Promising Benefit of Single Mesenchymal Stem Cell Injection in Critically ill COVID-19 Patients – A Pilot Phase Randomized Controlled Study

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Abstract

Background: COVID-19 infections represent a life-threatening condition secondary to respiratory and multi-organ failure as a result of a systemic inflammatory response. Stem cell therapy might ameliorate the underlying effects likely secondary to anti-inflammatory properties.
Methods: We report a randomized double-blind controlled trial using umbilical cord-derived stem cells as a single intravenous injection in addition to standard therapy compared to placebo in COVID-19 patients admitted to the critical care unit in a large metropolitan hospital. Primary endpoint was safety, secondary endpoints were tolerability and clinical outcomes. In addition, healthcare providers in daily close contact with COVID-19 patients received a similar stem cell injection compared to placebo to assess reduction in contagion. Endpoints were clinical outcome, COVID testing, respiratory symptoms or fever.
Results: Twenty-six patients received either a single 2cc injection of acellular stem cell-derived bioactive molecules or a placebo (n = 13 per group). Six patients in the placebo group died during follow-up (46.15%), one patient died in the treatment group (7.69%). No therapy-related side effects were documented in either group. None of the healthcare workers (n = 14) developed COVID symptoms or tested positive at the end of the trial.
Conclusion: Stem cells as a compassionate-use were shown to be a safe and promising therapeutic approach for COVID-19. No prophylactic effects were observed compared to placebo. Further large-scale studies are needed to verify these preliminary results.
KEYWORDS: COVID-19, stem cell therapy, cytokine storm, secretome

Introduction

Since the beginning of 2020, the global COVID-19 pandemic has swept across nations taking its toll on human life while simultaneously wreaking havoc on unprepared health-care systems worldwide. Several characteristics about this novel virus exacerbate the present health crisis and are driving the research community to postulate and test safety and efficacy of both traditional pharmaceuticals and more complex regenerative biologics.

With more than 70 registered clinical trials investigating therapeutic applications of stem cells for the novel virus, recent research findings support the hypothesis that regenerative biologics derived from human umbilical cord yield both safe and effective outcomes for patients suffering complications of COVID-19. The hypothesized mechanism of action by these allogeneic tissues constitute several distinct pathways in helping subjects recover from COVID-19.

The mesenchymal stem cell (MSC) secretome constitutes a concentrated, highly diverse population of macroscopic proteins and peptides. It is postulated that these macromolecules may help attenuate inflammation and the excessive or uncontrolled release of proinflammatory cytokines leading to cytokine storm and the biological consequences of cytokine overproduction (1). Evidence also suggests that MSCs may exert beneficial effects by

a)improving the lung microenvironment,
b) inhibiting immune system over-activation,
c) protecting lung alveoli epithelial cells,
d) promoting tissue repair,
e) preventing pulmonary fibrosis, and
f) improving lung function (2).

The acellular mesenchymal stem cell-derived bioactive molecule suspension used in the study (PrimePro™, Thomas Advanced Medical, CA, USA) is a minimally manipulated allogeneic tissue product derived from mesenchymal stromal cells sourced from human umbilical cord tissue. The product has been tested in hundreds of patients by our group for several indications with no significant adverse events.

The goal of this study was to test if an acellular MSC-derived bioactive molecule solution is both a safe and effective adjunct to standard of care treatment for patients suffering complications of COVID-19. Using a double-blind, placebo-controlled randomized study design, we intended to investigate potential beneficial effects of a single stem cell-derived product injection in severely ill patients with respiratory complications secondary to COVID-19 infection. In addition, we tested if prophylactic injections of a single dose of the agent could prevent healthy health care workers in close contact with COVID-19 patients from contracting the virus or getting the disease.

Methods

The present study was approved by the institutional review board of the International Cell Surgical Society (Palm Desert, CA, USA) in 2020 and was conducted at the Critical Care Units of the Southern California Hospital at Culver City (Culver City, CA, USA). All patients, or their legal representatives respectively, as well as participating health care personnel were informed about the experimental nature of stem cell therapy, provided informed consent prior to enrollment, and agreed to follow-up. Computer aided random sampling was used to assign patients and health care providers to either an intervention group or a placebo group. The primary investigator and the study participants were not informed about the according group affiliation before or after completion of the active trial phase until the final analysis was executed.

