Original Article

Use of Remdesivir as an Investigational Therapy in Moderately Severe COVID-19 Cases

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Background : The lack of an effective and safe pharmacologic agent to combat COVID-19 pandemic has led researchers to evaluate several molecules indicated for use in other diseases either as anti-viral or immune-modulating agents.

Materials and Methods : This observational study was conducted in patients with moderately severe COVID-19 disease that were treated with steroids and anti-thrombotic agents with or without Remdesivir. All patients received Remdesivir for 5 days (200 mg IV on Day 1 followed by 100 mg IV daily for 4 days). The primary outcome was the time to recovery or survival benefit, if any. Total 478 patients were studied (226 received Remdesivir and 252 received only steroid and heparin). Analysis revealed marginal survival benefit in patients treated with Remdesivir (p Value <0.108). It was also seen that starting Remdesivir early in the course of the disease offers greater benefits. However, the duration of hospitalization was not favorably affected by use of Remdesivir. Use of Remdesivir also resulted in early viral clearance. No serious adverse events were noted.

Conclusions : Remdesivir along with steroid and heparin improved survival in moderate COVID-19 infections and led to early viral clearance.

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Key words **: COVID-19, Remdesivir, Investigational Therapy.**

Since the identification of the COVID-19 virus (SARS-CoV-2) in China in December, 2019 till date, the pandemic caused by this highly infectious virus has taken the whole world by surprise[1]. Even the best of the health care facilities of the world appeared insufficient to tackle the menace caused by this organism. The lack of an effective pharmacologic agent has added to the mortality. Several molecules used as antivirals and immuno-modulating agents in various other diseases have been utilized to treat COVID-19 with variable benefits[2]. Remdesivir, which inhibits viral RNA dependent RNA polymerase, showed some benefits in treating patients with SARS-CoV and MERS-CoV and therefore was an obvious candidate trials in COVID-19[3]. Animals treated with Remdesivir did not show signs of respiratory disease, had reduced pulmonary infiltrates on radiographs and virus titers in bronchoalveolar lavages were significantly reduced as early as 12 hours after the first treatment was administered[4].

Editor's Comment :

- Remdesivir is seen to benefit patients with moderate severe COVID-19 infection.
- The benefit was noted in the form of decreased hospitalisation days, reduced need for supplimental oxygen and ICU care.

This study was conducted to evaluate the clinical efficacy and safety of Remdesivir in patients with moderately severe COVID-19 infection in Gauhati Medical College and Hospital.

Materials and Methods

Study Design :

The patients admitted in Dedicated Covid Hospital of Gauhati Medical College and Hospital (GMCH) from May to August,2020 were enrolled into the study. The patients fulfilling criteria of moderate COVID-19 disease as per ICMR/MoHFW, Government of India,defined as SPO2<95% in room air, respiratory rate >24 or respiratory distress were enrolled.

Remdesivir was available for use in GMCH from July, 2020. Therefore, the patients who were admitted

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in July and August received Remdesivir in addition to steroid and anti-thrombotics and this group constituted the study arm.The group of patients admitted in May and June, 2020, were treated with steroids and anti-thrombotics and they constituted the comparator arm.

All patients continued to receive the standard supportive care as per Government of Assam guidelines that comprised of Azithromycin 500 mg OD for 5 days, Zinc 50 mg OD, Vitamin C 500 mg OD, Vitamin D 60K IU Once Weekly and Famotidine 20 mg BD[5].

Steroid was given in the form of Dexamethasone 6 mg once daily (Intravenous or per oral) for a period of 10 days. Low molecular weight Heparin in a dose of 1mg/kg once daily subcutaneous (Or 5000 U Unfractionated Heparin subcutaneously once daily in case of patients with Chronic Kidney Disease) was given for a period of 10 days.

Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg dose given daily on day 2-5.

Remdesivir was not administered to patients who had altered liver function (AST or ALT >5 times the upper limit of normal or patients with decompensated cirrhosis) and significant renal insufficiency (eGFR<30 ml/min) at the time of enrollment.

The study protocol was approved by the Institutional Ethical Committee of GMCH and use of Remdesivir was approved as an Investigational Agent for use in COVID-19 after obtaining informed consent from patient or from the patient's legally authorized representative.

