

EFFECT OF REMDESIVIR IN COVID-19 IN TERMS OF HOSPITAL DISCHARGE AND MORTALITY BENEFITS

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Abstract

Background & Objective: There is no first line antiviral treatment for Corona Virus Disease 2019 (Covid-19). Remdesivir is used as antiviral drug for covid 19 in different parts of world with variable results. The objective of our study was to assess the effect of Remdesivir in Covid-19, in terms of time to discharge from hospital and mortality rate benefit.

Methods: An interventional, single-center study conducted at Corona Wards of DHQ University teaching hospital Gujranwala. Two categories were made using simple random sampling technique. First category was marked 'Remdesivir group', to whom after Informed Consent Injection Remdesivir (200 mg on the principal day followed by 100 mg every day for the following four days) was given. Second category was the 'Control group'; they were not given the injection Remdesivir. Total 248 patients were selected for the study. The Remdesivir category included 124 patients and the Control category involved 124 patients.

Collected data was analyzed using SPSS 23.0. All baseline characters and variables in history were calculated as Mean and standard deviations for quantitative variables and as percentages for frequencies of qualitative variables. Univariate comparison for binary variables was performed with Chi-Square test. A p-value of <0.05 was considered as significant.

Results: In the Remdesivir category 23 (18.5%) had mild illness, 50 (40.3%) had moderate illness and 51 (41.2%) patients had severe illness. In the Control category 26 (20.9%) had mild illness, and 50 (40.3%) had moderate illness and 48 (38.8%) patients had severe illness. The median hospital stay days in Remdesivir category was 13 (95% CI: 12 - 15) and total death rate was 36.44%. The median hospital stay days in Control category was 11 (95% CI: 10 - 12) and the death rate was 31.35%. p-value .40.

Conclusion: The information showed that Remdesivir was not better than the standard of care treatment in shortening the hospital stay days in patients with proven Covid-19. No Mortality benefit was seen with Remdesivir treatment.

Keywords (MeSH): COVID-19, Pandemics, Remdesivir, Treatment Outcome, Mortality

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Corona Virus disease which has become pandemic with its mutant genotype (Novel corona virus)

and has claimed millions of lives worldwide since December 2019. In 80% of the cases the disease is self-limiting with mild upper respiratory tract symptoms. Fifteen percent of the cases develop pneumonia that need supplemental oxygen and an additional 5% of the cases develop critical illness.

The study is aimed at finding out the Efficacy of Remdesivir in Covid-19. Till now different trials have been directed to test the adequacy of Remdesivir in Covid disease. Some trials have shown promising results with the drug, while others reported no difference

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in clinical outcomes as contrast to the control group. In a final report published by the well-known New England Journal of Medicine, the J.H. Beigel and his colleagues conducted a double blind; randomized, placebo-controlled trial of intravenous Remdesivir in grownups hospitalized with Corona virus. Their information showed that Remdesivir was better than placebo in shortening the chance of recuperation (ACTT-1).¹ In one more review distributed by the New England Journal of Medicine, Jason D. Goldman and his partners led a randomized, open-labeled, stage 3 preliminary including hospitalized patients with affirmed SARS-Cov-2 disease. In patients with extreme COVID-19 not needing mechanical ventilation their preliminary didn't show a huge contrast between a five-day course and a ten-day course of Remdesivir. With no placebo control anyway the extent of the advantage could not be determined.² In a study conducted by A.C. Kalil, T.F. Patterson and Colleagues it was demonstrated that Baricitinib plus Remdesivir was better than Remdesivir alone in lessening recuperation time and speeding up progress in clinical status among patients with Covid-19, eminently among those getting high stream oxygen or noninvasive ventilation.³ In spite of all the evidence shown above in favor of Remdesivir, there are still few studies which tell that there was no positive outcome found in patients who were administered intravenous Remdesivir.⁴ In a companion investigation of US veterans hospitalized with COVID-19, Remdesivir treatment was not related to survival however was related to longer hospitalization.⁵ Corona expert advisory group of Pakistan has also declared that injection Remdesivir has no role in the management of covid-19 cases.⁶

