e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 1385-1391
Original Research Article

A Study to Assess the Efficacy of Remdesivir in Managing COVID-19

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Received: 20-11-2023 / Revised: 13-16-2023 / Accepted: 19-01-2023
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Conflict of interest: Nil

Abstract:

Background: COVID-19, caused by the novel coronavirus SARS-CoV-2, emerged in December 2019 in Wuhan, China. It quickly spread globally, leading to a pandemic declaration by the WHO in March 2020. The virus primarily spreads through respiratory droplets, causing a range of symptoms from mild respiratory illness to severe pneumonia, posing significant public health challenges worldwide. The Present study was conducted to compare the efficacy of remdesivir in the management of COVID-19 disease.

Methods: The present retrospective study was conducted among 200 confirmed severe cases of COVID-19 diagnosed and admitted at the government medical college, Surat during the study. The study participants were divided into two groups: Group A: Those who received Remdesivir along with other standard drugs (as mentioned in proforma) used for COVID-19. Group B: Those who received standard treatment only without Remdesivir. Inclusion criteria were Age >18 years, Severe cases of COVID-19, and patients who gave written informed consent to participate in the study.

Results: The mean age of participants in groups A and B was 60.2 and 61 years, respectively ($p>0.05$). Around 44% of group A and 46% of group B had comorbidities like hypertension. Platelet counts at admission were 250910/µL for group A and 260900/µL for group B ($p<0.05$). Oxygen devices, including nasal cannula, were used more frequently in group A (64%) than in group B (40%) ($p<0.05$). Intubation rates were 34% for group A and 48% for group B ($p>0.05$). Hospital admission duration was shorter for group A (14.2 days) than group B (19.7 days) ($p<0.05$). Success rates for treatment and discharge were similar between groups A (93%) and B (84%) ($p>0.05$).

Conclusion: The overall parameters improved in the remdesivir group as compared to those not receiving it. The number of patients requiring mechanical ventilation was significantly lesser as compared to the group not receiving remdesivir. Death was only 7% of the remdesivir group as compared to the non-receiving group where 15% deaths were reported. No significant adverse reactions were reported in the remdesivir group. Therefore, it appears that remdesivir appears to be effective in the management of severe covid 19 in this population.

Keywords: COVID-19, Intensive Care Unit, Mechanical Ventilation, Remdesivir, SARSCoV-2.

Introduction

As of June 26, 2020, the World Health Organization (WHO) reported 492,085 global COVID-19 deaths and 9,724,146 confirmed cases, with numbers still increasing. The pandemic's magnitude threatens global public health, affecting even high-income countries. The WHO declared it a Public Health Emergency on January 30, 2020, expressing concern for nations with inadequate health systems. [1] Developing countries face challenges in managing the crisis, causing widespread panic. In India, during the first wave, the case fatality rate as of January 31, 2021, is relatively low at 1.435 percent, with 154,000 deaths and 10.76 million cases. [2]

As of May 15, the cumulative impact of the first and second waves in India revealed nearly 25 million reported cases and 270 thousand deaths. However, estimations project a much higher prevalence, indicating approximately 491 million infections (36% of the population) and 1.21 million deaths. This results in an estimated combined infection

fatality rate of 0.25%. [3, 4] Despite various approved drugs and investigational agents demonstrating antiviral activity against SARS-CoV-2 in vitro, there is currently a lack of proven antiviral therapies for treating severely ill COVID-19 patients. [5, 6] A randomized controlled trial (RCT) involving hydroxychloroquine and 150 hospitalized adults showed no significant impact on accelerating viral clearance. Another RCT, which included patients within 12 days of symptom onset, found that favipiravir exhibited superiority over arbidol in terms of the clinical recovery rate at day 7 for patients with mild illness. However, this advantage did not extend to those with critical illness, where the outcomes were comparable between the two treatments. [3, 4]

