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Safety and Feasibility of Mesenchymal Stem Cell Therapy in Patients with Critical COVID-19 Infection – A Comparative Study

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ABSTRACT

Objective: To determine the outcome of Mesenchymal Stem Cell therapy compared to controls in critically ill COVID-19 patients.
Study Design: Quasi-Experimental Study.
Place and Duration of Study: Department of Pulmonology, Pakistan Emirates Military Hospital, Rawalpindi Pakistan, from Oct 2020 to Apr 2021.
Methodology: We selected 104 critically affected COVID-19 cases from the COVID High Dependency Unit and Intensive Care Unit. All patients were in critical condition and were not improving on the set protocols with high oxygen dependency. In the Intervention Group (Group-A, n=52) mesenchymal stem cell transplant Group, procedure was done using an intravenous drip in addition to the standard treatment as per hospital protocol while in the Control Group (Group-B, n=52) standard treatment was given using the hospital protocol. The study outcomes were improvement in High Resolution Computed Tomography score and reduction in Fraction of Inspired oxygen (FiO2) dependency up to 28 days post-transfusion or up to discharge.
Results: The HRCT severity score (range from 0 to 40) significantly improved in MSCT Group 25.8/40±14.7/40 compared to the controls. Similarly, the FiO2 improved 0.58±0.30 in the MSCT-Group as compared to the Control-Group. Moreover, MSCT significantly decreased mortality 29(55.7%) vs 47(90.3%) compared to the controls.
Conclusion: Mesenchymal stem cell therapy is very effective in decreasing the severity of HRCT score, improving oxygenation index and mortality in critical COVID-19 patients.

Keywords; COVID-19, ICU, Mesenchymal Stem Cell Transplantation, Mortality, Severity Score.

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INTRODUCTION

The COVID-19 pandemic devastated the lives of millions of people around the globe.[1] Since its emergence in the Wuhan region of China, the virus affected more than 410 million people globally, and close to 6 million died with the majority of deaths witnessed in the US (1 million), Brazil (0.6 million), India (0.5 million), and Russia (0.3 million). So far close to 1.5 million people have got infected with COVID-19 in Pakistan, and approximately 30,000 have succumbed to it, resulting in a mortality rate of 2.0%.[2]

Initially, the preventive measures put forward were social distancing, face masks, and isolation of diagnosed COVID-19 cases. However, vaccination has been considered the basic and most effective strategy for its prevention.[3]

Those catching the COVID-19 infection are at high risk of severe respiratory distress syndrome and mortality. Despite global efforts to establish effective interventions for coronavirus disease and its major complications, such as respiratory distress syndrome (RDS), the treatment remains mainly supportive. Hence, identifying an effective and safe therapy for severe COVID-19 is critical for saving lives. A significant number of cell-based therapies have gone through clinical investigation. Some healthcare centers and investigators have utilized mesenchymal stem cells therapy and reported effective responses.[4]

Some recent studies showed that biological interventions are promising for the management of inflammatory responses and tissue treatment of degenerative diseases. Of these, Mesenchymal Stem Cell Therapy (MSCT) has found a special place in the therapeutic research of COVID-19.[5] MSCT-based treatments have been applied in several autoimmune disorders successfully and are approved to be a safe treatment.[6,7] It seems that MSCTs can exert a profound effect on COVID-19 treatment relying on its immunomodulatory effect and regenerating potential.

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Given the dearth of similar studies in our region, and the importance of the topic, we aimed to determine the effect of MSCT transfusion in comparison to the standard hospital protocol-based therapy in critically ill COVID-19 patients.

METHODOLOGY

The quasi-experimental study was conducted at Pakistan-Emirates Military Hospital (PEMH), Rawalpindi Pakistan, from October 2020 and April 2021. Ethical approval for the article was taken from the Institutional Ethical Review Committee (ERC) with ERC approval certificate number (A/28/24EC148712022). Sample size was calculated using an online statistical calculator assuming, 30% of the subjects in the active Control Group and 64% in the Test Group.[8]

Inclusion Criteria: Patients of either gender aged 18 to 85 years, presenting at COVID High Dependency Unit/Intensive Care Unit with severe COVID-19 Pneumonia were included.

Exclusion Criteria: Pregnant females and patients who had already received MSCT were excluded.

