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Renal Involvement and Outcomes in Severe COVID-19 Patients After Stem Cell Jet-Nebulization

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Abstract: *Introduction:* The COVID-19 pandemic presented an unprecedented challenge to identify effective drugs and means for their prevention and management. It is more difficult in severe cases due to complications in various vital organs such as the kidneys. *Methods:* An analytical study was carried out within the framework of the clinical trial "SENTAD-COVID Study" (ClinicalTrial.org, NCT04473170), whose objective was to describe acute kidney injury (AKI) in severe patients with COVID-19 and its relationship with clinical outcomes. A novel stem cells treatment for COVID-19 patients using an autologous peripheral blood nonhematopoietic-enriched stem cells cocktail was developed by the research team of the Abu Dhabi Stem Cells Center and applied at four Abu Dhabi Health Service Company hospitals. The sample consisted of the severe COVID-19 recruited patients: 20 in the experimental arm (Group A) and 24 controls (Group B). Both groups received COVID-19 standard treatment. *Results:* 29.5% of the patients studied suffered AKI. Mortality was lower in group A compared to the control group (20% vs. 30%, respectively), group A showed 25% AKI while group B 35%, sepsis was significantly lower in the treated group A compared to controls (25% vs. 35%; p=0.0095) Hazard Ratio=0.38, (95% CI: 0.16–0.86), given a Number Needed to Treat=2.5 patients. Group A had a significant reduction in inflammation markers at 25 days compared to the day of recruitment: C-Reactive Protein (median: 207.05 mg/L vs. 27.30 mg/L), IL-6 (median: 355.80 pg/L vs. 35.87 pg/L), and group A was the only one that presented a better proportion of patient with the recovery to normal values of the Neutrophil/Lymphocyte Ratio at 25 days, from 100% to 71.42% p=0.0108. *Conclusions:* One-third of the patients studied suffered AKI, group A patients showed a clear tendency to improve compared to controls, suggesting that the proposed therapy promotes healing and early recovery in severe COVID-19, which might be related to the anti-inflammatory effect of cellular therapy.

Keywords: COVID-19, SARS-CoV-2, Acute Kidney Injury, Hemodialysis, Sepsis, Stem Cell Therapies

1. Introduction

The COVID-19 pandemic caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) presented an unprecedented challenge to identify effective drugs for prevention and treatment. Many countries, including the United Arab Emirates (UAE), take every precautionary measure to slow and control the spread [1, 2]. Society required the intervention of all healthcare providers. Everyone got involved in different ways worldwide, especially the sanitary and health researcher sector, including physicians [3]. We must support the intensive care unit (ICU) work, no matter the specialization.

In Abu Dhabi Stem Cells Center (ADSCC), we felt the need to cooperate with the UAE National research efforts to find a better therapy for COVID-19. Therefore, a phase I/II clinical trial named "SENTAD-COVID Study" applying an autologous peripheral blood nonhematopoietic-enriched stem cells cocktail (PB-NHESC-C) was evaluated regarding its safety and efficacy in COVID-19 cases starting from April 2020. The study was retrospectively registered on July 16th, 2020, as ClinicalTrials.gov. NCT04473170 [4]. This potential breakthrough coronavirus treatment developed at ADSCC has shown promising results [5]. The virus and comorbidities related were seen to affect the urinary tract and kidney function, becoming an essential factor of morbidity and mortality [6-8]. Indeed, a study by Zou et al. reported the presence, almost 2.4%, of angiotensin-converting enzyme (ACE-2) positive cells in the bladder urothelium, making the urinary bladder more susceptible to SARS-CoV-2 infection [6].

Another critical factor is sepsis or septic shock. The resulting cytokine storm syndrome (induced due to high levels of cytokines) and consequently numerous adverse reactions in the human body have been observed. It can also be immune-mediated acute kidney injury (AKI) [6, 8], causing high mortality rates (60–90%) [9]. Given the potential of the stem cells in sepsis and clinical evolution of chronic conditions, with the stimulation by humoral factors, strategies such as stem cell-based therapy are being proposed to regulate inflammation, prevent or mitigate this cytokine storm through their immunomodulatory capacity [10].