Remdesivir (GS-5734), a nucleotide prodrug, exhibits broad-spectrum antiviral activity against various virus families in vitro, demonstrating efficacy in nonhuman primate models with Ebola and Nipah viruses. Studies on human airway cells show inhibition of diverse coronaviruses, including MERS-CoV. In mice, administered pre-peak virus replication, remdesivir effectively treats SARS-CoV, and MERS-CoV, even in Ces1c-/- mice lacking a relevant carboxylesterase. [7] In vitro, remdesivir impedes coronavirus replication by interfering with the viral polymerase, overcoming viral proofreading exoribonuclease. Despite partial resistance after in vitro passages with GS-441524, coronaviruses remain sensitive to higher remdesivir concentrations, compromising fitness compared to wild-type MERS-CoV. [8]

Material and Methods

This retrospective study was conducted at the Department of General Medicine attached to a tertiary care hospital in Gujarat, India from May 2020 to December 2020. The Purposive sampling method was used for the inclusion of the cases. Institutional Ethical approval was obtained for the study. All confirmed severe cases of COVID-19 diagnosed and admitted at this Tertiary care hospital, in Surat, Gujarat were included in the study.

Inclusion criteria

1. Age >18 years.
2. Moderate and Severe cases of COVID-19.
3. Patients who give written informed consent to participate in the study.
4. Rapid Antigen Tests (RAT) and RT-PCR positive patients.

Exclusion criteria

1. Age ≤ 18 years.
2. Mild cases of COVID-19.
3. Pregnant cases.
4. Patients who refuse to give consent.

Sample size: The study has included 200 confirmed cases of severe COVID-19. There were 2 groups included in the study as follows Group *A*: those who received Remdesivir along with other standard drugs (as mentioned in proforma) used for COVID-19 19 Group *B***:** those who received standard treatment only without Remdesivir

Data Collection: Detailed data of History and clinical examination in both groups A and B were documented. Demographic data including age, sex, socio-economic status, and rural or urban background was obtained. Data of routine blood investigations. Complete blood count, renal function tests, liver function tests, and random blood glucose levels were obtained according to the guidelines given at that time. In our study, 200 No. of confirmed cases of severe COVID-19 pneumonia were selected as per the guidelines given.

Pneumonia with respiratory failure (respiratory rate > 24/min, SpO2 < 94% on room air, PaO2 < 60 mm of Hg) with one of the following Red Flag signs considered as the "cytokine storm syndrome" It was as follows:

1. Neutrophil lymphocyte ratio > 3.5
2. Raised CRP, D- dimer, ferritin.
3. Raised IL-6 levels.
4. Chest imaging (chest x-ray or High-resolution computed Tomography (HRCT) scan)

Pneumonia with respiratory failure with sepsis and/or septic shock and/or multiorgan dysfunction syndrome.

Moderate cases of COVID-19: Pneumonia without respiratory failure (fever/cough/dyspnea) however SpO2 >90% but SpO2 <93% con room air, PaO2 >60 mm Hg, and Respiratory rate <24/min.

Severe cases of COVID-19: Adult with fever or suspected respiratory infection, plus one of the following: Respiratory rate >30 breaths/min or severe respiratory distress or SpO2 <90% on room air. The diagnosis is clinical; chest imaging was done to exclude complications.

Acute respiratory distress syndrome: Onset: New or Worsening respiratory symptoms within one week of known clinical insult. Respiratory failure is not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of edema if no risk factor is present.

As per Arterial Blood Gas Analysis: Mild ARDS: 200mmHg < PaO2/FiO2 300 mm of Hg (non-ventilated)

Moderate ARDS: 100 mmHg < PaO2/FiO2 mm of Hg (non-ventilated), Severe ARDS: PaO2/FiO2 <100 mm of Hg (non-ventilated). When PaO2 were not available groups, patients were assigned to four predefined risk groups: group I (SpO2/FiO2 ≥ 190 and PEEP < 10 cm H2O), group II (SpO2/FiO2 ≥

190 and PEEP ≥ 10 cm), group III (SpO2/FiO2 < 190 and PEEP < 10 cm H2O) and group IV (SpO2/FiO2 < 190 and PEEP ≥ 10 cm H2O). Septic Shock persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate > 2 mmol/L.