In our study one patient from each group refused to have his data shared in this study hence 52 patients were placed in each group. Patients flow is shown in Figure-1. MSCT was given in the intervention group (Group-A) while standard therapy and monitoring given in the controls (Group-B). Patients were recruited using non-probability consecutive sampling technique

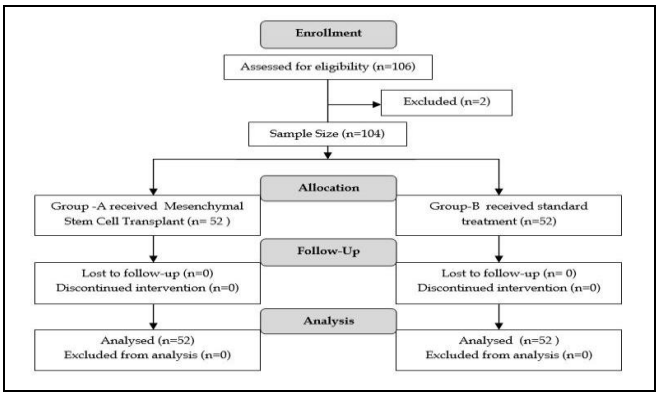
The patients were managed using a standardized protocol for severe pneumonia as being practiced at PEMH including steroids, antivirals, Tocilizumab, Plasma-pharesis and antibiotics. MSCT was initiated once no improvement was seen in the deteriorating condition even after all the standardized treatments given as per frequency and duration recommended in hospital protocol for up to two weeks. All patients had compromised oxygen saturation so were put on oxygen therapy immediately after admission. All of them were in severe to critical condition with high oxygen dependency and severe Covid Pneumonia as per HRCT chest severity score.

In the intervention arm, the MSCT procedure was done using an intravenous drip. The MSCs were suspended in 100 mL of normal saline, and total number of transplanted cells was 1 million cells/kilogram8 once. Every patient received one round of transplantation in total. The transplantation was performed over 1.5 hours with a speed of 30-60 drops per minute.

The study outcomes were measured as improvement in HRCT score and reduction in FiO2 dependency up to 28 days after MSC transfusion or up to discharge. Oxygen therapy flow rate and FiO2 was documented at 14th day of admission for both study and control groups and at 28th day Post MSC transfusion, just before discharge or death in both groups. The HRCT was done at14th day of admission for both study and control groups and 14th day post MSC in the study group and 28th day of admission for the control group. The maximum HRCT severity score was set at 40 in the study, the higher the score, the more critical the pneumonia and more severe lung involvement. The patients were closely monitored till the time they were considered fully recovered or up to 28 days post-MSC transfusion.

Data weas analyzed in Statistical Package for Social Sciences (SPSS) version 22. Categorical variables were presented as frequency and percentages and continuous variables were presented as mean and standard deviation. The mean scores of HRCT and oxygenation were compared using independent sample t-test between intervention and control groups. The *p*-value of ≤0.05 was considered significant.

Figure-1: Patient Flow Diagram (n=104) mesenchymal stem cell transplant (MSCT) Group, procedure was done using an intravenous drip in addition to the standard treatment as per hospital protocol while in the Control Group (Group-B, n=52)



RESULTS

Thirty-five patients (67.3%) in MSCT while 33(63.5%), in the control group were above 60 years of age. There were 8(15.4%) patients in MSCT and 4(7.7%) in the Control Group were younger than 50 years. The

mean age of patients was 63.80±11.00 years in MSCT group compared to 62.90±9.00 years in the control arm. Males were predominant with 37(71.2%) in MSCT and 36(69.3%) in the control group. The mean weight of patients was 67.50±9.60 kg in MSCT and 68.70±11.50 kg in controls. Close to one-fourth were smokers in both groups. Co-morbidities were equally distributed among both groups, there were 32(61.5%) patients with hypertension in MSCT group and 29(55.8%) in the control group. Diabetes mellitus was found in 27(51.9%) patients in MSCT and 30(57.6%) in the control group. The other frequent co-morbidity was ischemic heart disease 15(28.8%) in MSCT and 29(55.8%) in the control group. (Table-I)

Table-I: Baseline and Clinical Characteristics of Patients in Study Groups (n=104)

Characteristics	Group-A (n=52)	Group-B (n=52)
Age(years)		
Less than 50	8(15.4%)	4(7.7%)
50 to 60	9(17.3%)	15(28.8%)
Above 60	35(67.3%)	33(63.5%)
Mean±SD	63.80±11.00	62.90±9.00
Gender		
Male	37(71.2%)	36(69.3%)
Female	15(28.8%)	16(30.7%)
Weight (kg)		
Mean±SD	67.50±9.60	68.70±11.50
Smoking		
Yes	13(25.0%)	15(28.8%)
No	39(75.0%)	37(71.2%)
Co-morbidities		
Diabetes Mellitus (Type 2)	27(51.9%)	30(57.6%)
Ischemic Heart Disease	15(28.8%)	17(32.6%)
Asthma	2(3.8%)	4(7.7%)
Chronic Obstructive Pulmonary Disease	1(1.9%)	1(1.9%)
Hypertension	32(61.5%)	29(55.8%)