Tools like neutrophil-lymphocyte ratio (NLR) were used as a prognostic biomarker in urological diseases like kidney and bladder cancers [11, 12]. Several authors used this ratio as an independent indicator of short and long-term mortality during the pandemic, which does not require additional costs and is rapidly accessible [13, 14]. A recent meta-analysis noted that 35–75% of COVID-19 patients admitted at the ICU developed lymphopenia, a more frequent feature of patients who died of the disease [15, 16]. A low lymphocyte count was reported in the analysis of 67 COVID-19 patients from Singapore, therefore predictive for admission to the intensive care unit (ICU) [15, 17]. In this article, we analyzed the repercussion of the COVID-19 in kidney function and the stem cell treatment given with the outcomes.

2. Methods

2.1. Research Design

This search was carried out within the framework of the SENTAD-COVID Study [4]. Therefore, it is necessary to explain we were searching for data derived from an adaptive, multicentric, open-label, and randomized controlled phase I/II clinical trial involving hospitalized adult patients with confirmed COVID-19 infection during the outbreak in the Emirate of Abu Dhabi, 2020 conducted in four Abu Dhabi Health Service Company (SEHA) hospitals: Sheikh Khalifa Medical City, Al Rahba Hospital, Al Mafraq Hospital, and Al Ain Hospital.

2.2. Study Participants

The patient's disease severity for COVID-19 was recorded according to the ordinal 8 points WHO Blue-Print paper [18]. The sample consisted of 44 patients included as severe COVID-19 patients with scores between 5 to 7 on the day of recruitment in the Clinical Trial. Patients were randomized into the intervention group A (n=20) and the control group B (n=24). The ADSCC Scientific Commission and the ADSCC Research Ethics Committee (REC) approved the initial trial research project, and it was later approved by the Ministry of Health and Prevention (MOHAP) via the Emirates IRB for COVID-19 Research (ID Ref: DOH/ CVDC/2020/1172). Furthermore, following the World Medical Association (WMA) Declaration of Helsinki, study participants' rights were guaranteed, and written informed consent was signed [19].

2.3. Clinical Intervention and Follow-up

The novel stem cells cocktail was obtained by collecting 300 mL of peripheral blood (PB) and processed at the ADSCC Stem Cells Laboratory in a closed system by a patented procedure described previously [20]. For patients in group A, stem cell jet-nebulization with the autologous PB-NHESC-C, including platelet-derived growth factors (PDGF) and anti-SARS-CoV-2 antibodies, was done in two consecutive days 10 mL doses of the investigational product the next day after inclusion in the study. Nevertheless, both groups received COVID-19 standard treatment established by MOHAP [2]. An early follow-up was done for at least 28-days, or until they were discharged from hospitals. Laboratory tests were done for both groups during patient inclusion (before therapy) and 25 days after treatment. The total hospital length of stay (LOS) was also calculated.

A comparison was made between both groups of patients within the study framework, and particularly for group A, we compared biomarkers results before and after treatment. In addition, data were collected about demographic variables, including gender, age, comorbidities, and body mass index (BMI)[21], within 24 h of inclusion in the study. We also recorded vital signs, hospitalization stays, AKI as the need for

hemodialysis, sepsis, and mortality from both groups during the follow-up. Furthermore, clinical laboratory tests were performed according to ADSCC's Clinical Laboratory procedures, including C-reactive protein (CRP), D-dimer, Interleukin-6 (IL-6), the white blood cells count (WBC), neutrophil to lymphocyte ratio (NLR), and other biomarkers. Lymphopenia was defined as an absolute lymphocyte count $<1.00 \times 10^9$/L. NLR abnormal cut point used was ≥3 [13, 14]. For the rest of the laboratory test, we applied the internationally accepted normal ranges.

2.4. Statistical Analysis

Due to the non-normal distribution of the variables, nonparametric statistical methods were used. The *Chi-Square* test compares the BMI categories, comorbidities, and disease severity score. The NLR status before and after for both groups was calculated by MedCalc software [22]. The *U-Mann-Whitney* test was applied to calculate median and the median related 95% Confidence Interval (95% CI) for age and hospital LOS. Laboratory parameters comparisons, as well as the Hazard Ratio (HR), its 95% CI, and the Number Needed to Treat (NNT), were calculated for the sepsis complication using the Graph Pad software v.8 (la Jolla, CA. USA) [23]. P <0.05 was considered statistically significant.

