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Ribavirin Plus Therapy in Covid-19-A Single-Center Experience

[1]Budha Oinam Singh, [2]Gaurav Chikara, [1]Prasan Kumar Panda, [3]Yogesh Arvind Bahurupi, [4]Sarama Saha and [1]Venkatesh Srinivasa Pai

[1]Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Rishikesh, India
[2]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Rishikesh, India
[3]Community and Family Medicine, All India Institute of Medical Sciences (AIIMS), Rishikesh, India
[4]Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Rishikesh, India

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Corresponding Author:
Prasan Kumar Panda
Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Rishikesh, India
Email: motherprasanna@rediffmail.com

Abstract: COVID-19 infection has a similar clinical spectrum of disease presentation such as SARS and MERS in the past. These led to the assumption of the possibility to treat COVID-19 infection with antivirals which had been used to treat SARS and MERS. A retrospective analysis was done in symptomatic adult patients of COVID-19 infection to explore whether ribavirin antiviral combinations reduce the need for both Noninvasive and Invasive Ventilation (NIV/IV) in the treatment of COVID-19 infections. Cohort A consisted of 40 patients who received the standard therapy and Cohort B of 61 patients who received the ribavirin plus therapy (Ribavirin with Hydroxychloroquine or Lopinavir/Ritonavir). Cohort A required NIV and IV each in 12.5% of patients while Cohort B required the same in 18.03 and 16.39% of patients respectively (p = 0.456). There was a similar trend of reduction of organ dysfunctions with time in cohort A compared to B. The study concluded there was no statistically significant reduction in the need for ventilation (non-invasive/invasive) and the development of multi-organ dysfunction in COVID-19 patients treated with ribavirin plus therapy, rather clinically standard therapy was better in all aspects.

Keywords: Antivirals, Coronavirus Disease 2019, Hydroxychloroquine, Lopinavir/Ritonavir, Multi-Organ Dysfunction, Ribavirin

Introduction

COVID-19 infection caused by a novel beta-coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic and led the World Health Organization (WHO) to declare it as a global sanitary emergency on January 30, 2020). The pathophysiologic process accompanying this highly transmissible infection primarily affects the respiratory system and may manifest as mild respiratory infection (may be responsible for 20-30% of the common colds), moderate to severe respiratory infections (García, 2020). However, it also has a wide clinical spectrum of presentation and can involve various organs and organ systems (Cheong *et al*., 2020; Sachdeva *et al*., 2020; Pei *et al*., 2020; Whittaker *et al*., 2020).

While the world has witnessed this pandemic in many waves, especially in India the 2nd wave has shown to have a sharp spike in and an exponentially increasing incidence of ICU admissions, organ impairments with the increased proportion of patients requiring high levels of O_2 support and ventilator requirement in the recent times (Jain *et al*., 2021). As of now, many antivirals have been proven to be of little or no benefit in the symptomatic recovery of the acute manifestations of COVID-19 infection.

Severe COVID-19 infections have also been attempted to treat with steroids (dexamethasone) and low molecular weight heparins and these have been proven to

have some mortality benefit in moderate to severe cases of COVID-19 infections which also never led to a favorable outcome in mass scales before the progression of the severe pathophysiologic process (Horby *et al*., 2020a). Several kinds of research have been done on the prospects of hydroxychloroquine, lopinavir/ritonavir and ribavirin as individual agents for the treatment of COVID-19 infection with doubtful results of efficacy (Choupoo *et al*., 2020; Cao *et al*., 2020; Horby *et al*., 2020b; Molina *et al*., 2020; Pathak *et al*., 2020; Sevilla-Castillo *et al*., 2021; Tong *et al*., 2020). WHO Solidarity Trial Results have shown no benefit of these agents as indicated by no benefit on the overall mortality, initiation of ventilation and duration of hospital stay (Hung, 2020). Also, the use of these systemic drugs resulted in several adverse events (WHO Solidarity Trial Consortium, 2022).

Aim of the Study

This is a single-centered retrospective cohort analysis of COVID-19 patients to analyze if the ribavirin plus therapy holds any benefit in reducing the need for ventilators and the development of multi-organ dysfunctions in comparison to standard care.