As well just like a human misfortune, the Covid-19 has been a phenomenal monetary shock for the world economy. The worldwide result is assessed by the IMF to have fallen by 3.5 percent in 2020, and all nations - of all shapes and sizes, rich and poor - have been hit.⁷ Pakistan is a developing country. Remdesivir is a costly antiviral drug. Judicious use of resources is vital to bring COVID-19 under control. Corona Virus is an RNA virus and has immense capability for

mutation and to become drug resistant. Although most of the research done so far in the developed nations show that Remdesivir is quite effective to treat COVID-19, the research is intended to find out, if Remdesivir is also as effective in our population as it is in the developed nations of the world.

METHODS

After taking approval from the institutional review board (No. Admn. 339/GMC) at DHQ University teaching hospital Gujranwala, enrollment for the study began on 13 August 2020 till 24 May 2021.

COVID-19 patients were received through medical emergency and were isolated in a separate ward (Pulmonary bay). After taking all base line investigations and Nasopharyngeal swab, Patients requiring 2 to 10 liters of oxygen per minute were shifted to level one (Isolation). Patients requiring 11 to 50 liters of oxygen per minute were shifted to level two (HDU). Patients requiring more than 50 liters of oxygen per minute were shifted to level three (ICU).

Stratified random sampling technique was used to make Remdesivir group and Control group. 248 patients were selected for the review (124 patients in Remdesivir category and 124 patients in Control category). Each group was sub-divided into three distinct categories on the basis of disease severity i.e. Mild, Moderate and Severe. Every one of the patients under study had Corona infection sickness affirmed either through Nasopharyngeal swab RT-PCR or their HRCT had typical findings of COVID-19.

Following patients were included in the study:

- All category patients i.e. Mild, Moderate and Severe
- Patients of any age guys and females who have Corona virus disease confirmed through Nasopharyngeal swab RT-PCR
- Patients having classical radiological finding of Covid-19 on chest HRCT
- Minimum five days of hospital stay

Following patients were not included in the study:

- Presence of Stage 4 or above chronic renal failure

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- Minimum five days of hospital stay

Following patients were not included in the study:

- Presence of Stage 4 or above chronic renal failure

i.e. GFR less than 30ml/min/1.73m²

- ALT/AST > 5 times of upper limit of normal
- Pregnant women

A sample size of 248 (124 in each group) patients was calculated by taking a confidence interval of 95%, absolute precision as 10% and expected reduction on events of clinical deterioration as 10% in Remdesivir category and 30% in Control category. Basic random sampling method was used.

Chest X-ray, CBC, LFTs, RFTs, Serum Electrolyte along with specified inflammatory markers (CRP, D.Dimers, LDH, Serum Ferritin levels) were done daily of patients requiring more than 10 liters of oxygen per minute and on alternate day of patients requiring less than 10 liters of oxygen per minute. Use of experimental treatments and off-label marketed drugs intended to treat Covid-19 was prohibited.

The treatment protocols were set by Medicine Unit of the Hospital and were independently overseen by 'Corona Virus Patient Management Plan Committee'. The standard of care treatment comprised of steroids (Dexamethasone), anticoagulants (Clexane\ Enoxaparin\ Heparin), H2 receptor blockers (Ranitidine), vitamin C and D. The patient's condition was surveyed utilizing WHO Ordinal Scale³⁹ for Clinical Improvement. The groups are as follow; 1. No impediment of Activities 2. Limitation of activities 3. Hospitalized however no oxygen treatment 4. Oxygen by mask or nasal prongs 5. Non- invasive ventilation or high-flow oxygen 6. Intubation and mechanical ventilation 7. Ventilation in addition to extra organ support 8. Death.⁴ Adverse events during treatment in hospital were recorded according to grades of AE i.e. Grade 1 Mild AE Grade 2 Moderate AE Grade 3 Severe AE Grade 4 Life threatening or disabling AE Grade 5 Death related to AE.