3. Results

3.1. Patients Characteristics

The sample consists of 44 men with severe COVID-19 illness: 31 critically ill (score 7) and 13 severe patients (scores 5 and 6). Regarding the comorbidities, *Diabetes mellitus* and arterial hypertension were the most common diseases in both groups. Furthermore, both groups did not have any statistical differences on the day of inclusion, as shown in Table 1.

Table 1. *Patient's Clinical Characteristics on the Inclusion Day of the Study.*

Characteristics	**Group A (N=20)**		**Group B (N=24)**		***P*-value[a]**
	Median	**95% CI**	**Median**	**95% CI**	
Age (years old)	**50**	**45-56**	**50**	**39-58**	**0.8840**
Body Mass Index	**n**	**%**	**n**	**%**	***P*-value[b]**
Non-determined	1	5.00	0	0	0.6274
Normal	7	35.00	3	12.50	0.5419
Overweight	9	45.00	10	41.66	0.9115
Mild obesity	3	15.00	7	29.16	0.5557
Moderate obesity	0	0	2	8.33	0.5296
Morbid obesity	0	0	2	8.33	0.5296
Comorbidities					
Chronic Anemia	0	0	1	4.16	0.6575
Smoker	1	5.00	0	0	0.6274
Diabetes mellitus	9	45.00	7	29.16	0.8088
Hypertension	5	25.00	5	20.83	1.0000
Dyslipidemia	3	15.00	1	4.16	0.6332
Chronic Renal Disease	0	0	1	4.16	0.6575
Cardiac Diseases	1	5.00	0	0	0.6274
Chronic Respiratory Diseases	4	20.00	1	4.16	0.5191
Disease Severity Score					
5	3	15.00	7	29.16	0.5557
6	2	10.00	1	4.16	0.7851
7	15	75.00	16	66.66	0.9282

95% CI: Confidence interval of the Median; P: Significance level; [a]: U-Mann-Whitney test; [b]: Chi-square test.

3.2. Follow-up Outcomes

After the stem cells jet-nebulization, we found a lower hospital LOS in group A with a median (95% CI range) of 20.5 (16-33) days, with a minimum of 9 and a maximum of 41, and a range of 32 days, while in group B, it was 24.5 (16-33), minimum 4, a maximum of 122, and a range of 118 days, but without statistical significance. In addition, the mortality rate was lower in group A (20%) compared to group B (30%). 25% of the patients in group A required hemodialysis as continuous renal replacement therapy for AKI, compared with 35% in group B.

On the other hand, a lower proportion of patients from group A suffered from sepsis than group B (25% vs. 65%), HR=0.38 (95% CI: 0.16-0.86), p=0.0212. These results suggested an NNT=2.5. Furthermore, the secondary sepsis proportion was significantly lower in group A than in group B during the early follow-up (P=0.0095) (Table 2). This result was related to different bacterial strains: The pathogens causing sepsis in group A vs. group B were *Candida albicans* (5% vs. 22%), *Streptococcus pneumonia* (10% vs. 0%), *Pseudomonas aeruginosa* (5% vs. 9%), *Klebsiella pneumoniae* (0% vs. 17%), *Enterobacter aerogenes* (0% vs. 4%) and *Staphylococcus aureus* (5% vs. 4%) in group A vs. group B, respectively.

Table 2. *Clinical Outcomes for Both Groups After the Follow-up.*

Outcomes	Group A (N=20)		Group B (N=24)		*P*-value
	Median	95% CI	Median	95% CI	
Total Hospital Lengths of Stay (Days)	**20.5**	**16-33**	**24.5**	**16-33**	**0.7304[a]**
Other outcomes	**n**	**%**	**n**	**%**	
Mortality	4	20	6	30	0.4535[b]
Hemodialysis	5	25	8	35	0.4820[b]
Sepsis	5	25	15	65	**0.0095[b]

95% CI: Confidence interval of the median; P: Significance level; [a]: U-Mann-Whitney test; [b]: Chi-square test. **: highly significant.

On inclusion day, the absolute leucocytes (WBC) and neutrophil counts, creatinine, IL-6, CRP, and D-Dimer levels were out of the normal range in most patients, without significant differences between the groups. Still, a little bit worse in group A. Although lymphocytopenia was common in both groups; Indeed, the absolute lymphocytes count was significantly lower in group A (median: 0.85, 95% CI range 0.8-1.2) compared with group B (median: 1.20, 95% CI range 0.91-1.38) with p=0.0422. The NLR was also higher in group A than in group B, with a median (95% CI) of 9.76 (7.15-12.38) vs. 7.16 (4.0-9.95) (P=0.0125) (Table 3).