Materials and Methods

The study was a retrospective record-based cohort study to compare the effectiveness of antiviral combinations against the standard therapy of adults who were hospitalized with COVID-19 infection from May 2020-October 2021 where patients received these antiviral combination therapy as per institute protocol. The cohort was segregated into Cohort A which consists of patients who received the standard therapy and Cohort B which consists of patients who received the Ribavirin plus therapy (Ribavirin with Hydroxychloroquine or Lopinavir/Ritonavir) after assessing enrolment criteria (Table 1).

Inclusion criteria were adults ≥18-year-old who presented with signs and symptoms of COVID-19 infection and who were confirmed RT-PCR positive and who were treated with these experimental therapies and without. Exclusion criteria were applied to patients who required non-invasive and invasive ventilation within 24 h of the study, who were left against medical advice during the treatment period and who had refused consent for the use of clinical data for research purposes.

The primary objectives set were to compare the need for ventilators (non-invasive and invasive and to compare the development of multi-organ dysfunction involving two or more organs in between cohorts. The secondary objectives were to correlate the baseline patient characteristics with the above outcomes in between cohorts, to determine and compare the average period from the date of hospitalization to the need for ventilators (non-invasive and invasive), to determine and compare the average period from the date of hospitalization to the development of acute organ dysfunction and to compare the need of invasive ventilators from non-invasive ones in between cohorts.

All the baseline characteristics of selected patients were collected including demographics, symptoms, duration of illness, vitals at presentation and on follow-ups, pre-existing co-morbidities, baseline blood investigations and the parameters of specific organ dysfunction on presentation and follow-ups, the requirement of invasive and noninvasive mechanical ventilation on a subsequent period of the study period. These were categorized based on the type of study groups have received the treatment.

Table 1: Interventions received by the patients of the two cohorts

Cohort A: Standard Therapies	Cohort B: Experimental therapies
1. Strict Isolation	1. B1-(Hydroxychloroquine 400mg BD on day1 followed by 400 mg once daily + Ribavirin (2.4 gm orally as a loading dose followed by 1.2 gm orally every 12 h) for 10 days +
2. Standard Precautions (Hand hygiene, Cough Etiquette, Wearing surgical mask)	2. B2- Lopinavir (400 mg) + Ritonavir (100 mg) two tablets twice daily + Ribavirin (2.4 gm orally as a loading dose followed by 1.2 gm orally every 12 h) for 10 days +
3. Fluid Therapy	
4. Supportive Pharmacotherapy (Antipyretic, Antiallergic, Cough Suppressant)	
5. Oxygen supplementation (As required)	
6. Invasive ventilation (As required)	
7. Antibiotic agents for other associated infections (according to 2019 ATS/IDSA guidelines for non-ICU and ICU patients)	
8. Asopressor support	
9. Renal-replacement therapy	
10. Treatment of Comorbid Diseases	
11. Oseltamivir (75 mg BD) for patients who tested positive for H1N1	

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Organ dysfunction of specific organ systems was defined as respiratory system involvement by the requirement of oxygen support (radiological images not used since images were not uniformly available for all patients), hepatobiliary system by the elevation of serum SGOT of more than or equal to two times from baseline (chronic hepatitis ruled out from history and other routine investigations deemed necessary by the attending clinician), the involvement of renal system by elevation of serum creatinine of more than or equal to 1.5 mg/dL after ruling out CKD from history (since baseline creatinine values are not available for most patients) and elevated leukocyte count as a marker of sepsis after ruling out dehydration and other non-infective causes of leukocytosis. The outcome of the patient and time to symptomatic recovery in survivors (defined as the period from admission till resolution of symptoms or normalization towards the baseline) were also noted.

Analysis was carried out such that categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Quantitative variables were compared using the independent t-test (as the data sets were normally distributed) between two groups. Multivariate regression (logistic for categorical and linear for continuous dependent variables) was used to determine the significant predictor variables. A p-value of <0.05 was considered statistically significant. The study was approved by the institutional ethics committee, AIIMS, Rishikesh (Letter No-AIIMS/IEC/21/526).

Results

From a sample of 111 patients during the study period, 101 were included after exclusion and distributed in Cohort A (40 patients) and Cohort B (61 patients) (Fig. 1). A precise 50/50 sample size between the two cohorts couldn't be derived. And Cohort B consists of a bigger sample size as it constitutes patients receiving combination therapy of two subgroups viz. Ribavirin with Hydroxychloroquine in one and Ribavirin with Lopinavir/Ritonavir as another subgroup. Comparing basic patient characteristics in between two cohorts, it was observed that both have the same proportion of age, co-morbidities and baseline lab characteristics, however severe COVID-19 was more in cohort B (Table 2). Type 2 diabetes mellitus, hypertension, chronic cardiac disease and COPD all in descending order of frequency were the major co-morbid conditions with which the patients presented.

