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Salama m. El- shennawy

Abdalla Abo Hassen

Talal Ibrahim Hagag

Asherf I Zahra

Reham Salama

See next page for additional authors

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ORIGINAL STUDY

Studying the therapeutic effect of umbilical cord stem cell in pneumonia caused by COVID-19

Salama M. El-shennawy [a], Abdalla A. Hassen [b], Talal I. Hagag [c,*], Asherf I. Zahra [d], Reham Salama [e], Mariam A. Fouad [e]

[a] Microbiology Unit, Shebin El-Kom Teaching Hospital, Egypt
[b] Tanta Cardiothorathic Center, Tanta, Elgharbia, Egypt
[c] ICU, Shebin El-Kom Teaching Hospital, Egypt
[d] Cardiothorathic Surgery, Shebin El-Kom Teaching Hospital, Egypt
[e] Clinical Pathology, Shebin El-Kom Teaching Hospital, Egypt

Abstract

Context: **Coronavirus disease (COVID-19) with severe respiratory morbidity and mortality, rapidly spread all over the world, caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) varying from mild symptoms to pulmonary fibrosis(Li et al., 2020). Mesenchymal stem cells (MSCs) can have a critical role, by promoting pulmonary parenchyma regeneration and subsequently decreasing the symptoms of COVID-19 and help the immune system to act against the virus (WHO, 2020).**

Aim: **To evaluate the efficacy and safety of using stem cell in the treatment of COVID-19 patients.**

Setting and design: **We performed this case−control study during the period from November 2020 to April 2021.**

Methods and material: **The study was conducted on patients with COVID-19-induced pneumonia at the emergency room divided into two groups: group 1: included 10 patients as a control group and group 2 ($n = 5$) with severe disease who received two cycles of UC-MSCs treatment one by inhalation and the other IV. Baseline characteristics of all patients and medical treatment were recorded. There were no serious adverse events associated with UC-MSCs infusion.**

Statistical analysis of the data: **Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.**

Result: **After using stem cell there was no statistically significant decrease in Pao2/FIO_2 ratio more in cases after receives management. There was no difference in use of MSCs in survival of patient with severe late acute respiratory distress syndrome (ARDS) patients and control.**

Conclusion: **UC-MSCs treatment for patients with COVID-19 may be safe but not effective.**

Keywords: Acute respiratory distress syndrome (ARDS), Coronavirus disease (COVID-19), Mesenchymal stem cells (MSCs), Pulmonary fibrosis, (SARS-CoV-2)

1. Introduction

A newly appeared disease, Coronavirus disease (COVID-19), with severe respiratory morbidity and mortality, first appeared in China and then rapidly spread all over the world It was caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an enveloped RNA virus [1]. It was presented with a confusing manifestation ranging from asymptomatic patients to severely ill patients with acute respiratory distress syndrome (ARDS) and pulmonary fibrosis [2].

Severe cases of COVID-19 are characterized by upregulation of pro-inflammatory cytokines and chemokines, aberrant cellular immune responses, abnormal coagulation indices, respiratory and cardiovascular failure, end-organ damage, and even death. It is likely that abnormal and extreme immune responses caused by SARS-CoV-2 infection in the host are concerned in the pathogenesis of lung and multi-organ injury [3].

The symptoms of COVID-19 could be mild, including fever (82%) and cough (81%) and severe, which are characterized by acute respiratory distress

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* Corresponding author at: Shebin El-Kom, Menoufyia, Egypt.
E-mail address: talalihagag@gmail.com (T.I. Hagag).

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syndrome (ARDS) and cytokine storm (14%). Finally, some severe cases suffer from multiple organ failure involving the heart, kidney, liver, gastrointestinal system, and sometimes mortality [4].

The 'Cytokine storm' is a hyper-inflammatory response in ARDS. Besides, ACE2 expression in other tissues, including the heart, liver, kidney, and gastrointestinal organs, may cause multiple organ failures (i.e., myocardial injury, arrhythmia, acute kidney injury) lead to shock and death of affected patients [1].

There was a need to cure the increasing number of patients who develop pneumonia despite of developed vaccine. So MSCs can have a critical role, by promoting the pulmonary parenchyma regeneration and subsequently decreasing the symptoms of COVID-19 and help the immune system to act against the virus [5].

Mesenchymal stem cells (MSCs) were first tested as a cellular therapy in humans in 1995 and have since been used in basic research and clinical applications due to immune-modulatory, regenerative, and differentiation properties of nonhematopoietic cells (MSCs) [6].

MSCs are considered to suppress the over-activated inflammatory response, promote recovery of lung function, and potentially influence the progress of pulmonary fibrosis [7].