Out of 200 patients selected, the data of investigations were collected on the day of administration of remdesivir and the fifth day along with standard treatment given. 100 patients of moderate and severe cases of COVID-19 were given standard treatment along with Remdesivir which was documented as Group A as given in the proforma.

The details of which are given below: Supportive care given: Maintain hydration/Antipyretics/antitussives/ multivitamins were given.

1. Tab Hydroxychloroquine (400mg) BD on day 1 followed by (400mg) OD for 4 days.
2. Inj. Methylprednisolone (1-2 mg/kg) in 2 divided doses for 5-10 days
3. Inj. Low molecular weight Heparin (0.5 mg/kg) subcutaneously BD
4. Inj. Remdesivir (200 mg) OD in 100 ml Normal saline intravenously on day 1 followed by (100 mg) OD in 100 ml Normal saline for 4 days
5. Tab Vitamin C (1000 mg) per day.
6. Tab Zinc (50 mg) per day.
7. Vitamin D 60000 IU stat.

100 patients were given only standard treatment as mentioned above without Remdesivir documented as Group B.

Statistical Method: Collected data has been entered in the Excel data sheet and data analysis was done with the help of Epi. Info.7.2 software. Descriptive Statistics: For continuous variable range, mean and standard deviation will be calculated and for categorical variables, proportion and percentage will be obtained. Bi-Variate analysis: To know the association between dependent and independent variable chi-square, a t-test will be applied accordingly.

Results

Out of 200 cases divided equally into two groups of 100 cases each. There we 55% of males and 45% of females in group A similarly, 53% of males and 47% of females in group B. Table 1 shows both groups seem to have a majority of participants above 50 years old (Group A: 55%, Group B: 54%). The age distribution appears slightly skewed towards younger ages in Group A compared to Group B. Higher percentage of participants in the 18-30 and 31-40 age groups in Group A. Lower percentage of participants in the 51-60 and above 60 age groups in Group A compared to Group B. However, the p-values for both comparisons (0.96 and 0.18) are non-significant.

Table 1: Age distribution of study participants

Age Group (in years)	Group A (n=100)	Group B (n=100)	P value
18-30	09	10	0.96
31-40	14	12	
41-50	19	23	
51-60	22	21	
>60	36	34	
Mean ± SD	60.2 ± 14.7	61.0 ± 9.4	0.18

Table 2 shows the distribution of cases based on the BMI categories. We found that both groups have a similar distribution of participants across the BMI categories, with the majority falling within the "Normal weight" and "Overweight" ranges. Group A has a slightly higher percentage of participants in the "Normal weight" category (31%) compared to Group B (29%). Group B has a slightly higher percentage of participants in the "Overweight" (34%) and "Obese Class I" (18%) categories compared to Group A (37% and 14%, respectively). However, the p-value for the comparison between the two groups is non-significant (0.772), and non-significant.

Table 2: BMI distribution of study participants

BMI classification (wt in kg/m2 in cm)	Group A (n=100)	Group B (n=100)	P value
18.5 – 24.9	31	29	0.772
25 – 29.5	37	34	
30 – 34.5	17	19	
35 – 39.9	14	18	
≥ 40	1	0	

Table 3 compares the mean values and standard deviations (SD) of five vital parameters in two groups (A and B) of study participants, each containing 100 individuals. Additionally, it shows the p-values for the comparison between the groups using the student's t-test. Both groups have very similar mean values for body temperature, with no statistically significant difference (p=0.25). Pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) show slightly higher mean values in Group B compared to Group A. These differences are statistically significant for pulse rate (p=0.03), SBP (p=0.04), and DBP (p=0.02). SpO2:FIO2 ratio, a measure of oxygen saturation adjusted for inspired oxygen fraction, is considerably higher in Group B compared to Group A, although the difference is not statistically significant (p=0.58). The slightly higher pulse rate, SBP, and DBP in Group B suggest a potentially elevated baseline level of cardiovascular activity compared to Group A. However, the small magnitude of the differences and the context of the study are needed for further interpretation. The non-significant difference in temperature and SpO2:FIO2 ratio indicates no major variations in these parameters between the groups.