Monitoring :

Patients were assessed daily during their hospitalization, from day of enrollment till the day of discharge or death. The patient's clinical status was recorded each day. Laboratory investigations including CBC, DLC, NLR (Neutrophil:Lymphocyte Ratio), Creatinine, LFT was done at baseline and repeated on Day 5 and Day 14 or Day of discharge. RTPCR for COVID-19 was repeated every 3rd day till tested negative or death. All adverse events were recorded.

Statistical Analysis :

The primary outcome measure was survival benefit, if any, attributable to the use of Remdesivir added to steroids and anti-thrombotics in moderately COVID-19 infection.

Other outcome measures included :

(1) Reduction in duration of hospitalization by either discharge or shifting to a non-covid set-up for patients who tested negative for COVID-19 but requiring hospitalization for other medical conditions

(2) Viral clearance was defined as the time taken for RTPCR test to turn negative

Sub-group analyses comparing the effects of age groups (18-40 years, 40-60 years and >60 years), gender, presence of co-morbidities and duration of symptoms before initiation of therapy on the outcome measures was also carried out to look for statistically significant associations.

Results

Patient recruitment :

A total of 478 patients admitted in Gauhati Medical College Covid Hospital, were enrolled in the study.All patients were diagnosed with RTPCR for COVID-19.

A total of 226 patients, who received Remdesivir along with Steroid and Heparin were hereafter referred to as Group A. All patients in Group A completed 5 days of Remdesivir therapy.

Another Group of 252 patients who were treated with Steroid and Heparin were enrolled as comparator and this group is hereafter referred to as Group B.

Both the Groups (A & B) continued to receive standard supportive care protocol followed in Gauhati Medical College, that consists of Azithromycin 500 mg OD for 5 days, Zinc 50 mg OD, Vitamin C 500 mg OD, Vitamin D 60K IU Once Weekly and Famotidine 20 mg BD.

Both the groups, were closely monitored during the entire period of hospitalization for clinical improvements / deterioration (Tables 1&2).

Baseline characteristics :

The mean age of patients in Group A was 54.27 years and 49.80 years in Group B.

Group A had 15.90% patients below 40 years of age and 35.40% patients above 60 years of age. Group B had 27.40% patients below 40 years of age and 29.80% patients above 60 years of age. Males constituted 74.80% of patients in Group A and 65.50% of patients in Group B.

Both the groups had patients with co-morbid illness, commonest being Diabetes Mellitus, Hypertension, Chronic Kidney Disease and Coronary Artery Disease, with similar distribution in both the groups.

A total of 181 patients (37.9%) out of 476 enrolled had one or more co-existing medical illness. Out of these Group A had 18.4% and Group B had 19.5% patients with co-morbidities. The most common conditions were T2DM (26.6%-35.9%), CKD (17.4%-24.2%), Hypertension (21.95-23.9%), CAD (7.6%-7.8%) besides others (15.2%-19.5%). Others included Bronchial Asthma, Systemic lupus Erythematosus, Rheumatoid arthritis, Congenital Heart Disease, Seizure Disorder, Allergic Rhinitis etc.

Most patients had either one (27.0%) or two or more

Table 1 — *Baseline Demographic and Clinical Characteristics of Participants in both the Groups*

Parameters	Group A n= 226	Group B n= 252	P value
Clinical characteristics [absolute no (percentage) or Mean ± Standard Deviation]			
Age (years)	54.27±15.33	49.80±17.48	0.003
<40	36 (15.9)	69 (27.4)	0.0036
40-60	110 (48.7)	108 (42.9)	0.2370
>60	80 (35.4)	75 (29.8)	0.2238
Gender :			
Male	169 (74.8)	165 (65.5)	0.0269
Female	57 (25.2)	87 (34.5)	
Duration of symptom (Days)	3.55±1.90	2.98±0.99	0.004
Co morbidity [absolute no (percentage)]			
CAD	7 (7.60)	10 (7.80)	0.9555
DM	33 (35.9)	34 (26.6)	0.1832
HTN	22 (23.9)	28 (21.9)	0.8472
CKD	16 (17.4)	31 (24.2)	0.2928
Others	14 (15.2)	25 (19.5)	0.5173
Laboratory Investigations (Mean ± Standard Deviation)			
Hb	11.7±2.55	12.9±2.13	0.131
TC	12.04±7.49	10.0±4.07	0.014
Neutro	75.75±10.48	70.68±11.45	0.001
Lympho	18.74 ±11.20	23.05±10.05	0.003
NLR	5.94±4.73	3.97±2.78	<0.0001
Platelet	210.82±82.81	201.88±76.46	0.436
RBS	179.60±111.86	124.08±50.10	0.005
Creatinine	1.38±2.26	1.54±1.96	0.595
Billirubin	1.57±4.25	2.30±6.67	0.402
AST	85.53±201.10	65.89±43.91	0.421
ALT	90.14±184.63	60.18±61.55	0.218
Albumin	4.26±6.87	3.73±0.91	0.598
Alkaline Phosphatase	111.11±45.325	128.04±59.539	0.447
SpO_2 (Mean ± Standard Deviation)	95.09±5.05	95.98±1.94	0.01
O_2 requirement (L/min)	6.23±2.60	4.67±2.36	<0.0001