Thus, the use of MSCs to develop better clinical outcome of the patients with severe cases of COVID-19 disease still necessitate evaluation. MSCs derived from different tissues, including human bone marrow, umbilical cord tissue, adipose tissue, lung tissue, dental pulp, and placenta, have been used in humans, without serious adverse events to treat corticosteroid-resistant graft-versus-host disease, multiple sclerosis, heart failure, acute respiratory distress syndrome (ARDS), and other indications [8].

The umbilical cord is the most adequate source for MSCs, for several reasons: (i) high concentration of MSCs, (ii) UC-MSCs can be done by non-invasive techniques during or after birth (iii) the Wharton-jelly is considered cryo-preserved high quality product around the world in (iv) these cells are closer to embryonic-stem-cells (ESCs) when compared to bone-marrow or adipose tissue MSCs; (v) in contrast the UC-MSCs are safer than ESCs because are not tumorigenic; (vi) can be used as an allogenic treatment since these cells are immune evasive and express low levels of major histocompatibility complex class 1 molecules and no major histocompatibility complex class II [9]. The IV administration is the selected route for the treatment with UC-MSCs, as most of the infused UC-MSCs will be trapped in the lungs, the most affected organ in COVID-19 patients [10].

However, their use and safety profile in patients with COVID-19 needs to be determined in light of the multi-system nature of disease-associated coaggulopathy [3].

MSCs may have very hopeful outcomes, when considered for the treatment of lung disease by the regulation of the immune system in the lung, by suppressing of infiltrated cells and diminishing edema [11]. MSCs have been reported to efficiently cure ALI/ARDS (acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), principally by paracrine mechanisms based on the action of EVs (extracellular vesicles), such as microvesicles and exosomes [12]. Therapeutic efficacy on mice with ALI induced by influenza A (H5N1) virus was reported byin vitro studies.UC-MSC demonstrated Researchers confirmed that UC-MSCs presented effective results for the restoration of damaged alveolar fluid clearance and protein permeability of influenza A infected alveolar epithelial cells [13].

2. Aim of the work

This study aimed to evaluate the efficacy and safety of using stem cell in the treatment of COVID-19 patients.

3. Patients and methods

This study was conducted in the clinical pathology department in collaboration with the ICU Department at Shebin El-Kom Teaching Hospital during the period from November 2020 to April 2021.

Approval was taken from the research committee of general organization of teaching hospitals and institutions (GOTHI) with approval NO (HSH00031).

The study was a case–control study conducted on patients with COVID-19-induced pneumonia were presented to the emergency room.

The participants were divided into two groups.

(1) Group 1: included 10 patients as a control group (3 male & 7 female), their ages ranged from **(52–79) years old.**
(2) Group 2 included 5 patients (4 male & 1 female), their ages ranged from 44 to 83 years old.

All patients were diagnosed clinically and confirmed by CT, PCR for nasal swab to detect COVID-19.

3.1. Inclusion criteria

(1) Positive pressure ventilation by an endotracheal or tracheal tube with a PaO_2/FiO_2 ratio of <200 with at least 8 cm H2O positive end-expiratory airway pressure,
(2) Bilateral infiltrates consistent with pulmonary edema on the frontal chest radiograph,
(3) Without clinical evidence of left atria hypertension or a pulmonary arterial occlusion pressure ≤18 mmHg.
(4) confirmed by CT, PCR for nasal swab to detect COVID-19

3.2. Exclusion criteria

(1) Inability or unwillingness to sign informed consent.
(2) Vital organ de-compensation e.g. (kidney, liver, heart)
(3) Lung carcinoma, other organs or hematological malignancies.
(4) Previous Lung surgery.

3.3. Methods

Patients were subjected to the following.

(1) Full history taking and clinical examination including vital signs.
(2) Radiological Examination: Chest X-ray and CT
(3) Routine investigations:
  (a) CBC with differential counts by CELL-DYN Ruby Hematology Analyzer by Abbott (Ruby, Abbott Company)
  (b) Liver function test, Kidney function tests and Random Glucose Level By AU 480 auto analyzer
  (c) ECG and Echo
  (d) Erythrocyte sedimentation rate (ESR)
  (e) Virology (HCV Abs, HBS Ag, HIV Abs)
(4) Staging:

According to Berlin 2012 ARDS diagnostic criteria.

Mild: 200 mmHg < PaO_2/FiO_2≤300 mmHg with PEEP or CPAP ≥5 cm H_2O ‡

Moderate: 100 mmHg < PaO_2/FiO_2≤200 mmHg with PEEP ≥5 cm H_2O

Severe:PaO_2/FiO_2≤100 mmHg with PEEP ≥5 cm H_2O

Acute hypoxemic respiratory failure not due to cardiac failure as a primary cause.