Table 3: Mean of vitals distribution of study participants

Vital parameters	Mean ± SD		P value
	Group A (n=100)	Group B (n=100)	
Temperature, °C	37.9 ± 0.8	37.8 ± 0.9	0.25*
Pulse, beats/min	97.6 ± 17.8	97.0 ± 18.3	0.03*
Systolic BP, mm Hg	109.1 ± 17.4	110.2 ± 19.4	0.04*
Diastolic BP, mm Hg	60.8 ± 11.3	61.1 ± 12.0	0.02*
SpO2:FIO2 ratio	355.8 ± 114.6	419.7 ± 108.8	0.58*

* - Student 't' Test

Table 4: Mean of laboratory parameters at admission day distribution of study participants

Laboratory Parameters	Mean ± SD		P value	95% CI
	Group A (n=100)	Group B (n=100)		
C-reactive protein, mg/dL	48.2 ± 7.3	50 ± 8.1	0.36*	0.42-3.1
Platelet count, ×103/µL	250910 ± 68000	260900 ± 72550	0.01*	-0.04 – 0.14
White blood cell count, cells/µL	14500 ± 2800	14800 ± 3200	0.001 *	-0.28 – 0.76
Hemoglobin, g/dL	10.5 ± 1.2	10.1 ± 1.5	0.51*	-0.68 – 0.06
D-dimer, µg/dL	2800 ± 498.1	2300.4 ± 503.8	0.04*	-5.9 – (-4.1)
IL-6 (pg/ml)	2.29±0.478	2.08±0.706	0.035	0.042- 0.378

Table 4 shows the mean parameters on day 1. The mean of CRP level of study participants of Group A & group B was 48.2 with 7.3 SD & 50 with 8.1 SD respectively. The Mean Platelet count of study participants of group A & group B was 250910 / µL with 68000 SD & 260900 / µL with 72550 SD respectively. The difference between the mean Platelet count of study participants of both groups was 0.01% with a confidence interval of -0.04 – 0.14. The Mean WBC count of study participants of group A & group B was 14500 / µL with 2800 SD & 14800 / µL with 3200 SD respectively. The difference between the mean WBC count of study participants of both groups was 0.001% with a confidence interval of 0.28 – 0.76. The Mean of the Hb level of study participants of group A & group B was 10.5 gm/dL with 1.2 SD & 10.1 gm/dL with 1.5 SD respectively. The difference between the mean Hb level of study participants of both groups was 0.51% with a confidence interval of -0.68 – 0.06. The Mean D-dimer level of study participants of group A & group B was 2800 µg/dL with 498.1 SD & 2300.4 µg/mL with 503.8 SD respectively. The difference between the mean D-dimer level of study participants of both groups was 0.04% with a confidence interval of -5.9 – (-4.1). The mean of Ferritin level of study participants of group A & group B was 2.29ng/dl with 0.478 SD & 2.08 ng/dL with 0.706 SD respectively. The mean of IL-6 level of study participants of group A & group B was 2.29pg/ml with 0.478 SD & 2.08 Pg/ml with 0.706 SD respectively.

Table 5: Mean of laboratory parameters distribution on day 5 among study

Laboratory Parameters	Mean ± SD		P value	95% CI
	Group A (n=100)	Group B (n=100)		
C-reactive protein, mg/dL	11.1 ± 8.2	8.7 ± 8.3	0.12*	-3.7 – (-1.1)
Platelet count, ×103/µL	15911 ± 90800	216850 ± 92455	0.001*	-0.3 – (-0.2)
White blood cell count, cells/µL	7900 ± 5200	8000 ± 6851	0.03*	-5.2 – 7.2
Hemoglobin, g/dL	12.5 ± 1.9	12.4 ± 1.8	0.26*	-0.1 – 0.3
D-dimer, µg/dL	2000 ± 500.3	2100 ± 570.4	0.01*	0.2 – 1.7
IL-6 (pg/ml)	1.55± 0.730	2.13± 0.720	0.168	-0.782 - 0.378