There was no statistically significant difference in the proportion of patients requiring Non-Invasive Ventilation (NIV) and Invasive Ventilation (IV) in Cohort A vs Cohort B (12.5% vs 18.03% and 12.5% vs 16.39% respectively; Table 3). A similar observation was also made in regard to the average number of days of NIV and IV requirement in Cohort A vs Cohort B (1.4 days vs 2.54 days and 3.2 days vs 3.11 days respectively). Cohort A had better organ dysfunction-wise improvement in follow-up compared to cohort B, but without any statistical significance (Fig. 2). There were no observed major drug side effects in patients of both cohorts.

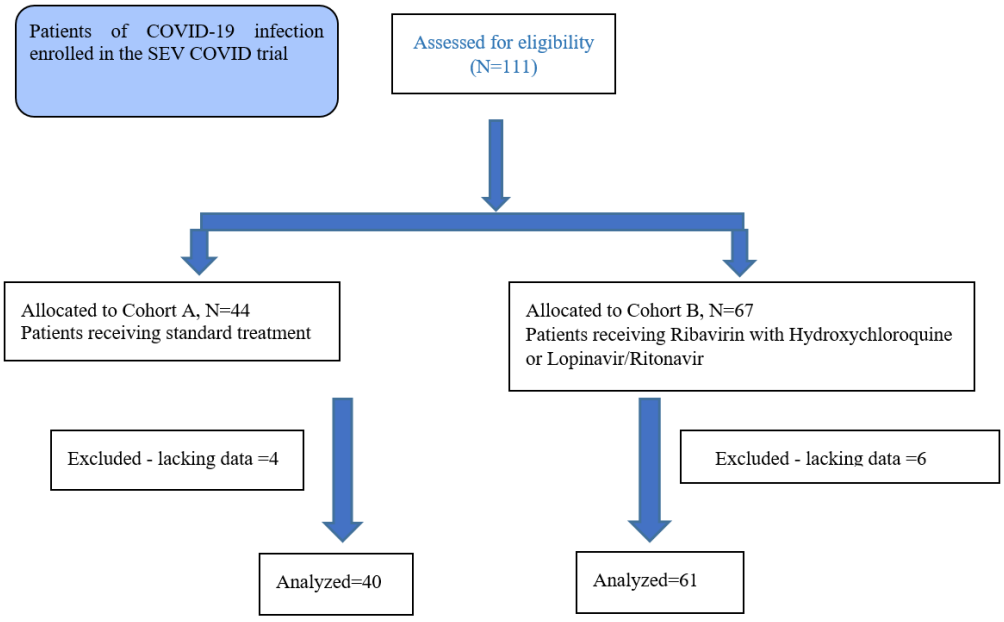

Fig. 1: The study flow

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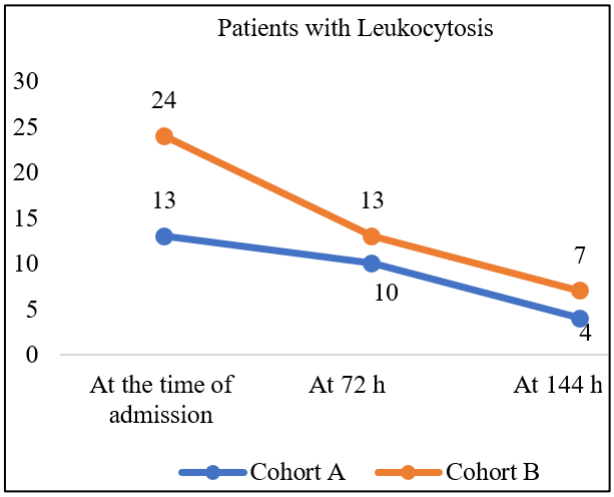
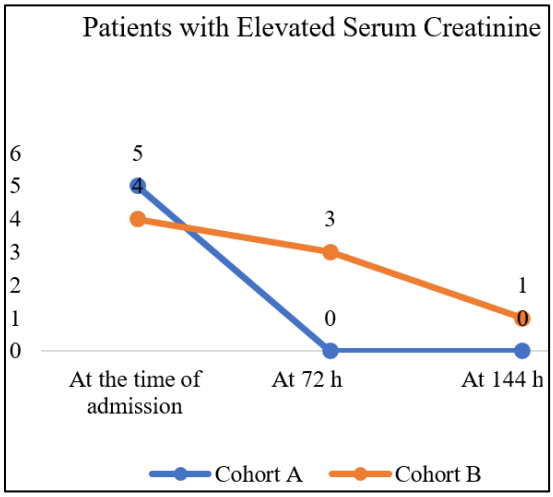
Table 2: Comparisons of the two cohorts A and B-Demographic, Clinical Presentations, and laboratory parameters