Cells

Two cc (35 x 10^6 MSCs) of an acellular stem cell-derived bioactive biomolecule suspension sourced from umbilical cord and placenta tissue (PrimePro™, Thomas Advanced Medical, Los Angeles, CA, USA) were used as a single intravenous injection. Allografts were sourced from eligible donated birth tissues. Stem cells and their contents (i. e., proteins, exosomes, cytokines, and growth factors) were extracted into a 10% glycerol USP solution. Postliminary, the contained stem cell derived bioactive molecules were isolated through a series of centrifugation and filtration processes. The obtained cell suspensions were vailed and cryopreserved for storage in liquid nitrogen at -80° C or colder, in conformity with Food and Drug Administration (FDA) Article 21 Code of Federal Regulations (CFR) Part 1271. All aforementioned processes were executed inside an International Organization for Standardization (ISO) Class 3 cleanroom following Current Good Manufacturing Guidelines (CGMP).

Prior to the injection, the frozen material was thawed to room temperature and aspirated into a 2 cc syringe under sterile conditions. For the purpose of double-blind study conduct, stem cell preparations and saline solutions were stored in visually indistinguishable vials, which were assigned to the recipient using a unique code. The computer-assisted randomized assignment of patients and health care workers was practically executed by a preselected member of the group and remained undisclosed to the principal investigator (PI) during the trial phase. Injections were administered through peripheral intravenous catheters. Both the preparation and administration of injections were conducted by the PI.

Patients

Participants were enrolled in the context of critical care treatment in a large metropolitan community hospital and randomized into an intervention group (group 1, n = 13) or a placebo group (group 2, n = 13). Patients received either 2 cc of an acellular stem cell-derived bioactive molecule suspension (group 1) or the same amount of saline (group 2) as an intravenous injection via peripheral venous catheters. All patients received standard care according to the current guidelines for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Inclusion criteria were:

- Active SARS-CoV-2 infection as diagnosed by clinical assessment and antigen testing;
- Age 18-89 years;
- Respiratory distress as proven by O_2 saturation < 80% and ventilator therapy,
- Clinical indication to be hospitalized secondary to COVID-19 infection with respiratory compromise.

Exclusion criteria were:

- Cardiopulmonary arrest during recent or current hospital stay;
- History of malignancy in the last two years;
- Inability to provide consent.

At admission, pre-existing conditions (i.e., dementia, respiratory diseases, congestive heart failure, and renal disease without/with dialysis) and basic lab tests [i.e., white blood cell count (WBC count), hemoglobin, hematocrit, and platelets] were recorded for each patient. Furthermore, chest X-rays were assessed for pulmonary infiltrates and COVID-

19-related medication (i.e., antibiotics, Remdesivir, Hydroxychloroquine) was documented. Patients were observed for the duration of their hospital stay after the procedure (clinical duration time) until death or discharge. A survival analysis was performed based on overall survival and clinical duration time. Patients were followed daily during their complete stay and after 30 days, a follow-up clinic visit was scheduled.

Healthcare providers

Fourteen healthcare providers, who were deployed at COVID-19 wards and thus exposed to SARS-CoV-2 on a daily basis, were recruited in critical care units of a community hospital and randomly assigned to a treatment group (group 3, n = 7) or a control group (group 4, n = 7). Individuals in the treatment group received 2 cc of an acellular stem cell-derived bioactive molecule solution through an intravenous catheter, while participants in the placebo group received the same amount of saline.

Inclusion criteria were:

- 5/7 days of work in close contact with COVID-19 patients over the last months and ongoing;
- Availability for follow-up and COVID-19 testing.

Exclusion criteria were:

- Current positive testing or development of symptoms of COVID-19;
- History of malignancy in the last 2 years.

All health care providers completed an assessment about their overall health (i.e., pre-existing conditions, current health complaints) and provided a negative COVID-test prior to the stem cell injection. At a 30-day-follow-up, participants underwent a second COVID-test and repeated the assessment for current health complaints. Moreover, health care providers were advised to report any treatment-related adverse events.

Statistics

Statistical analysis was performed in SPSS Statistics Version 26 (IBM, Armonk, NY, USA). Data are presented as mean ± Standard Deviation (SD). Differences with p values < 0.05 were declared significant. Pairwise T-Tests were performed to investigate differences between groups. A survival analysis was conducted under implementation of Kaplan-Meier-Estimates in order to detect potential survival benefits. Clinical course duration time was defined as days between the procedure and either death or discharge. However, due to the small sample size, no claim is made to statistical significance. The analysis is intended to serve as a preliminary review of potential survival benefits of the investigational drug. Thus, no a priori power calculations were performed.