Collected data was analyzed using SPSS 23.0. All baseline characters and variables in history were calculated as Mean and standard deviations for quantitative variables and as percentages for frequencies of qualitative variables. Univariate comparison for binary variables was performed with Chi-Square test. A p-value of <0.05 was considered as significant.

Treatment modality for the patients was decided by considering oxygen requirement and co morbid conditions. Simple face mask was used for level one patient. Second level patients were given oxygen using a Non-Re breather mask, a high flow device or BIPAP machine. Third level patients were given oxygen using Ventilators (both non-invasive and invasive). Patients in every level were assessed thrice daily by Medical specialist. Using WHO ordinal scale for clinical improvement, daily quantitative modifications were made in their treatment tickets. Clinical condition in terms of improvement and deterioration were recorded daily by on duty doctors. Treatment related to all hypersensitivity responses and adverse events were recorded daily.

RESULTS

The primary analysis was to compare for mortality benefit in between the two groups. Secondary outcome was to obtain a stratified log-rank test of time to recovery in Severe Disease Category as compared to Critically Sick Category.

In the Remdesivir category 23 (18.5%) patients had mild illness (20 cured, 03 expired) with mean hospital stay of 14 days. 50 (40.3%) patients had moderate illness (47 cured, 03 expired) with mean hospital stay of 13 days. 51 (41.2%) patients had severe illness (11 cured, 40 expired) with mean hospital stay of 10 days. The Mortality rates were 9.52%, 4.16% and 79.59% in Mild, Moderate and Severe categories. The mean hospital stay in Remdesivir category was 13 days (95% CI: 12 - 15) and Kaplan-Meier mortality estimate at day 28 was 36.44%, hazard ratio 0.87.

In Control category 26 (20.9%) patients had mild illness (21 cured, 05 expired) with mean hospital stay of 11 days. 50 (40.3%) patients had moderate illness (47 cured and 03 expired) with mean hospital stay of 10 days. 48 (38.8%) patients had severe illness (16 cured, 32 expired) with mean hospital stay of 15 days. Mortality rates were 16.66%, 4.16% and 67.39% in Mild, Moderate and Severe categories. The mean hospital stay in Control category was 11 days (95% CI, 10 to 12) and Kaplan-Meier mortality estimate at

day 28 was 31.35% P-value .40 chi-square statistic 0.68.

As evident from table 1, co-morbidities played a critical role in determining the severity of disease