Parameters	Group	Number	Mean	Std. deviation
Age (In years)	Cohort A	40	51.02000	14.05200
	Cohort B	61	49.28000	14.88600
TLC (thousand/dL)	Cohort A	40	9.08150	3.83629
	Cohort B	60	8.90420	4.23509
Total bilirubin (mg/dL)	Cohort A	38	0.81500	0.99637
	Cohort B	58	0.83340	0.69996
Direct bilirubin (mg/dL)	Cohort A	38	0.35000	0.14411
	Cohort B	58	0.43720	0.43802
SGPT (U/L)	Cohort A	38	59.80500	45.46440
	Cohort B	57	66.84400	47.11790
SGOT U/L)	Cohort A	38	44.79000	50.30260
	Cohort B	57	50.14000	48.94820
Urea (mg/dL)	Cohort A	37	45.62000	62.73100
	Cohort B	56	38.36000	19.87700
Creatinine (mg/dL)	Cohort A	39	1.02620	0.34030
	Cohort B	57	1.08750	0.72086
		WHO severity Class-non-severe	WHO severity Class-severe	
Severity of illness	Cohort A	16 (40%)	24 (60%)	
	Cohort B	17 (27.87%)	44 (72.13%)	
		Cohort A	Cohort B	N
Comorbid condition	Anyone	22 (55%)	34 (55.7%)	56
	DM	5	23	28
	HTN	2	31	33
Chronic cardiac		2	10	12
	COPD	2	6	8
	Asthma	0	2	2
	Malignancy	1	0	1

Table 3: Requirements of Non-Invasive Ventilation (NIV) and Invasive Ventilation (IV) of Cohort A and B

	Cohort A		Cohort B	
	Count	Percentage %	Count	Percentage %
NIV	5	12.5	11	18.03
IV	5	12.5	10	16.39
Average days of NIV requirement	1.4 days		2.54 days	
Average days of IV Requirement	3.2 days		3.11 days	





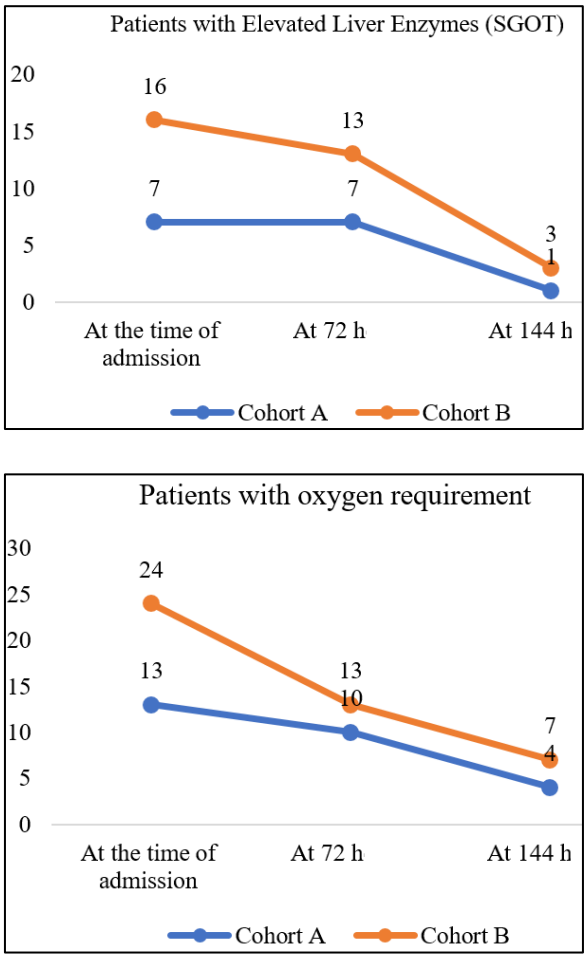


Fig. 2: Time periods for development of leukocytosis and acute organ dysfunctions (elevated liver enzymes, elevated serum creatinine, and increase oxygen requirement) between the two Cohorts A and B