Results

Twenty-six patients were enrolled and randomly assigned to either a treatment group (group 1, n = 13) or a placebo group (group 2, n = 13). All patients presented to the hospital emergency department and were admitted with symptoms secondary to COVID-19 infection. The mean age in group 1 was 60.07 ± 15.93 (females: N = 5, 55.4 ± 14.74 years, males: N = 8, 63 ± 16.89 years) and 70.61 ± 10.71 years (females: N = 7, 67.71 ±

12.08 years, males: N = 6, 74 ± 8.62 years) in group 2, respectively [non-significant (NS)]. Seven patients presented with dementia (2 in group 1 versus 5 in group 2; NS), 11 individuals with congestive heart failure (6 in group 1 versus 5 in group 2; NS), 17 subjects with renal disease (9 in group 1 versus 8 in group 2, NS), and seven participants had chronic pulmonary conditions (2 in group 1 versus 5 in group 2; P = NS). Blood analysis including white blood cell count, hemoglobin, hematocrit, and platelets at baseline showed no significant differences between the groups (NS). Detailed demographics are presented in table 1.

Six patients in group 1 and 11 patients in group 2 showed pulmonary infiltrates on chest imaging studies. Four patients in group 1 and 7 patients in group 2 required intubation and ventilator therapy (NS between groups). Standard treatment consisted of intravenous (iV) fluids and symptomatic therapy. All patients received antibiotics and dexamethasone. One individual in group 2 (placebo group) received Hydroxychloroquine. None of the patients included in the analysis received Remdesivir (since it was unavailable at the time of enrollment).

Tolerability and Adverse Events in Patients

All patients were closely monitored by specialized health care personnel in the context of critical care in the intensive care units. Injections were well tolerated and none of the participants demonstrated adverse reactions after the intervention. No injection-related changes of hemodynamic parameters, allergy-related symptoms or other serious side effects were documented.

Survival Analysis of Patient Sample

In group 1, one patient died in the hospital following a COVID-19 infection, 12 participants left the hospital in a stable condition 16.77 ± 3.72 days after the injection. Six patients in group 2 died, while the remaining eight participants were discharged following adequate recovery ($p < 0.05$ versus group 1) after 6.72 ± 1.87 days post injection (clinical duration time, $P < 0.05$ versus group 1). The 30-day survival rate in group 1 was 92.3% versus 53.8% in group 2, respectively ($P < 0.05$; image 1). There was no difference with regard to either WBC count, anemia, chest imaging findings, or concomitant treatment between the two groups.

Health Care Providers

Fourteen health care providers were recruited from COVID-19 wards and randomly assigned to a stem cell group (group 3, n = 7) or a placebo group (group 4, n = 7). None of the participants had underlying chronic or acute health conditions. No therapy-related adverse events were reported or observed. A follow-up COVID-19 test after 30 days revealed negative results for all health care workers in both groups. None of the participants showed coronavirus-related symptoms (i. e. fever, cough, respiratory symptoms, pharyngitis) at follow-up. No group differences were reported.

Discussion

We report a small randomized double-blind placebo-controlled study investigating the effect of acellular stem cell-derived bioactive molecules on patients with severe COVID-19 infections. We further explored the safety and potential prophylactic effects of stem

cell injections in health care workers with extensive exposure to the novel Coronavirus. Stem cell therapy was observed to be safe as no adverse events were noted and injections were well tolerated in both patients and health care workers. Of interest, the thirty-day survival rate in the patient intervention group was significantly higher compared to the placebo group (92.3% versus 53.8%, $P < 0.05$). A single intravenous stem cell injection might therefore be associated with improved survival in severely ill COVID-19 patients.
While the exact mode of action for the effect of stem cell therapy on COVID-19 has to be fully elucidated, we propose the following underlying biomechanisms:

1. *Anti-inflammatory properties and immunomodulation*

Coronavirus-related pneumonia is highly associated with elevated secretion of pro-inflammatory cytokines and chemokines (cytokine release syndrome, cytokine storm) (3). Following the entry of SARS-CoV-2 into respiratory endothelial cells, pathogenic Th_1 cells promote inflammatory cytokine production including but not limited to interleukins (i.a., IL-1-b, -2, -6, -7, -8), granulocyte colony-stimulating factor (GCSF), granulocyte–macrophage colony-stimulating factor (GMCSF), interferon gamma (IFNγ), IFNγ-induced protein 10 (IP10), macrophage inflammatory proteins (MIP), vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNFα) (3-5). Hereupon, elevated systemic concentration of pro-inflammatory cytokines positively correlates with exacerbated disease severity (5). In synopsis with weak anti-viral interferon responses and thus increased viral replication, prolonged cytokine storms account for fulminant disease progression (4). As a result, pulmonary edema, impaired gas exchange and cardiopulmonary failure culminate in acute respiratory distress syndrome (ARDS) and increased mortality (3,6). Stem cells might suppress the hypersecretion of pro-inflammatory mediators in the pulmonary vascular bed via direct cell-to-cell communication and paracrine immunomodulation (7-9). In that context, stem cell therapy might induce the secretion of anti-inflammatory cytokines and inhibit T-cell-dependent immune responses through the release of PGE2, TGF-b, nitric oxide (NO), and indoleamine2,3-dioxygenase (IDO). Moreover, increased proliferation of regulatory T-cells (T_{reg}) can promote the down-regulation of effector T-cell production and activation. Neutrophil-dependent immune responses might be modulated with regards to enhanced phagocytic activity and reduced intravasation resulting in decreased TGF-b activation (10-13) and a subsequent amelioration of the cytokine storm. MSCs have further been shown to facilitate the differentiation of regulatory dendritic cells (regDC), which might induce a shift from T-Helper Cells Type 1 (Th_1) immunoreactions towards Th_2 responses (14-16).

2. *Tissue regeneration*

Stem cells can promote endogenous repair mechanisms through secretion of angiopoietin-1 (AP-1) and keratinocyte growth factor (KGF) as well as proliferation into type II alveolar epithelial (ATII) cells. Consequently, the alveolar capillary barrier can be both preserved and restored, thus obviating further inflammation and viral intrusion (7,16,17). By protection of alveolar type II endothelial cells from aerolized uptake of SARS-CoV-2 and prevention of pulmonary fibrosis, maintenance of structural and functional integrity could be provided (19-23).

A small number of clinical trials and anecdotal reports have shown promising results implementing stem cells as a therapeutic approach for COVID-19 (24-28). Among the identified trials, study designs varied with one retrospective analysis (25) and four prospective studies, which were conducted as non-randomized open-label testing (24,26-28). Hereupon, Leng et al. compared their findings to a control group receiving standard care (24). Sample sizes ranged from one to 25 patients. Across the trials, a total of 63 patients received stem cell therapy, whereas 54 (85.71%) participants showed signs of clinical improvement and/or were discharged, five (7.94%) individuals remained in a critical condition and four (6.35%) patients died (28-32). Four groups reported positive overall tolerability (24,26-28). Chen et al. observed adverse events in 12% (n = 3) of their patient population (i.e. heart failure, liver dysfunction, and allergic rash), that reversed completely.

Furthermore, genetic analysis of MSCs revealed the absence of angiotensin-converting-enzyme II (ACE_2) and transmembrane serine protease II (TMPRSS2), pointing at prevailing properties of MSCs against cellular invasion of SARS-CoV-2 (25).

With regards to hematologic surrogate parameters, five out of six studies found significant improvements of lab results (24,26-28). In that context, pro-inflammatory factors [(IL-6, TNF-α, C-Reactive Protein (CRP)] were found to be reduced (24,26,28), T_{reg} and DC subsets (28) as well as CD^{3+}, CD^{4+} and CD^{8+} blood cell counts (24,26-28), were increased, and concentrations of D-Dimer and Ferritin diminished (26,27). However, the research group surrounding Chen et al. found no significant changes in white blood cell count (WBC), CRP, procalcitonin (PCT), and IL-6 measures after stem cell transplantation (25).

Moreover, differentiation of MSC into type 2 alveolar endothelial cells was observed by Leng et al., suggesting therapy-related tissue restoration (24).

The synopsis of those findings supports our proposed modes of action, specifically anti-inflammatory, immunomodulatory, and tissue regenerative properties, as pivotal mechanisms in the amelioration of coronavirus-related cytokine storms. Furthermore, the identified data is in accordance with our observations regarding the safety profile of stem cell therapy.

Limitations

Our observations are limited due to a number of determinants. First of all, the sample size is relatively small and the sampling procedure was performed implemented in a single hospital (single-center study) which limits the presented conclusions to preliminary observations. Furthermore, no direct measurement of inflammatory parameters beyond standard lab tests such as CBC and CMP were performed. Thus, neither the number of patients, who experienced a cytokine storm, nor potential corresponding ameliorating effects of stem cell therapy could be retraced. In that regard, patients did also not undergo additional study related imaging as the present study constitutes a pilot phase trial of observational nature. The study is not designed to deliver statistically conclusive results, however, even in this small study cohort benefits in survival were observed. Large scale studies are warranted to further solidify these preliminary investigations.