(52.1%) of the prespecified coexisting conditions at enrollment, most commonly hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%).

The mean SPO_2 on oxygen supplementation on the first day of hospitalization was 95.09 % in Group A whereas it was 95.98% in patients enrolled in Group B. The mean O_2 requirement was 6.23 L/min in group A compared to 4.67 L/min in patients of Group B.The mean duration of symptom onset prior to initiation of therapy was 3.55 days in Group A (q2-q3 = 2-6). compared to 2.98 days in Group B (q 2-q3 = 2-4).

Patients enrolled in Group A had a mean Neutrophil to Lymphocyte Ratio (NLR) of 5.94 compared to 3.97 in Group B (p Value ≤0.0001). The mean Random Blood Sugar (RBS) levels was 179.60 mg/dlin Group A whereas it was in 124.08 mg/dl in Group B (p Value ≤0.005).The other laboratory parameters namely Total Leucocyte count, Platelet Count, Creatinine and Liver Function Tests did not reveal any significant differences.

Table 2 — *Presence of Co-morbidities in the study population*

Co-morbidity (overall)	Frequency	Percent
No	258	53.97
Yes	220	46.03
Total	478	100
Co-morbidity (Group wise)	Frequency	Percent
Group A (Co-mrobidity-absent)	134	59.29
Group A (Co-mobidity-present)	92	40.71
Group B (Co-mrobidity-absent)	124	49.20
Group B (Co-mrobidity-present)	128	50.79

Evaluation of Outcome Measures :

The overall mortality in our study was 21.5% (103). 41 patients died in Group A (18%) and 62 died in Group B (24.6%). Although not statistically significant, the survival was marginally better in patients receiving three drugs (Remdesivir+ Steroid+Heparin) compared to those receiving only Steroid and Heparin (p value-0.108) (Table 3).

Time of initiation of Remdesivir and survival (Table 4).

A statistically significant difference in survival status based on the Remdesivir starting day after symptom onset is observed. For those who were alive the mean day of starting Remdesivir after onset of symptoms is 6.4 days compared to those who died when Remdesivir was used at 8.2 days, p=0.003 (Table 3 and Fig 2). Also a 5.9% increased risk of death (HR 1.059, P=0.043) was observed for delay in use of Remdesivir after onset of symptoms (Table 3.2).

Age and Outcome :

Of the 41 patients that died in Group A, 13 patients were more than 60 years of age (31.7%) and 28 patients (68.29%) were less than 60 years of age. In Group B, out of 62 deaths, 13 patients were aged more than 60 years (20.96%) and 49 patients were aged less than

Table 3 — *Showing deaths and survivors in both the groups*

Group A (n=226) Mortality		Group B (n=252) Mortality		Overall Mortality (n-478)		Chi square test, P value
41	18%	62	24.6%	103	21.5%	2.573
Alive (Group A)		Alive (Group B)		Alive (Overall)		
185	82%	190	75.4%	375	78.5%	0.108

Table 4 — *Interval of initiation of Remdesivir in survivor and non-survivors*

Remdesivir used	n	Mean	Standard Deviation	95% confidence interval for mean Lower bound	Upper bound	Minimum	Maximum	p value
Day of starting Remdesivir after symptom onset :								
ALIVE	185	6.4066	2.39434	5.9079	6.9052	1	14	
DEAD	41	8.2113	5.01402	7.0245	9.3981	1	22	0.003
TOTAL	226	7.1975	3.8655	6.5978	7.7973	1	22	

60 years of age (79%). No significant difference in outcome was noted.