In this study, the average HRCT severity score was 25.80/40±14.70/40 in patients post MSCT Group compared to 34.50/40±6.40/40 in the controls and this difference was found statistically significant (*p*-value=0.001). The mean oxygen therapy flow rate was 11.20±5.70 liters in MSCT group patients while in the control group 14.60±8.30 liters and this difference in the two means between groups was statistically significant (*p*-value=0.04). Similarly, the mean FiO2 was found significantly greater in the control group compared to the MSCT cases (0.74±0.17 vs 0.58±0.30, *p*-value, 0.005). This shows a significant effect of MSCT therapy in critical COVID-19 patients. (Table-II)

The outcome of patients in terms of mortality was compared between the patients on MSCT and those given standard therapy according to hospital protocol for COVID-19. There were 29(55.7%) deaths in MSCT group compared to 47(90.3%) in the control arm. It was witnessed that MSCT reduced the risk of mortality 0.616(0.403– 1.053) significantly when compared with the standard COVID-19 therapy (Table-III).

In both MSCT and control groups in great majority of the cases, the cause of death was respiratory failure secondary to severe COVID pneumonia 26(89.6%) and 45(95.7%) respectively. In few of the cases, pulmonary edema was the cause of death. (Figure-2)

Table-II: Comparison of HRCT Score and Oxygenation Between Intervention and Control groups (n=104)

Parameters	Group-A (n=52)	Group-B (n=52)	*p*-value
HRCT severity score (range 0-40)			
Mean±SD	25.80±14.70	34.50±6.40	<0.001
Oxygen therapy speed (liters)			
Mean±SD	11.20±5.70	14.60±8.30	0.04
FiO2 (Fraction of Inspired Oxygen)			
Mean±SD	0.58±0.30	0.74±0.17	0.005

Table-III: Outcome of Patients in the Two Groups (n=104)

Outcome	MSCT Group (n=52)	Control Group (n=52)
Deaths	29(55.7%)	47(90.3%)
Alive	23(43.3%)	5(9.7%)

Relative Risk=0.616(0.403–1.053)

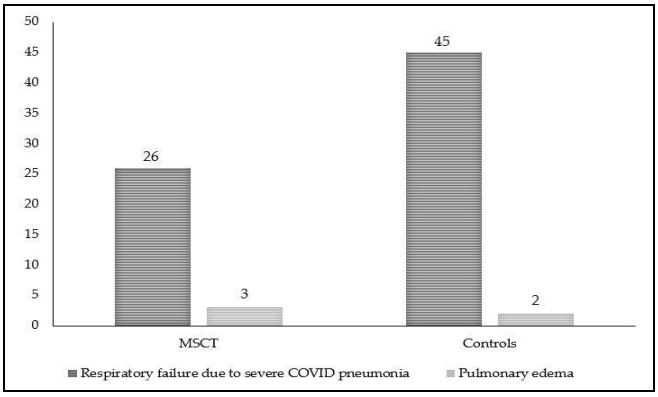


Figure-2: Cause of Death in the Study Groups (n=104)

DISCUSSION

International studies have reported that the outcome of patients improved after MSCT intervention showing oxygenation index and severity of disease improved enormously with MSCT intervention.[9,10] A study from the US reported similar findings after MSCT.[11] These are in line with our findings.

In the current study, the rate of mortality was notably lower in the MSCT group than controls. MSCT transfusion significantly reduced the risk of mortality

RR (95% CI) 0.616 (0.403–1.053) between groups. Previous evidence suggests that severe COVID-19 pneumonia is significantly associated with mortality as indicated by a study from Wuhan region which showed mortality of 45.2% in their severe to critical COVID-19 patients.[12] A study from Italy reported 26.0% mortality from their ICU.[13] Another Italian study also witnessed a similar trend of mortality with 23.0% mortality due to COVID-19.[14] The comparative high mortality rate in the controls in our study population could be attributed to older age and comorbidities. However, the effect of MSCT is evident and must be replicated in other settings and geographical regions to validate these findings.

In the present study, selective analysis on factors associated with mortality depicted that patients with Diabetes Mellitus, Ischemic Heart Disease and Hypertension were significantly associated with mortality. Previous studies have shown that COVID-19 is more likely to affect older males with comorbidities and even result in fatal respiratory diseases like acute respiratory distress syndrome.[15-18]

LIMITATIONS OF THE STUDY

There were some limitations as well as only HRCT severity score after therapy was measured and no pathological laboratory findings were collected which could have given insight into the patient's suffering and biochemical and blood imbalance if any.

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CONCLUSION

Mesenchymal stem cell therapy has a beneficial role in critical COVID-19 patients with significant improvement in HRCT severity score and oxygenation index. MSCT reduces the risk of mortality in these patients as well.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SA & MZHM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MH & NA: Study design, drafting the manuscript, critical review, approval of the final version to be published.

AR & SS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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