Table 3. *Laboratory Parameters Distribution at the Study Inclusion Day.*

Parameters	Group A (N=20)		Group B (N=24)		*P*-value[a]
	Median	95% CI	Median	95% CI	
WBC ($\times 10^9$/L)	9.95	7.80-15.80	9.35	7.58-12.31	0.4371
Neutrophils ($\times 10^9$/L)	8.7	6.4-14.3	6.94	5.66-9.64	0.2074
Lymphocytes ($\times 10^9$/L)	0.85	0.8-1.2	1.20	0.91-1.38	*0.0422
NLR (Ud.)	9.76	7.15-12.38	7.16	4.0-9.95	*0.0125
Creatinine (mg/L)	1.165	0.94-1.36	1.40	0.90-2.12	0.7661
D-Dimer (mg/mL)	1.78	1.09-5.09	1.40	1.05-3.24	0.3113
CRP (mg/L)	207.05	70.0-310.2	166.8	74.6-265.9	0.4761
IL6 (pg/L)	335.80	136.1-955.8	326.8	59.9-966.0	0.7291

95% CI: Confidence interval of the median; P: Significance level; [a]: U-Mann-Whitney test; *: significant difference; WBC: Withe Blood Cells; NLR: Neutrophil/Lymphocytes Ratio; CRP: C-Reactive Protein, IL-6: Interleukin-6.

For group A, the median (95% CI) levels of creatinine, WBC, and absolute neutrophils count did not show statistically significant variations after 25 days of follow-up in a lab check-up. Nevertheless, the lymphocytes, CRP, and IL-6 count statistically improved after the stem cells cocktail therapy combined with the standard care, as shown in Table 4.

Table 4. *Group A Patients Before and 25 Days After Stem Cells Treatment.*

Parameters	On the Inclusion Day		After-treatment		*P*-value[a]
	Median	95% CI	Median	95% CI	
WBC ($\times 10^9$/L)	9.95	7.80-15.80	14.00	9.30-20.30	0.2929
Neutrophils ($\times 10^9$/L)	8.70	6.4-14.3	9.90	5.80-18.10	0.7150
Lymphocytes ($\times 10^9$/L)	0.85	0.8-1.2	1.60	0.70-4.60	*0.0193
NLR (Ud.)	9.76	7.15-12.38	4.13	1.80-20.11	0.1795
Creatinine (mg/L)	1.165	0.94-1.36	0.915	0.62-1.19	0.0802
D-Dimer (mg/mL)	1.78	1.09-5.09	2.22	0.20-6.28	0.7662
CRP (mg/L)	207.05	70.0-310.2	27.30	4.50-158.5	**0.0093
IL-6 (pg/L)	335.80	136.1-955.8	35.87	4.27-237.0	*0.0151

95% CI: Confidence interval of the median; P: Significance level; WBC: white blood cells; NLR: Neutrophil/Lymphocyte Ratio; CRP: C-Reactive Protein; IL-6: Interleukin-6 [a]: U-Man-Whitney test; *: significant; **: highly significant.

The NLR ≥3, which remarked a higher risk of mortality in patients in group A (100%) on the inclusion day, compared to group B patients (79%), (p=0.0313), dropped from 100% to 15 patients (75%) after the intervention, with statistical significance (p=0.0183). In contrast, group B kept the same proportion of abnormal NLR (Table 5).

Table 5. *Neutrophil-Lymphocyte Ratio Findings Before and After 25 days of Treatment.*

Neutrophil-Lymphocyte Ratio	Group A (N=20)		Group B (N=24)		*P*-value[b]
Abnormal (cut-off ≥3)	**n**	**%**	**n**	**%**	
At inclusion	20	100	19	79.16	*0.0321
After treatment	15	71.42	19	79.16	0.5560
P-value	*0.0108		1		

P: significance level; *: Significant difference. [b]: Chi-square test.

4. Discussion

Our study data showed only male COVID-19 patients admitted to the ICU (no females with critical scores were found during the study period). However, the early experience from China and elsewhere confirmed a male predominance in ICU incidence of this disease compared to females [24]. Furthermore, it was also found that patients with diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and chronic kidney disease exhibit worse clinical outcomes when are infected with SARS-CoV-2 [25, 26]. Following other studies, our data reported cardiovascular, *Diabetes mellitus*, hypertension as common comorbidities observed among the severe COVID-19 patients, together with higher concentrations of D-Dimer and NLR as independent risk factors for poor outcomes [27, 28].