Conclusion

The present study investigates the effects of stem cell-derived bioactive molecules on a small cohort of COVID-19 patients reflecting on a randomized, double-blind and controlled study design. It is reasonable to postulate that stem cell injections were safe both in healthy subjects and individuals contracting SARS-CoV-2. Stem cell therapy further improved survival in critically ill COVID-19 patients.

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Disclosure

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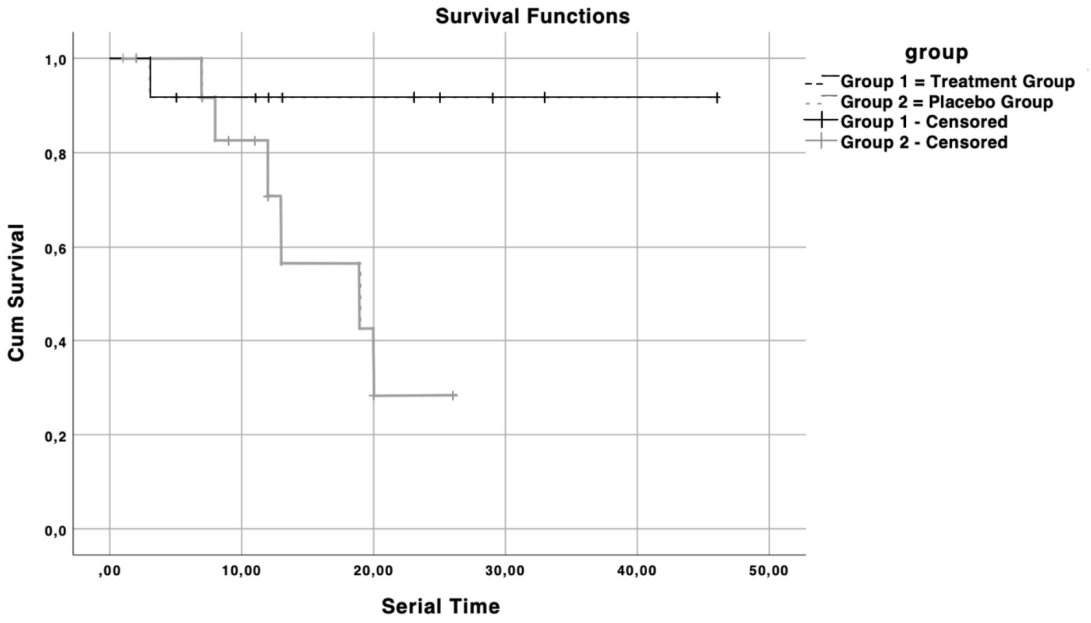
Table 1: Patient Demographics

Characteristics (n = 26)	Group 1 (n = 13)	Group 2 (n = 13)	P-value
Age [a]	60.08 ± 15.93	70.62 ± 10.7	NS
Males	*63 ±5.97*	*74 ±3.52*	*NS*
Females	*55.4 ±6.59*	*67.71 ±4.57*	*NS*
Chronic Conditions [n = (%)]			
Dementia	*2 (15.39%)*	*6 (46.15%)*	NS
Congestive Heart Failure	*5 (38.46%)*	*4 (30.77%)*	*NS*
Pulmonary Diseases	*2 (15.39%)*	*3 (23.08%)*	*NS*
Renal Diseases	*9 (69.23%)*	*7 (53.85%)*	*NS*
Dialysis	*4 (30.77%)*	*4 (30.77%)*	*NS*
Blood Cell Counts			
White Cell Count [x10^9/L]	*7.83 ±4.35*	*7.22 ±3.41*	*NS*
Hemoglobin [g/dL]	*9.95 ±2.61*	*11.46 ±1.78*	*NS*
Hematocrit [vol%]	*30.75 ±7.82*	*34.76 ±5.28*	*NS*
Platelets [x10^9/L]	*192 ±65.05*	*196.31 ±118.22*	*NS*
Deaths	1 (7.69%)	6 (46.15%)	< 0.05

Data are mean ±Standard Deviation, NS = Non-significant

Image 1: Kaplan-Meier-Survival-Function Group 1 (black line, stem cells) versus Group 2 (grey line, placebo).



Kaplan-Meier-Survival Estimate. Graphs are representing survival times [days] of all individuals in one group each. Censored Data: Type of missing data, survival time of individuals is at least as long as observation period. In group 1 (stem cell group), one event (= deaths; 1/13) occurred, in group 2 (placebo group), six events (6/13) occurred.