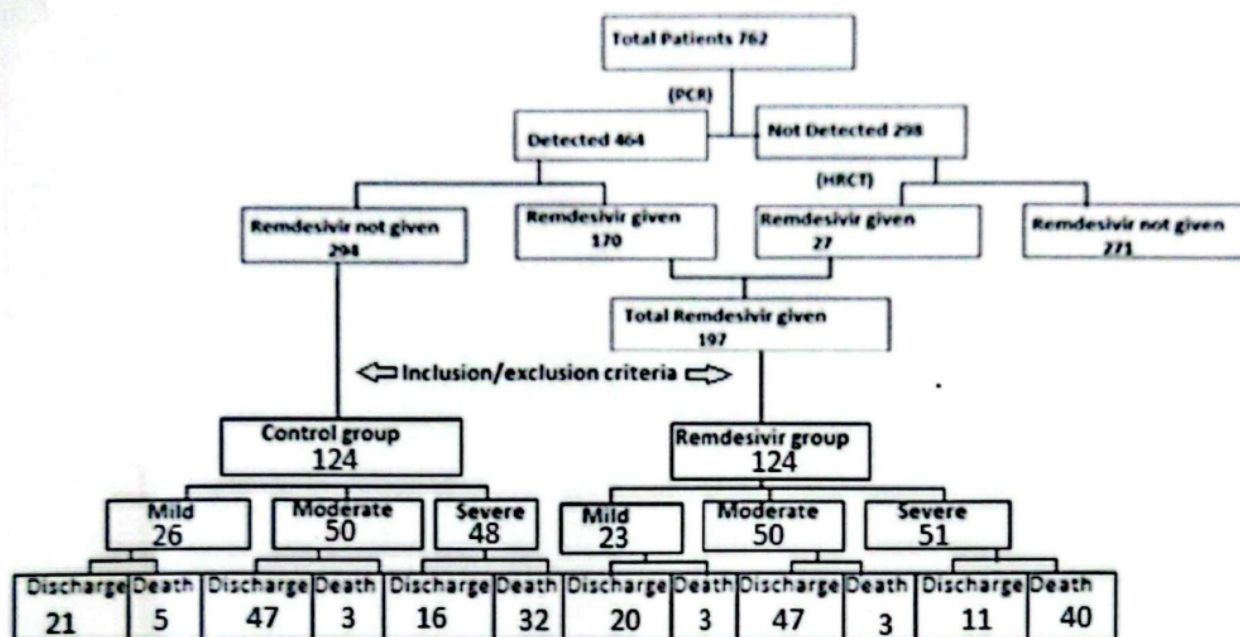


Figure 1. Categorization of patients into Remdesivir group and Control group

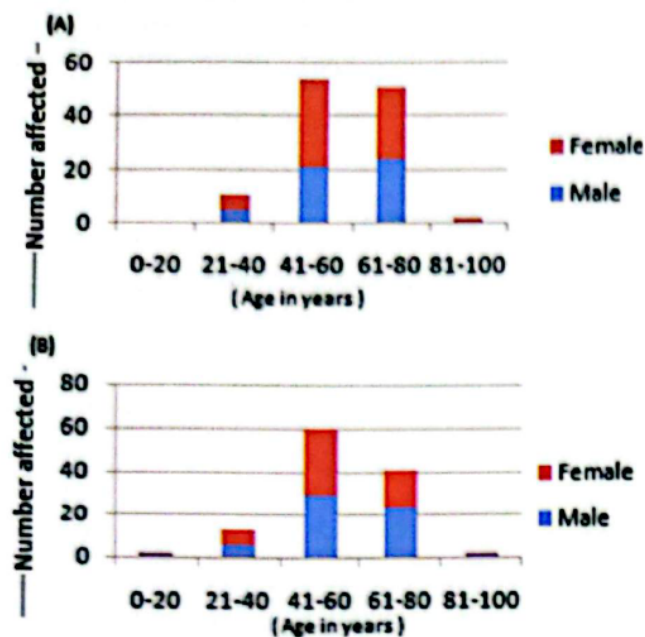
Table 1: Clinical Characteristics of Patients at Baseline

Characteristics	Remdesivir group (N = 124)	Control group (N = 124)	Total (N = 248)
Age of subjects			
Age - yr (mean ± SD)	58.76±16.72	54.22±13.13	56.49±14.92
Gender of subjects			
Male	54 (46.2)	63(53.8%)	117(100 %)
Female	70 (53.4%)	61(46.6%)	131(100%)
Comorbidities			
One	32(46.4%)	37(53.6%)	69(100%)
Two or more	34(50.8%)	33(49.2%)	67(100%)
Hypertension alone	16(53.4%)	14(46.6%)	30(100%)
Diabetes alone	09(42.9%)	12(57.1%)	21(100%)
Hypertension and diabetes	31(56.4%)	24(43.6%)	55(100%)
Smoking	03(37.5%)	05(62.5%)	08(100%)
COPD	00(00%)	01(100%)	01(100%)
Chronic Liver disease	03(42.9%)	04(57.1%)	07(100%)
Chronic Kidney Disease	01(16.7%)	05(83.3%)	06(100%)
Ischemic Heart Disease	05(31.3%)	11(68.7%)	16(100%)

