Efficacy of Remdesivir in Covid-19 Patients; Multicenter Study in Lahore

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Abstract: Introduction: This Pandemic of Covid-19 has shaken the world and devastating and unpredictable nature of the disease and scenario becomes worse when we see limited treatment options for this disease. Objectives: The objective of the study was to assess the efficacy of Remdesivir in patients having early phase of the disease. Methodology: Study Settings: The study was conducted in two major tertiary care hospitals, Fatima Memorial Hospital, Bahria international Hospital, Lahore. Sample size & Sampling Technique: A total of 60 patients were selected for this study who were suffering from COVID 19, out of which 30 were given Remdesivir and 30 patients were kept in control group. Participants were enrolled in the study after fulfilling inclusion and exclusion criteria. It was Probability sampling. Study design: Non-randomized control interventional study. Data Analysis: Data was analyzed with respect to demographics and clinical characteristics. Outcome was observed in terms of recovery and death. Also, the oxygen requirement and respiratory rate was measured on presentation and on 14th day of admission. Furthermore, coexisting conditions such as diabetes, hypertension, ischemic heart disease and chronic kidney disease were also considered regarding outcome in case group and control group. Results: Mean age of the study participants was 53.2 with standard deviation (SD)±14.6 years, whereas average age of cases was 49.2±15.1 and control 57.1±13.1 years. Male were 60% of the patients and 40% were females, whereas both cases and control had 57% males. The most common co existing disease was hypertension which attributed to 53% of the total sample size followed by diabetes which was present in 47% of the study participants. 23 (38%) participants did not have any coexisting disease. The data did not show any promises with Remdesivir therapy in patients with or without ventilatory support in comparison with participants who did not receive Remdesivir.

Keywords: COVID 19, Pneumonia, Remdesivir

Introduction
The novel corona virus, severe acute respiratory syndrome 2, (SARS-CoV-2), which causes COVID-19 disease has become the major pathogen of emerging respiratory disease outbreaks that have affected social, medical and economical aspects.[1] Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxemic respiratory failure, acute respiratory distress syndrome and multiorgan failure leading to mechanical ventilation. Patients with diabetes, cardiovascular disease, chronic kidney disease, hypertension and who require mechanical ventilation have high mortality.[2] Covid-19 is a single-stranded RNA virus that can be isolated. It has a complex pathological mechanism producing pneumonia and other complications leading to multiorgan failure. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. So far available data indicates that the viral infection is capable of producing an excessive immune reaction in the host.

In some cases, a reaction takes place which as a whole is labeled a 'cytokine release storm' causing extensive tissue damage with dysfunctional coagulation process. Other condition like micro clots (micro vascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome) has been associated with underlying lung viral injury causing the inflammatory reaction and the micro vascular pulmonary thrombosis.[3]

No specific antiviral drug has been proven yet effective for treatment of patients with severe coronavirus disease 2019 (COVID-19).[4] Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro.[5,6]

Materials and Methods
Objective: To assess the efficacy of Remdesvir in covid-19 pneumonia
Study design: It was be non-randomized control interventional study carried out in 3 months. Patients not willing for research will be considered as control

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group who will be provided other standard treatment modalities. Probability sampling was with the total sample size of 60 divided in two groups: Case and Control, with 30 participants in each group.

Patients was assigned as per inclusion criteria. Patients were offered convalescent plasma therapy first, in case if they were unable to arrange plasma then Remdesivir was started as per protocol. Both therapies (plasma, Remdesivir) were not given to same patient. Clinical assessment including chest x ray were done. Laboratory parameters were sent. After informed consent from patient/authorized representative, patients were allowed to continue concomitant medical care.

Remdesivir Adminstartion Protocol:
Patients on mechanical ventilation and or/ECMO (extracorporeal membrane oxygenation) Intravenous infusion of remdesvir 200 mg as loading dose over 60 to 120 mints on day 1 and daily infusion 100 mg was given from day 2 to day 10.

1) Patients not requiring mechanical ventilation and or/ECMO were given 200 mg loading intravenous (IV) infusion on day 1 and maintenance 100 mg infusion on day 2 to 5 if clinical improvement not demonstrated then additional 5 doses were given(i.e., up to day 10 total).

Patient were assessed daily. Assessment included daily vital signs, oxygen requirement and drug reaction. Lab testing was done daily (day 1 to day 10). Electrocardiography (ECG) was recorded on day 1 and 14. Nasopharyngeal swab for covid-19, polymerase chain reaction (PCR) was taken at day 14.

Drug was discontinued on occurrence of drug reaction, alanine/aspartate aminotransferase >5 times than upper normal limit, bilirubin >2 times than upper normal limit, e GFR <30 ml/min.

Inclusion Criteria:
1. PCR confirmed covid-19 pneumonia with radiographic findings
2. Duration of symptoms <12 days
3. Age>18 years
4. SaO_2 94 % or <94% on room air/supplemental oxygen

Exclusion Criteria:
1. Pregnancy
2. Breast feeding
3. Alanine aminotransferases (ALT)/aspartate aminotransferases (AST) >5 times than upper normal limit
4. On maintenance hemodialysis (H.D)/peritoneal dialysis (P.D)
5. Liver cirrhosis
6. Estimated glomerular filtration rate (GFR) <30ml/min

Data analysis: Data was entered and analyzed using SPSS24.0. Frequency and percentages were calculated for the qualitative variables like gender, comorbidities, response to treatment. Quantitative variables of the study like age, laboratory parameters were expressed as Mean ± SD.