Full patient history, complain examination findings, laboratory results and radiological images all brought together to get a decision of patient eligibility for study.

(5) Procedure:
  (a) Umbilical cord blood Harvesting: Under complete aseptic conditions, immediately after delivery of the baby and before the delivery of the placenta the umbilical cord was clamped from the baby side (as near as possible to preserve the longest available part of the cord). The cord was then washed with 70% ethanol swab, and the umbilical vein was punctured in the CB collection bag containing CPDA-1 as anticoagulant. Blood was allowed to flow by gravity, and the needle was removed when the blood flow ceased then blood was transferred to the laboratory in a container and processed within 12 h postcollection.

−5 ml of the sample withdrawn to the laboratory for screening of viral infections, blood grouping and cross-matching with the patient expected to receive the cells. If the sample is eligible the sample undergone isolation of stem cells within 6 h of collection.

Mononuclear cells were separated by sedimentation gradient technique then washed by normal sterile saline twice then cultivated on HEPES tissue culture for 48 h (HiMedia Laboratories LLC, 507 School House Rd., Suite 200, Kennett Square, PA19348, USA. Cells were collected by centrifugation and washed twice by saline. A total of 15 patients were joined, five of them with severe disease received two cycles of UC-MSCs treatment one by inhalation and the other IV. The other ten patients also with severe disease and were assigned to be the control group.

Baseline characteristics of all patients, including, sex, clinical classification, age, co-existing co-morbidities, duration of MV (days), length of stay, Charlson score, time to admission, anti-viral, Actimra, corticosteroids, death, APACHI-intravenous and medical treatment were recorded (Table 1).

3.4. Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro−Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median. Chi-square test for categorical

Table 1. Comparison between the two studied groups according to different parameters.

	Cases ($n = 5$)	Control ($n = 10$)	Test of sig.	P
Sex				
Male	4 (80%)	3 (30%)	$\chi^2 = 3.348$	$^{FE}P = 0.119$
Female	1 (20%)	7 (70%)		
Age (years)				
Mean ± SD.	64.4 ± 15.5	65.5 ± 7.0	t = 0.151	0.886
Median (Min. – Max.)	65 (44–83)	64.5 (52–79)		
DM	3 (60%)	5 (50%)	$\chi^2 = 0.134$	$^{FE}P = 1.000$
HTN	3 (60%)	3 (30%)	$\chi^2 = 1.250$	$^{FE}P = 0.329$
IHD	1 (20%)	0 (0%)	$\chi^2 = 2.143$	$^{FE}P = 0.333$
CVS	1 (20%)	0 (0%)	$\chi^2 = 2.143$	$^{FE}P = 0.333$
Thrombophilia	0 (0%)	0 (0%)	–	–
PE	0 (0%)	0 (0%)	–	–
DVT	0 (0%)	0 (0%)	–	–
Dialysis	0 (0%)	2 (20%)	$\chi^2 = 1.154$	$^{FE}P = 0.524$
MV	5 (100%)	8 (80%)	$\chi^2 = 1.154$	$^{FE}P = 0.524$
Duration of MV (days)				
Mean ± SD.	8.6 ± 7.1	6.3 ± 4.2	U = 20.50	0.594
Median (Min. – Max.)	7 (2–20)	5.5 (2–14)		
Length of stay				
Mean ± SD.	27.0 ± 22.2		–	–
Median (Min. – Max.)	20 (8–65)	–		
Charlson				
Mean ± SD.	5.8 ± 0.8	5.8 ± 0.8	t = 0.000	1.000
Median (Min. – Max.)	6 (5–7)	6 (5–7)		
Time to admission				
Mean ± SD.	8.0 ± 8.0	6.4 ± 4.2	U = 24.5	0.953
Median (Min. – Max.)	5 (2–22)	5.5 (2–14)		
Antiviral	3 (60%)	10 (100%)	$\chi^2 = 4.615$	$^{FE}P = 0.095$
Actimra	0 (0%)	1 (10%)	$\chi^2 = 0.536$	$^{FE}P = 1.000$
Corticosteroids	5 (100%)	10 (100%)	–	–
Death	5 (100%)	10 (100%)	–	–
APACHI- IV				
Mean ± SD.	14.0 ± 1.58	12.60 ± 1.07	t = 0.151	0.866
Median (Min. – Max.)	14.0 (12–16)	13.0 (11.0–14.0)		

χ^2: Chi-square test.
FE: Fisher Exact.
t: Student t-test.
U: Mann Whitney test.
P: *P* value for comparing between cases and control.
SD, Standard deviation.

variables, to compare between different groups Fisher's Exact correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test for normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. Wilcoxon signed ranks test for abnormally distributed quantitative variables, to compare between two periods. Significance of the obtained results was judged at the 5% level.