Table 2: Patient classification according to WHO Ordinal Scale

Patient classification according to WHO Ordinal Scale			
	Remdesivir group	Control group	Total
Class 4 (Oxygen given by simple mask or nasal prongs)	21(46.7%)	24(53.3%)	45(100%)
Class 5 (High-flow oxygen/ non invasive ventilation)	48(50.0%)	48(50.0%)	96(100%)
Class 6 (invasive ventilation)	47(51.1%)	45(48.9%)	92(100%)
Class 7 (Invasive ventilation plus additional organ support)	02(66.6%)	01(33.4%)	03(100%)
Class 8 (Death)	43(53.7%)	37(46.3%)	80(100%)

in both Remdesivir Group and Control Group. Sixty-one percent of the patients who were admitted with Covid-19 had co-morbidities, almost equally distributed amongst all three categories in each group. Hypertension, Diabetes and Ischemic heart disease were the leading co-morbidities. There seemed to exist a negative relationship between the administration of Remdesivir and presence of co-morbidities on the overall outcomes in terms of prolonged hospital stays



and increased mortality rates.

Figure 2. Age and Sex Desegregation data (A) Remdesivir group (B) Control group

From the data given in (Fig.2), it is obvious that socially active age groups have become more infected

with the disease. The study sample comprised of 248 patients. 124 were placed in Remdesivir group and 124 were placed in control group. 46.2 % of the patients in Remdesivir group were male and 53.4 % were female. 53.8 % of patients in Control group were male and 46.6 % of patients were female.

In both Remdesivir and Control group, the incidence rate of covid-19 was highest in 40 to 80 years old population with same incidence for male to female gender. This is due to the contagious nature of the disease affecting the vulnerable population.

This study showed (Fig.3) that in patients with COVID-19, Remdesivir increased the duration of hospital stay as compared to the control group. The median hospital stay days in Remdesivir category was 13 days (95% CI: 12 - 15) and death rate was 36.44%. The median hospital stay days in Control category was 11 days (95% CI: 10 - 12) and the death rate was 31.35%. The benefit in mortality was seen in patients with mild disease. In patients with moderate disease, hospitalization was prolonged in the Remdesivir category in contrast with Control category but zero benefit in death rate was observed. In patients with severe disease, time to recovery was shortened with Intrave-