Recent evidence shows that AKI is common in COVID-19 critically ill patients. Accordingly, one study from Wuhan, China (27), found in 52 critically ill patients admitted in the ICU that AKI was the most common extrapulmonary complication, observed in 15 patients (29%), more common than cardiac injury (23%), and liver dysfunction (23%). Furthermore, of all AKI patients, eight (25%) needed continuous renal replacement therapy, and 12 (80%) died with a median duration from ICU admission to death of 7 days (Inter-Quartile Range: 3-11) [25, 27]. This result suggests that kidney abnormalities are more common than expected and are fatal complications associated with higher mortality.

The data for hospital LOS in days, mortality, and especially sepsis was better in group A than B. Although the median comparison in-hospital LOS was not significantly different between groups, the range was much shorter in group A than in group B. It means better homogeneity, probably related to the intervention. In addition, the stem cells cocktail perhaps can facilitate the prediction of disease behavior, which was around 32 days. In comparison, group B showed 118 days due to the statistical dispersion of the group B data. This phenomenon may explain the lower incidence of sepsis in group A because the stem cells were protective against nosocomial infections, as other authors also point out [29].

It was statistically found that for each patient treated in group A, we need to treat 2.5 patients in group B to have the same beneficial effect of stem cell nebulization. In addition, attenuation of bacterial sepsis mediated by stem cells has been described via several mechanisms, such as improving the phagocytic ability, secreting antimicrobial peptides [10, 26], and increasing bacterial clearance [10, 30].

Likewise, predictive biomarkers improved after receiving the treatment, such as NLR, CRP, absolute lymphocyte count, and IL-6 levels. Especially the last one is considered promptly and transiently produced in response to infections and tissue injuries. It can contribute to host defense through the stimulation of acute-phase responses, hematopoiesis, and immune reactions. Although transcriptional and posttranscriptional mechanisms strictly control its expression, dysregulated continual synthesis of IL-6 plays a pathological effect on chronic inflammation and autoimmunity [31], and of course, in the so-called cytokine COVID-19 storms [32].

The NLR itself is considered an independent biomarker of severity and mortality risk [14, 33]. In these severe COVID-19 patients, all critically ill cases had elevated acute phase reactants before the intervention. In patients of group A, we found a higher risk of mortality due to lymphopenia and high NLR. Still, it was undoubtedly reverted after 25 days in a higher proportion of patients treated with the stem cells cocktail therapy. In contrast, there were no changes in the follow-up of this biomarker in group B. Therefore, we accredited the result as the beneficial effect of the intervention.

There is a polemic discussion among clinicians regarding the pathophysiology of kidney damage. It was demonstrated the virus's presence in tubular epithelial cells by immunohistochemistry and in situ hybridization [25, 34]. Still, other authors suggested that AKI in COVID-19 patients could result from cytokine release syndrome [35] rather than active viral replication in the kidney. Furthermore, it is well known that stem cells can differentiate into lung cells, among others, reprogramming the immune response to reduce destructive inflammatory elements and directly replace damaged cells and tissues [10].

On the other hand, the PDGF in the cocktail has paracrine effects on the modulation of the cytokine storm in the lungs and throughout the circulatory system, explaining this phenomenon found in our study, evidenced by a decrease in acute phase reactants. Perhaps, if those patients were treated earlier, we could avoid the AKI and hemodialysis requirement since the stem cells cocktail immunomodulating capacity can suppress the cytokine storm. Additionally, because this therapy is an autologous treatment, there are no immunological reactions to this preparation. Therefore, only rare adverse effects like fainting and dizziness may occur linked with blood collection.

Nevertheless, treatment of more patients and data meta-analysis could help better interpret our results in kidney features in this pandemic situation, so we recommend further studies.

5. Conclusions

In this study, about one-third of the severe patients had kidney failure, and sepsis was significantly lower than controls in the treated group A. Also, they showed a better tendency to improve than those in the control group, evidenced by an improvement in the NLR and a significant reduction in inflammation markers like CRP and Il-6. The jet-nebulized cells therapy promotes healing and early recovery in severe COVID-19 infections as an add-on to other supportive treatments.

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