4. Results

Our study was a case–control study that investigated patients in Shebin Elkom Teaching Hospital ICU and we divided patient into two groups: Group 1 included 10 patients as a control group (3 male & 7 female) and Group 2 included 5 patients (4 male & 1 female).

We compared the two groups according to demographic data and there was no statistically significant difference in sex, age, or race and also there was no statistically significant difference between groups in risk factor (DM, HTN, IHD) and also there was no statistically significant difference in risk of thrombo-embolic, thrombophilia, DVT, pulmonary embolism) and also there was no statistically significant difference in MV or length of stay or time to admission.

There was no statistically significant difference in co-morbidity index Charlson score.

In management, there is also no significance difference between 2 group in receiving anti-viral,

Table 2. Comparison between the two studied groups according to PaO_2/FIO_2 and platelets.

	Cases ($n = 5$)	Control ($n = 10$)	U	*P*
PaO_2/FIO_2				
1st				
Mean ± SD.	50.0 ± 10.0	63.0 ± 7.1	7.50[a]	0.028[a]
Median (Min. − Max.)	50.0 (40.0−60.0)	60.0 (50.0−75.0)		
2nd				
Mean ± SD.	48.0 ± 8.4	59.4 ± 12.0	10.0	0.075
Median (Min. − Max.)	50.0 (40.0−60.0)	56.0 (50.0−90.0)		
p_0	**0.317**	**0.283**		
Platelets				
1st				
Mean ± SD.	177.0 ± 80.36	90.0 ± 49.05	9.0	0.055
Median (Min. − Max.)	190 (62−273)	67.5 (50−200)		
2nd				
Mean ± SD.	160.40 ± 100.19	72.50 ± 26.27	8.50[a]	0.040[a]
Median (Min. − Max.)	141 (55−290)	67.5 (50−135)		
p_0	**0.893**	**0.888**		

U: Mann Whitney test.
P: *P* value for comparing between **cases** and **control.**
p_0: *P* value for **Wilcoxon signed ranks test** for comparing between **1st** and **2nd**.
SD, standard deviation.
[a] Statistically significant at $P \leq 0.05$.

actimra, corticosteroids levels and also APACHI E IV risk score.

There was a statistically significant difference between 2 groups in PaO_2/FIO_2 with ratio less in cases than control before using therapy. After using therapy there was no statistically significant decrease ratio in PaO_2/FIO_2 more in cases after re.ceive management but there is no statistically significant difference between two groups.

Also, there was statistically significant decrease in fever and CRP after using stem cell.

There was no statistically significant difference in ALT between 2 groups before and after management (Tables 2 and 3).

Table 3. Comparison between the two studied groups according to fever and CRP.

	Cases ($n = 5$)		
	1st	2nd	Control ($n = 10$)
Fever			
Mean ± SD.	37.6 ± 0.4	37.0 ± 0.0	37.8 ± 0.2
Median (Min. − Max.)	37.5 (37−38)	37 (37−37)	37.8 (37.5−38)
Sig. bet. Grps	$P_1 = 0.063$, $P_2 = 0.513$, $P_3 = 0.001$[a]		
CRP			
Mean ± SD.	53.8 ± 89.4	37.6 ± 38.6	107.0 ± 35.6
Median (Min. − Max.)	4 (3−210)	24 (12−106)	105 (50−150)
Sig. bet. Grps	$P_1 = 0.686$, $P_2 = 0.075$, $P_3 = 0.013$[a]		
ALT			
Mean ± SD.	49.40 ± 16.43	137.8 ± 185.5	49.20 ± 8.22
Median (Min. − Max.)	50 (24−67)	40 (30−464)	50 (40−65)
Sig. bet. Grps	$P_1 = 0.500$, $P_2 = 0.679$, $P_3 = 0.768$		

P_1: *P* value for **Wilcoxon signed ranks test** for comparing between **1st** and **2nd** in cases group.
P_2: *P* value for **Mann Witney test** for comparing between **1st** and **control.**
P_3: *P* value for **Mann Witney test** for comparing between **2nd** and **control.**
SD, Standard deviation.
[a] Statistically significant at $P \leq 0.05$.