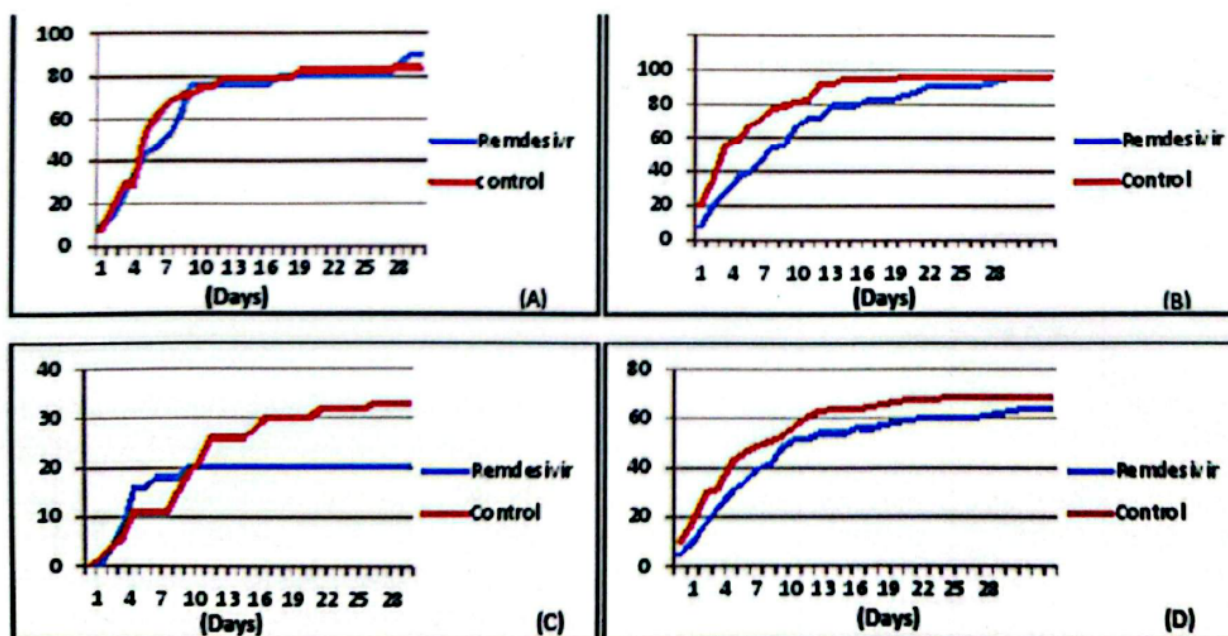


Figure 3: Kaplan-Meier estimates in survival analysis (A) Mild disease, (B) Moderate disease, (C) Severe disease, (D) Over all

nous Remdesivir but mortality was markedly increased.

DISCUSSION

In contrast to ACTT-1 Trial,¹ the study showed that intravenous Remdesivir therapy in Covid-19 was related with prolonged hospitalization in mild and moderate disease and was not related to further developed endurance in moderate disease. Mild mortality benefit was observed in Mild disease. Mortality was increased with intravenous Remdesivir as compared to Control group when given in severe disease. Intravenous Remdesivir has very less side effects then why is intravenous Remdesivir associated with prolonged hospitalization in the study? Current treatment rules advise against keeping patients in the hospital just to get done with a course of Remdesivir therapy.⁸ Remdesivir is just accessible as an intravenous formulation;⁹ therefore it is possible that the treating clinicians could have retained the patients just to complete the intravenous Remdesivir course of 5 or 10 days, which could have possibly prolonged the hospitalization days.

The results of study are in accordance with many studies.⁴⁶ The study which was done by Michael E. Ohl M, MSPH, Donald R. Miller S, Brian C. Lund and colleagues, published on 15 July 2021 to check the association of Remdesivir treatment with survival and length of hospital stay among us veterans hospitalized with covid-19, showed that Remdesivir was not related with improved survival and was associated with longer Hospitalization. There could be multiple reasons for these results; one of them could be the new emerging strains which might have developed resistance against the once effective Remdesivir. Similar results were obtained by Dr. Najeeb Ullah and his colleagues in a multicenter study at Lahore Pakistan, who published their research article on November 2020 stating Remdesivir, had no efficacy in shortening the hospitalization period of patients admitted to hospitals for covid-19.

As part of standard care of treatment anticoagulants were given to both Remdesivir group and Control group. Due to an increased demand during the pande-

mic, the study had to face acute shortage of anticoagulants on and off. Depending upon the market availability, three different anticoagulants had to be used during this study i.e. Heparin, Clexane and Rivaroxaban. Covid-19 is a hyper inflammatory state which builds weakness to systemic thromboembolic complexities that can add to quick clinical disintegration and death.^{10,11} Multiple Grade 1 to Grade 5 thromboembolic complications were seen during the study including Stroke, myocardial Infarction, Pulmonary embolism and limb ischemia. Thus the choice of anticoagulant might have altered the course of thromboembolic complications and subsequent hospitalization.

The mean hospital stay in Remdesivir category was 13 days (95% CI, 12 to 15), Death rate was 36.44%. The mean hospital stay in Control category was 11 days (95% CI, 10 to 12) and death rate was 31.35%. P-value .40, Hazard ratio 0.87.

There are certain limitations to the study. The study is single centered, non-blinded with limited sample size. We suggest multi-centered larger study with larger sample size to verify these results.

CONCLUSION

The information showed that Remdesivir was not better than the standard of care treatment in shortening the hospital stay days in patients with proven Covid-19. No Mortality benefit was seen with Remdesivir treatment.

Conflict of Interest None

Funding Source None

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**The good physician treats the disease;
the great physician treats the patient
who has the disease.**

William Osler