Gender and Outcome :

Gender distribution was not significant in Group A comparing Outcome (p value 0.957), whereas males had more mortality in Group B (p value<0.0001).

Co-morbid conditions and Outcome :

With respect to presence of associated Co-morbid conditions, it was found that those with Co-morbid conditions had increased mortality (HR 1.64, 95% CI, p value <0.0001)

Comparing patients with Co-morbidities, both group showed poor outcome in the high risk patients.

In Group A those with co-morbid illness had 1.883 times higher risk of death (p value 0.008) as compared to 3.049 times higher risk in Group B (p value <0.001)

Mean duration of hospitalization was higher (10.01 days) in group A compared to (7.47 days) Group B (p value <0.0001).

Mean duration of ICU stay was higher (4.29 days) in group A compared to (3.33 days) Group B (p value <0.0002).

The mean days of viral clearance (number of days from first swab till day of RTPCR Negative) in Group A is found to be 12.9 days (12.2-13.5, 95% CI) as compared to Group B which is 15.1 days (13.3-16.8, 95% CI).

Applying Unpaired T Test with Welch Correction, the mean difference of the two groups is found to be 2.185 (0.31-4.1). Two Tailed p Value is 0.0224, considered significant. This implies that the mean days of virological response in Group A is nearly 2.2 days earlier than those in Dual Therapy, which is found to be statistically significant.

Adverse events :

A total of 82 patients reported adverse events. The most common were elevated hepatic transaminases, hyperglycemia and altered renal function. We noted increase of AST and ALT upto 3 to 4 times upper limit of normal in 26.6% of patients receiving Remdesivir and in 6.7% in those not receiving Remdesivir. However, none of the patients required discontinuation of Remdesivir and the levels of transaminases stabilized towards day 14.

The blood sugar levels showed increasing trend in both Group A and B, with mean values of 201.2 mg/dl on day 5 and 194.0 mg/dl on day 14 in Group A and Group B showed a mean value of 205.8 mg/dl on day 5 and 196.4 mg/dl on day 14.

The Serum Creatinine levels increased by a margin of 8-12% in both Group A & B with a mean of 1.42 mg/dl on day 5 and 1.40 mg/dl on day 14, whereas Group B recorded a mean of 1.41 mg/dl on day 5 and 1.33 mg/dl by day 14 (Table 2)

Discussion

The overall mortality in our study was 21.5% (103). 41 patients died in Group A (18%) and 62 died in Group B (24.6%). Although not statistically significant, the survival was better in patients receiving three drugs (Remdesivir + Steroid + Heparin) compared to those receiving only Steroid and Heparin (Table 3).

This finding is consistent with other studies which showed reduction of mortality in patients treated with Remdesivir with or without use of other drugs in combination[6].

Beigel, *et al* found that their results from the 1059 patients (538 assigned to Remdesivir and 521 to Placebo) with data available after randomization indicated that those who received Remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan Meier estimates of mortality by 14 days were 7.1% with Remdesivir and 11.9% with placebo

Table 5 — *Cox regression analysis showing effect of gender and presence of Co-morbidities on outcome*

		HR	95.0% CI for Exp(B)		Signifi-cance
			Lower	Upper	
Gender :	Male	Ref			
	Female	0.886	0.652	1.204	0.439
Co-morbidity :	No				
	Yes	1.64	1.244	2.161	<0.0001
Remdesiver used+ Male	Group A (Male)	Ref			
Remdesiver used+Female	Group A (Female)	0.986	0.586	1.658	0.957
Remdesiver Not used +Male	Group B (Male)	1.971	1.399	2.777	<0.0001
Remdesiver Not used+Female	Group B (Female)	1.554	1.019	2.37	0.041
Remdesiver Used (Co-mrobidity-absent)	Group A (Co-mrobidity-No)	Ref			
Remdesiver Used (Co-mrobidity-present)	Group A (Co-mrobidity-Yes)	1.883	1.181	3	0.008
Remdesiver Not Used (Co-mrobidity-absent)	Group B (Co-mrobidity-No)	2.041	1.349	3.088	0.001
Remdesiver Not Used (Co-mrobidity-present)	Group B (Co-mrobidity-Yes)	3.049	2.006	4.634	<0.001

(hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)[6].