Table 5 compares the mean values, standard deviations (SD), p-values for statistical significance, and 95% confidence intervals (CI) of six laboratory parameters measured on day 5 of the study in two groups (A and B) with 100 participants each. C-reactive protein (CRP): Group A has a slightly higher mean CRP but the difference is not statistically significant (p=0.12). Platelet count: Group B has a significantly higher mean platelet count compared to Group A (p=0.001). White blood cell count (WBC): Group B has a slightly higher mean WBC count, but the difference is marginally significant (p=0.03). Hemoglobin: Both groups have very similar mean hemoglobin levels with no statistically significant difference (p=0.26). D-dimer: Group B has a slightly higher mean D-dimer level, which is statistically significant (p=0.01). Interleukin-6 (IL-6): Group B has a slightly higher mean IL-6 level, but the difference is not statistically significant (p=0.168).

Table 6: Oxygen devices used in the treatment of study participants

Oxygen devices	Group A (n=100)	Group B (n=100)	P value
The nasal cannula or face mask	64	40	0.001
High-flow nasal cannula	19	23	0.48
Non-invasive positive pressure ventilation	2	8	0.06
Mechanical ventilator	15	29	0.04

Table 6 shows Nasal cannula or face mask: Group A had a significantly higher proportion of participants using low-flow oxygen devices (nasal cannula or face mask) compared to Group B (64% vs. 40%, p=0.001). High-flow nasal cannula: The use of high-flow nasal cannula (HFNC) was similar between the groups (19% in Group A, 23% in Group B), and the difference was not statistically significant (p=0.48). Non-invasive positive pressure ventilation (NIV): Group B had a slightly higher proportion of participants requiring NIV compared to Group A, but the difference was not statistically significant (8% in Group B, 2% in Group A, p=0.06). Mechanical ventilator: Group B had a significantly higher proportion of participants requiring mechanical ventilation compared to Group A (29% vs. 15%, p=0.04). Group A seems to have had less severe respiratory needs based on the higher use of low-flow oxygen devices and lower reliance on mechanical ventilation compared to Group B. The higher use of NIV and mechanical ventilation in Group B suggests they have experienced more severe respiratory distress requiring advanced respiratory support.

Intubation was required in 15% of participants of Group A and 29% of participants of Group B respectively. The p-value as per the distribution of study participants according to the requirement of intubation was 0.06%. the mean duration of hospital admission was 14.2 days with 2.3 SD and 19.7 days with 4.4 SD of study participants of groups A & B respectively. The p-value difference between the mean duration of hospital admission was 0.001%. Resuscitation is required in 15% of participants of Group A and 25% of participants of Group B respectively. The p-value as per the distribution of study participants according to the requirement of Resuscitation was 0.009%. The study found that 93% of the participants of Group A and 84% of the participants of Group B were treated & discharged successfully, and 7% of participants of Group A and 16% of participants of Group B died during treatment. The P value distribution of study participants of both groups according to the outcome of treatment was 0.04%.

Discussion

The present retrospective study included 400 confirmed severe COVID-19 cases admitted to the Surat government medical college, conducted with Institutional Ethics Committee (IEC) approval. Participants were divided into two groups: Group A received Remdesivir alongside standard COVID-19 drugs, while Group B received only standard treatment. The study aimed to compare Remdesivir's efficacy in COVID-19 management. Objectives included analyzing participants' socio-demographic characteristics, comparing laboratory parameters between Remdesivir and non-Remdesivir groups, and assessing outcomes such as ICU admission, mortality, hospital stay duration, and respiratory support requirements. Inclusion criteria were age >18, severe COVID-19, and written informed consent. Exclusion criteria were age ≤18, mild COVID-19, pregnancy, and refusal of consent. The Present study found that HTN was the most common risk factor noted in both groups (44% & 46%) followed by DM (32% & 25%) & CAD (27% & 24%) respectively. Spinner CD et al. [9] noted coronary artery diseases were the most common comorbidity followed by hypertension (HTN).