Results: Patients were distributed according to age, gender and comorbidities. Mean age of the study participants was 53.2 with SD±14.6 years, whereas average age of cases was 49.2±15.1 and control 57.1±13.1 years. Male were 60% of the patients and 40% were females, whereas both cases and control had 57% males. The most common co existing disease was hypertension which attributed to 53% of the total sample size followed by diabetes which was present in 47% of the study participants. 23 (38%) participants did not have any coexisting disease.

Table 1 Demographic and clinical characteristic of patients at baseline(n=60)

Characteristic	All (N=60)	Case (N=30)	Control (N=30)
Age (Years)	53.2±14.6	49.2±15.1	57.1±13.1
Gender:			
Male	34(60)	17(57)	17(57)
Female	26(40)	13(43)	13(43)
Comorbidity:			
Diabetes	28(47)	16(53)	12(40)
Hypertension	32((53)	18(60)	14(47)
Chronic Kidney Disease	6(10)	3(10)	3(10)
Ischemic Heart Disease	10(17)	8(27)	2(7)
No Comorbidity	23(38)	10(33)	13(43)

Table 2 shows the outcome of cases and control with respect to the gender and type of comorbidity present in the patients. Also, the patients who didn't have any coexisting disease were including in this analysis. Overall, 22 cases recovered from COVID 19 out of which 13 were male and 9 were female. Furthermore, 76% of male cases who had the disease, recovered. Whereas, in control 88% of affected males and 92% females were recovered. Out of 16 diabetic cases 10(63%) participants recovered and 6 died. Almost similar trend was seen with hypertension. However, 11(92%) controls who had diabetes were recovered and 12(86%) hypertensive controls recovered. 90% (9) cases without any coexisting disease recovered and similar trend was seen in controls. Total 9 patients were on mechanical ventilation; mortality rate was 100% despite of being in case or control group.

Table 2 Outcome of Cases and Controls according clinical and demographic characteristics

	Case(n=30)		Control(n=30)	
	Recovery (22/30)	Death (8/30)	Recovery (26/30)	Death (4/30)
Gender:				
Male	13(76)	4(24)	15(88)	2(12)
Female	9(69)	4(31)	11(85)	2(15)
Comorbidity present	13(65)	7(35)	15(88)	2(12)
Diabetic	10(63)	6(37)	11(92)	1(8)
Hypertension	11(61)	7(39)	12(86)	2(14)
Chronic kidney disease	2(67)	1(33)	3(100)	0(0)
Ischemic heart disease	4(50)	4(50)	2(100)	0(0)
No comorbidity	8(80)	2(20)	11(85)	2(15)
On mechanical ventilation	0(0)	7(100)	0(0)	2(100)

Table 3 illustrates respiratory rate and oxygen requirement in cases and controls on presentation and on day 14 of the admission. It is evident that there was not significant decrease in respiratory rate in cases as compared to controls however, oxygen requirement decreased significantly in both cases and controls with a greater decrease in cases as compared to controls. Average oxygen requirement decreased from 13.4±4.3 liters to 8.6±8.9 liters in cases whereas in controls it decreased form 10.8±6.8 liters to 7.5±6.3 liters.

Table 3: Oxygen requirement, respiratory rate and eGFR in cases and controls on presentation and 14th day of admission

	Case		Control	
	On presentation	Day 14	On presentation	Day 14
Respiratory rate/min	22±2	21±6	22±2	18±3
Oxygen requirement (liters)	13.4±4.3	8.6±8.9	10.8±6.8	7.5±6.3
eGFR ml/min/1.73m2	73.4±20.4	71.9±22.4	76.9±11	75.6±16.5

Discussion

The results in this study mainly shows that Remdesivir had some better outcome in patients in terms of symptoms but there was no significant benefits that could lower the mortality rate as compared to patients not receiving the drug. This research has included many different aspects of demographic and clinical characteristics. Comparison was done in patients with co-existing medical conditions, such as diabetes, hypertension, chronic kidney disease and underlying ischemic heart disease.

It was also observed that in co-existing conditions the percentage of mortality was higher in people receiving Remdesivir. The only positive outcome was short term decrease in oxygen requirement of cases as compared to controls. A similar study done by Beigel, J.H., et al. with a sample size of 1062 concluded that Remdesivir was only beneficial for shortening the time of recovery in admitted patients which was also not significant enough to be mentioned as a fact. These findings were consistent with the preliminary report on the same patients.[7,8]

A study published by Wang, Y., et al.[9] about the role of Remdesivir in adults with severe COVID 19 showed that it was not associated with statistically significant clinical benefits but there was appreciate able reduction in time to clinical improvements in the patients who were treated earlier in the course of the disease. Similar results were shown in this study.[9] Goldman, J.D., et al.[10] conducted a study with 5 days

and 10 days course of Remdesivir in patients with severe disease. No significant difference in efficacy was observed in both cases but it was observed that the 10 days course may have a benefit in patients on mechanical ventilation.[10]. In contrast this study showed 100 % mortality in patient with COVID 19 who required mechanical ventilation despite of the administration of Remdesivir.

Another study performed regarding the safety of Remdesivir administration by Adamsick, M.L, et al.,[11] showed that there is still lack of evidence regarding the risk and benefits due to limited number of studies, however this study showed that there was no significant change in eGFR when cases and control were compared.[11]

Limitations: The sample size was not adequate in this study as many participants were hesitant to give consent for administration of Remdesivir. Also, the cost of injectable Remdesivir is not affordable for majority of the public. Furthermore, not much literature is available for comparison with other similar researches.

Recommendation: Further multicenter larger studies with larger sample size are required to establish the efficacy of this novel drug in Covid-19 so that we may establish local guidelines for the administration of intravenous Remdesivir in cases of COVID-19 disease.

Conclusion: There was no significant positive outcome found in patients who were administered intravenous Remdesivir in patients who required mechanical ventilation or not or whether they had any co-existing disease or not.

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