Discussion

The study was done to assess whether ribavirin plus therapy poses any benefit in regard to the reduction of the need for both NIV and IV requirements and the prevention/recovery from the development of MODS as a result of COVID-19 infection. However, it could not establish the benefit of ribavirin plus therapy over the supportive measure with respect to the outcomes examined. This data is also supported by the previous findings from across the country as in the study by Al-Shargi *et al.* (2023); Laxminarayan *et al.* (2020).

Ribavirin, a prodrug, is marketed for Hepatitis-C infection (Laxminarayan *et al.*, 2020). Considering repurposing therapy in COVID-19 infection, its utility is evidenced in many clinical trials so far. Tong *et al.* (2020) trial showed a lack of negative conversion time for the SARS-CoV-2 virus and of improved mortality rate (Te *et al.*, 2007). Combination with interferon beta-1b and lopinavir-ritonavir also failed in a phase II trial during initial pandemics (Tong *et al.*, 2020). In the given institute, another trial was undertaken where results failed to show the statistical superiority of any antiviral combination therapies to that of the standard therapy in both severe and non-severe COVID-19 (Hung *et al.*, 2020). However, clinically hydroxychloroquine + ribavirin therapy was showing better recovery by 7.4% than standard therapy for severe COVID-19. And standard therapy in the non-severe COVID-19 was beneficial by 6.6%. In our present study, too, ribavirin plus therapy (Ribavirin with Hydroxychloroquine or Lopinavir/Ritonavir) has no clinical or statistical benefit compared to standard therapy.

In regard to the need for NIV and IV between the two Cohorts, the study treatment center employed the previous recommendations concerning the use of the ventilator support. Studies like Nicolas (Bonnet *et al.*, 2021) concluded a favorable outcome with the use of HFNC to avoid the use of invasive ventilation (Panda *et al.*, 2021). Whether its use might have resulted in a positive impact on the outcomes of the present study is a question that was not answered by the parameters defined in this study. However, among all deaths in the same center in another study, 55.9% used NIV which shows very less use of HFNC in routine practices (Bonnet *et al.*, 2021). In regard to the development of multi-organ dysfunctions, the numbers in each sub-groups were too small for the derivation of any statistically relevant and significant data.

The strict enrolment criteria of the primary study are a strong point in the times when studies on various antivirals and other therapeutic measures are taken on a large scale. While enrolling patients, the proportion of patients in both cohorts was fairly comparable as it constitutes a ratio of 2:3 between cohorts A and B. The findings of our study were consistent with similar observations made with respect to epidemiological characteristics as in age groups, co-morbid conditions and severity of illness.

Certain limitations may also be highlighted as the limited number of samples in the study which have impacted in deriving any statistically significant outcomes in the parameters used for the analysis. The data collected was dependent on the primary study and was not refined for a longer duration of observation due to various physical and logistic challenges imposed by the measures taken up during the pandemic. The results of the imaging studies such as X-ray and CT Thorax which is one of the primary modalities of classifying the severity of COVID-19 infection avoided in the analysis due to lack of producible results and hence a possibility of bias is certainly present while classifying the severity of COVID-19 infection. Finally, to generalize the results of the effects of these drugs which were used in plus as a representative effect regarding the parameters of this study may also pose a certain bias.

Conclusion

There was no difference in regard to the need for NIV/IV or reduction of development of multi-organ dysfunctions between the two Cohorts: Ribavirin Plus therapy vs standard therapy in this single-center cohort study.

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Author's Contributions

Budha Oinam Singh: Did literature search, collected data, drafted the manuscript and approved.

Gaurav Chikara and Yogesh Arvind Bahurupi: Did literature search, analyzed data, reviewed the manuscript, and approved.

Prasan Kumar Panda, Sarama Saha and Venkatesh Srinivasa Pai: Gave concept and design, interpreted data, reviewed critically the manuscript, and approved.

Ethics

The study was approved by the Institutional Ethics Committee, AIIMS, Rishikesh (Letter No-AIIMS/IEC/21/526). We declare that we have no conflicts of interest.

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