The 'remdesivir group' (Group A) had a slightly lower average temperature (37.9°C) compared to the 'without remdesivir group' (Group B) (37.8°C). Group A also showed a slightly higher pulse rate (97.6 beats/min) but slightly lower mean systolic and diastolic blood pressure compared to Group B. The SpO2:FIO2 ratio was lower in Group A but not statistically significant. On day 5, the mean C-reactive protein levels for Group A and Group B were 11.1 mg/dL (SD=8.2) and 8.7 mg/dL (SD=8.3) respectively, with no statistically significant

difference ($p>0.05$). However, the mean platelet count and white blood cell count differed significantly between the groups ($p<0.05$).

These findings align with previous studies demonstrating a heightened risk of severe illness, increased mortality, and prolonged hospitalization among older COVID-19 patients. [10, 11] Age-related factors like immunosenescence and comorbidities may contribute to poorer outcomes in this population. [13] Recognizing age's impact on remdesivir's efficacy is crucial for tailoring treatments and improving patient outcomes. Moreover, the higher proportion of male patients in the remdesivir group, as indicated by the study, aligns with existing literature identifying male gender as a risk factor for severe COVID-19 and higher mortality rates. [14] Biological disparities between genders, including variations in immune response and the influence of sex hormones, could elucidate these differences in disease severity and clinical outcomes. [14, 15] Compared to the control group, the remdesivir group had a higher proportion of patients with severe or critical COVID-19 disease, impacting the assessment of remdesivir's efficacy. Previous studies suggest that early remdesivir administration may be more effective in improving outcomes. [16-18] Therefore, the timing of remdesivir treatment relative to disease severity is crucial. [16] Additionally, the remdesivir group exhibited a higher prevalence of comorbidities such as obesity, diabetes, and cardiac or vascular diseases, known to exacerbate COVID-19 severity and outcomes. [19] The existence of these comorbidities could impact the pharmacokinetics and pharmacodynamics of remdesivir, potentially influencing its safety and efficacy. [17] Moreover, managing these comorbidities might require concurrent medications that could interact with remdesivir, shaping patient outcomes. [16-18]

This study found that Intubation required among cases of ‘remdesivir group’ (group A) (34) was statistically not significantly very lower than the cases of ‘without remdesivir group’ (group B) (48). Lapadula G et al. [19] observed that remdesivir treatment in COVID-19 has a favorable effect in shortening the duration of mechanical ventilation and accelerated recovery. This study found that the duration of hospital admission was noted statistically significantly lower among the cases of the 'remdesivir group' (group A) (14.2 days) compared to the 'without remdesivir group' (group B) (19.7 days). In patients treated with Remdesivir, the pooled mean recovery time from a few studies was 15.84 days. [19-21] Few other studies observed range of duration of hospitalization was 16-28 days. [22, 23] Garibaldi BT et al. [24] observed that receipt of remdesivir was associated with a significantly shorter time to clinical improvement. This study also found that death was reported statistically significantly in nearly half of the cases of the 'remdesivir group' (group A) (7%) compared to cases of the 'without remdesivir group' (group A) (16%). Beigel et al80 observed Mortality rate was 7.1% in the remdesivir group than of 11.9% in the control group. Grein et al 79 observed Mortality rate was 13% in the remdesivir group whereas Mandhane G et al 89 observed Mortality rate was 18.5% in the remdesivir group. Lapudula G et al 95 observed Mortality rate was 15.2% in the remdesivir group.

Conclusion

The present study found that a greater number of males were with covid 19 as compared to females. The overall parameters improved in the remdesivir group as compared to those not receiving it. The number of patients requiring mechanical ventilation was significantly lesser as compared to the group not receiving remdesivir. Death was only 7% of the remdesivir group as compared to the non-receiving group where 15% of deaths were reported. No significant adverse reactions were reported in the remdesivir group. Therefore, it appears that remdesivir appears to be effective in the management of severe covid 19 in this population.

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