5. Discussion

Rapid transmission among humans and relatively high mortality rate of coronavirus disease (COVID-19) has attracted the interest of the world. Many studies to find the best therapeutic approach for the disease and its management were done. Regenerative medicine offers various cell-tissue therapeutics and related products, such as stem cell therapy, Chimeric antigen receptor (CAR) T cell therapy, exosomes, natural killer (NK) cell therapy and tissue products [1].

Stem cells, especially MSCs, have immune-modulatory effects and may have possible aspects in COVID-19 treatment. However, the idea of cell-based therapy has not been accepted by several scientific communities due to some concerns of shortage of reasonable clinical studies; still, the MSCs and their clinical outcomes have showed the potency and safety of this therapeutic approach in several diseases, especially in some incurable diseases and immune-mediated inflammatory diseases and. MSCs release cytokines either by paracrine secretion or direct interaction with immune cells, contributing to immune modulation. In other words,

the cytokines secreted by activated leukocytes increase the immune-modulatory function of mesenchymal cells. Mesenchymal cells inhibit the production of hydrogen peroxide by stimulated neutrophils, and thereby reducing the intensity of inflammatory stimulation [6].

Many study show the effect of MSCs in the treatment of severe COVID-19 infection defined as SPO2 less than 94% Or Pao2/Fio2 ratio less than 300 [17].

This study aimed to evaluate the efficacy and safety of using stem cell in the treatment of COVID-19 patients trying to document if there is a benefit or hazard depending on the importance of the immune-modularity effect of stem cell on severe critical patients as enrolled by high apache score not severe respiratory illness alone as the prevouse trial.

This was a cohort study including 15 patients in Shebin El-kom teaching hospital with severe COVID-19 admitted to ICU and received anti-viral and corticosteroids from November2020 to April 2021, five were assigned to the UC-MSCs treatment group and ten to the control group. The patients in each group were approximately matched for sex, age, and clinical characteristics.

In this study, there was no statistically significant difference in demographic data between the two groups and this may raise the significance of our study.

There was no statistically significant difference between 2 groups regarding receiving anti-viral, Actimera, and corticosteroids. And also there was no statistically significant difference in Apache score IV risk score.

There were no serious adverse events associated with UC-MSCs infusion. Pulse oxygen saturation and electrocardiography monitoring were conducted during cell transfusion, and no electrocardiography abnormalities occurred in any of the patients.

There was a statistically significant difference between 2 groups in Pao_2/FIo2 with ratio less in cases than in control before using therapy. After using stem cell there was no statistically significant decrease in Pao2/FIO2 ratio more in cases after receives management.

Also, there was statistically significant difference in fever and CRP between two groups with nonsignificant decrease of CRP and fever after using stem cell. This was agreed with [14] who made a study of seven patients with severe COVID-19 confirmed the clinical efficacy and safety of intravenous MSCs and Patients showed a decrease in inflammatory markers and cytokines (such as CRP and TNF), an increase in lymphocyte count, and an increase in anti-inflammatory cytokine (IL-10).

Also [15] reported that treatment with intravenous MSCs was accompanied by the reversal of COVID-19-related immune abnormalities which include lymphopenia and inflammation.

There was no statistically significant difference in ALT between 2 groups before and after management.

There was no difference in use of MSCs in the survival of patient with severe late ARDS patients and control.

The above-mentioned findings indicated that UC-MSCs treatment for patients with COVID-19 may be safe but not effective.

This was in contrast with [3] reported that intravenous UC-MSCS infusion in patients with moderate and severe COVID-19 is safe and well-tolerated and all patients recovered and discharged.

Also [16] who reported that the transplantation of MSCs significantly lowered the mortality rate, with no adverse effects. He suggested that MSCs improved the survival rate and considered a promising therapeutic alternative for treating COVID-19.

This difference between our study and [16] may be due to the small sample size in our study and our study implemented on very severe and Late critical COVID-19 patients high APACHE score around 14 in comparison to severe respiratory COVID-19 AS defined affecting respiratory system alone. So, we think that early time of intervention before more system affection and immune modulation is needed, may give the good response in the early process of disease.

Our small size due to financial issue on the process of preparation of MSCs so we present as case−control.

5.1. Conclusion

There is no statistically significant benefit in spite of safety from using UC-MSCS in severe late critically ill COVID-19atients admitted to icu according to high APACHE score around 14 in comparison to severe respiratory COVID-19 AS defined affecting the respiratory system alone in other trial.

5.2. Recommendation

More evaluation and large meta-analysis is recommended to observe more cases in different stages. It may be beneficial in the future.

Institutional Review Board (IRB) Approval Number

HSH00031.

Conflicts of interest

There are no conflicts of interest.

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