sepsis and ARDS disrupt the immune response and eventually lead to damage, organ dysfunction, and death. MSCs strengthen and modulate immune system cells, in such a way that they reduce the highly activated immune response and prevent the weakening and death of immune system cells; even the immune system can regain its function (23).

Based on preclinical animal studies, MSCs have inhibitory effect on immunomodulatory function of a variety of immune cells such as T lymphocytes, B lymphocytes, natural killer (NK) cells, and dendritic cells, which, in turn, reduce and regulate the immune system (24). Besides, MSCs downregulate helper molecules on the surface of monocytes, which in turn reduce the proinflammatory cytokines of IL-12 and TNF- α . On the other hand, they upregulate anti-inflammatory cytokines (such as IL-10) on monocytes and affect and inhibit the innate immune system by inhibiting NK cells. This inhibitory function is achieved by reducing the expression of NKP30, NKG2D, and NKP44 receptors on the surface of these

cells and inhibiting their proliferation and preventing the production of γ -IFN. MSCs inhibit the production of hydrogen peroxide by activated neutrophils, thus the intensity of inflammatory stimulations is reduced. Figure 3 shows inhibition of the severity of inflammation in the treatment model of ARDS with pneumonia (25, 26). Studies have shown that MSCs have therapeutic properties in the preclinical model of sepsis by affecting the regulation and inhibition of perturbation of the immune system in cases of sepsis-induced endotoxemia, colitis and peritonitis. Among the therapeutic properties of MSCs include an increase in the enzyme co-oxygenase-1 in peritonitis. In addition, MSC therapy along with antibiotic therapy has been used in sepsis, and the combination therapy was of interest to the researchers considering its role in reducing mortality rate as compared to cell therapy or antibiotic therapy alone (27, 28).

According to precious studies, systemic injections of MSCs increase the immune system's tolerance, a monocyte-absorbing protein secreted by MSCs absorbs activated T cells. These cells are absorbed at inflammation site and eventually lead to cell death. T cells that die from this pathway are phagocytosed by macrophages, and then TGF- β is released by macrophages, resulting in the differentiation of T cells into regulatory T (Tregs) cells. The presence of Tregs in the peripheral blood increases the tolerance of the immune system through the secretion of factors such as (IL-4, IL-10) (28, 29).

In addition, in the presence of peripheral blood mononuclear cells, MSCs inhibit the transport of NF-KB transcription factor into the leukocyte nucleus, thereby inhibiting T cell proliferation (7). Studies demonstrated that the immunomodulatory function of MSCs in animal models are effective in the treatment of autoimmune diseases such as arthritis and cystic fibrosis (30). Severe inflammatory process in the

early stages of ARDS and sepsis disrupts the immune response. Overexpression of inflammatory cytokines and lack of neutrophil death process will be associated with destruction of host body tissues. At this stage of sepsis, neutrophils lose their function, have poor motility and slowed cell death process, resulting in their infiltration into the tissues, spreading inflammation, and host tissue damage. Many studies have reported the regulatory and inhibitory effect of MSCs in reducing the severity of ARDS by reducing neutrophil infiltration with the help of macrophages and ultimately reducing tissue damage (31, 32). Other therapeutic properties of MSCs include their effect on the coagulation process. Sepsis leads to thrombocytopenia (platelet depletion), and then mortality. A decrease in platelet count can be a response in the early stages of the inflammatory process due to sepsis. There will also be a reduction in coagulation factors following severe fluid loss and vascular damage. ARDS also causes severe lung damage by disrupting the regulation of the coagulation system and causing inflammation. Platelets induce the invasion and activation of neutrophils in the lungs and induce the expression of molecules such as ICAM-1, thromboxane A₂, and P-Selection.

MSCs exert a procoagulant effect on the bloodstream resulting in activation of the coagulation cascade. These cells also act as hidden regulators of fibrinolytic cascade by targeting plasminogen, a blood plasmin precursor protein whose role is to destroy fibrin clots (33, 34). The multifactorial mechanisms of MSCs make them interesting in the treatment of sepsis and ARDS, although they are heterogeneous. Besides, these cells can be extracted from several tissue sources, including bone marrow, umbilical cord, and adipose tissue (7). Comparison of the results of three studies by Zheng (2014) (35), Wilson (2014) (36), and Matthay (2019) (18) did

not show adverse hemodynamic complications or exacerbation of ARDS symptoms following MSC therapy. Although, some patients experienced recurrent septic shock or died after treatment; these consequences were not significantly related to the treatment. According to the results of studies, high doses of MSC therapy are tolerable by patients (18, 21, 36). A review of preclinical studies of animal models regarding the therapeutic effects of MSCs in ARDS and sepsis, Johnson et al. (2017) showed the antimicrobial properties of these cells by clearing the intra-alveolar fluid and improving the condition of lung tissue (37, 38). Curley et al. (2013) reported an improvement in ventilation status by increasing the capacity of the alveolar sacs and decreasing the thickness of the alveolar membrane following intravenous and intracheal injection of allogeneic bone marrow MSCs (38). In this systematic review, the results of the study by He et al. (2018) pointed to the proliferative properties of UC-MSCs compared to bone marrow MSCs; however, since UC-MSCs can be accessed without the need for an invasive method compared to bone marrow stem cells, therefore, they can be further studied in basic science studies (17).

4-1. Study Limitations

Since sepsis and ARDS are two heterogeneous syndromes and include a subset of clinical symptoms that may somehow respond to MSC therapy, existence of controlled studies as well as studies used combination therapy, i.e. MSC and antibiotics, seem to be limitations of the present review study. Overall, there is a lack of human studies on the simultaneous MSC treatment for two syndromes.

5- CONCLUSION

Multipotent MSCs have an extraordinary ability to respond and

manage the immune system and have been studied in animal and human studies as an immunomodulatory tool in improving acute disease conditions such as sepsis and ARDS. In recent years, there has been a great deal of interest in the use of MSCs in the treatment of various diseases. In the meantime, MSCs are widely used clinically and many extensive studies have been performed in this regard. These cells have been studied as an immunomodulatory in improving acute conditions of the disease. Findings from studies referred to MSCs in the treatment of sepsis and ARDS as a promising strategy that can deal with both syndromes. These cells, considering their multipotent properties, have an extraordinary ability to respond and manage the immune system. However, there has always been a vital need to carry out further extensive studies, especially clinical ones, and increase information on function of these cells.

6- CONFLICT OF INTEREST: None.

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