A statistically significant difference in survival status based on the Remdesivir starting day after symptom onset was observed. For those who survived, the mean day of starting Remdesivir after onset of symptoms is 6.4 days compared to those who did not survive when Remdesivir was used at 8.2 days, p=0.003 (Table 4 and Fig 1).

We observed that starting Remdesivir early in the course of the disease, leads to significant reduction in risk of death in comparison to starting late after onset of symptoms. This data is consistent with the fact that Remdesivir has shown both as antiviral and clinical effects both *in vitro* and *in vivo* and also early administration of Remdesivir have shown better clinical outcomes (M Wang, *et al* 2020; Williamson, *et al* 2020; Pizzorno, *et al* 2020)[4,7,8].

Williamson, *et al* 2020., found that therapeutic Remdesivir treatment initiated early during infection has a clear clinical benefit in SARS-CoV-2 infected Rhesus Macaques. This data supports early Remdesivir treatment initiation in COVID-19 patients to prevent progression to severe pneumonia[4].

In the study by Wang, *et al* in 2020, however, the primary outcome, time to clinical improvement was 21 *versus* 23 days with Remdesivir and placebo, respectively (HR 1.23, 95% CI 0.87 to 1.75). 28-day mortality was similar 14 *versus* 13%, -1.1% (95% CI -8.1 to 10.3%). The authors conclude that 'intravenous Remdesivir did not significantly improve the time to clinical improvement, mortality or time to viral clearance in patients with serious COVID-19, compared with placebo[7].

Goldman, *et al* noted that discharge rates were higher in the overall population among patients who had had symptoms for less than 10 days before receiving the first dose of Remdesivir (62%) than among those who had had symptoms for 10 or more days before receiving the first dose (49%)[9].

It was found that those with Co-morbid conditions had increased mortality (HR 1.64, 95% CI, p value <0.0001). Both group showed poor outcome in the high risk patients. In Group A those with Co-morbid illness had 1.883 times higher risk of death (p value 0.008) as compared to 3.049 times higher risk in Group B (p value <0.001) (Table 5, Fig 2).

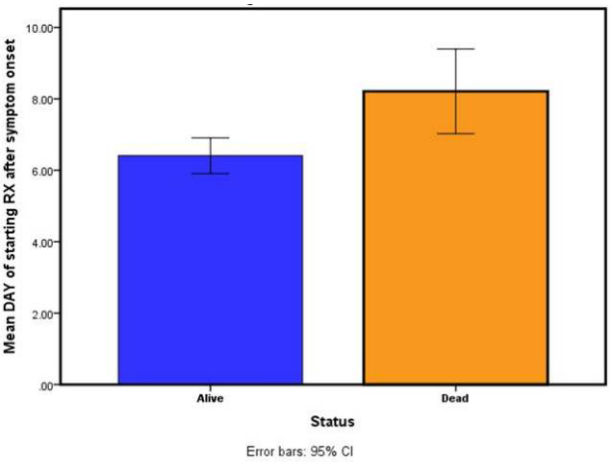

Fig 1 — Mean duration of starting Remdesivir and outcome

Co-morbidity and age (above 65 years) with COVID-19 are one of the greatest risk factor of increased mortality[10]. In our study consistent data have been

Table 6 — *Mean duration of hospitalization and ICU stay*

	Group A			Group B			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P Value
DoH	226	10.01	5.24	252	7.47	4.06	<0.0001
DolCU	119	4.29	2.90	175	3.33	2.58	<0.0002

Table 7 — *Mean duration of Viral Clearance in the study population*

Viral Clearance	Group A	Group B	P Value (T-test/Chi Square Test with Welch Correction)	P Value
Days	12.8 ± 4.31	15.06 ± 9.02	0.0224	0<0.0001

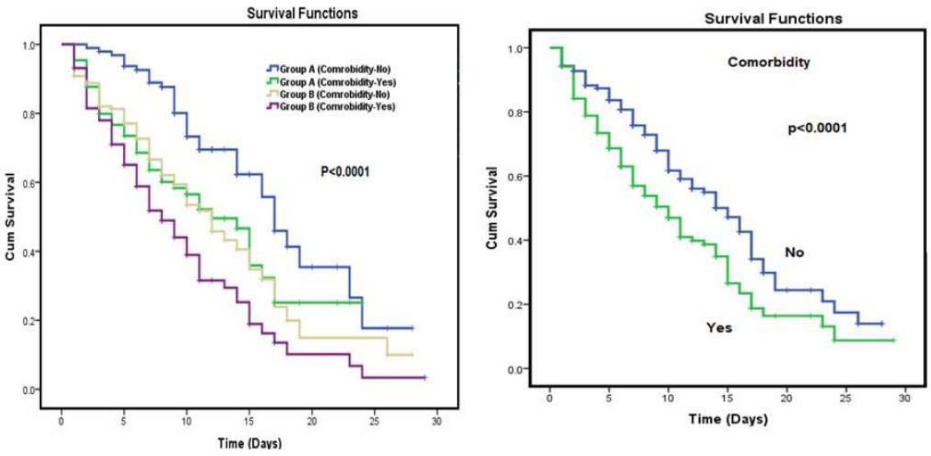

Fig 2 — Kaplan Meier survival curve showing survival benefit in patients without Co-morbidity

found in cases having Co-morbid conditions, the percentage survival decreased significantly (P< 0.0001) as expected. The percentage of survival in co-morbid cases was 56.90% whereas it was 75.80% in persons without Co-morbidity in 7 days. Median survival days in comorbid cases is 10 days whereas in others without Co-morbidity is 15 days.

Yang, *et al* in 2020 concluded that older patients (>65 years) with comorbidities and ARDS are at increased risk of death[10].

Mean duration of hospitalization was higher (10.01 days) in group A compared to (7.47 days) Group B (p value <0.0001). Mean duration of ICU stay was higher (4.29 days) in group A compared to (3.33 days)Group B (p value <0.0001)(Table 6).

The viral clearance in Group A was found to be 2.2 days earlier (mean 12.9 days) as compared to Group B (mean 15.1 days)(Table 7).

We observed that use of Remdesivir with standard supportive treatment leads to quicker virologic response as compared to Dexamethasone and Enoxaparin which signifies Remdesivir being an effective antiviral in addition to the baseline drugs used.

Williamson, *et al* found that 12 hours after the first Remdesivir treatment was administered, the infectious virus titer in BAL was ~100-fold lower in Remdesivir-treated animals than controls. By 3 dpi (day post inoculation), infectious virus could no longer be detected in BAL from Remdesivir-treated animals. However, despite this reduction in virus replication in the lower respiratory tract, neither viral loads nor infectious virus titers were reduced in nose, throat or rectal swabs collected from Remdesivir-treated animals, except a significant difference in virus titer in throat swabs collected on 1 dpi and in viral loads in throat swabs collected on 4 dpi[4].

Our patients demonstrated 3-4 fold rise in hepatic transaminases in both the groups, more so in the Remdesivir treated group. However, none were severe (Table 8).

Table 8 — *Mean values of laboratory parameters*

	Group A				Group B			
	N	Mean D0	Mean D5	Mean D14	N	Mean D0	Mean D5	Mean D14
RBS	97	179.6	201.2	194.0	36	124.08	205.8	196.4
Creat	143	1.38	1.42	1.40	83	1.54	1.41	1.33
AST	139	85.53	151.2	100.3	70	65.89	146.9	82.7
ALT	139	90.14	163.3	106	61	60.18	139.4	72

Conclusion

Our study showed improved survival in patients treated with Remdesivir along with Steroids and Heparin. We also noted that early initiation of Remdesivir offered greater clinical benefits. The Remdesivir treated group also demonstrated early viral clearance. However, no favorable effect on duration of hospitalization was found with use of Remdesivir.

Our study however, was an observational retrospective analysis involving a relatively small sample size. To comment on the positive effects Remdesivir noted in our study, a randomized prospective study involving larger cohort in multiple centres across the state or country would be required.

However, this is the first of its kind study conducted in the entire North East India looking into the therapeutic efficacy of Remdesivir.

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