JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Dexamethasone, dexamethasone + remdesivir in treating moderate to severe COVID-19: retrospective observational cohort study

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Abstract

Introduction: The aim of this study was to demonstrate the purpose of adding antiviral (remdesivir) to the existing steroidal (dexamethasone) therapy in treating coronavirus disease 2019 (COVID-19).

Methodology: A retrospective observational case cohort study was carried out to compare the effect of dexamethasone alone and in combination with remdesivir in treating moderate and severe COVID-19 disease. The patients were divided into 2 groups: Group 1 included patients treated with dexamethasone alone, and Group 2 included patients treated with dexamethasone and remdesivir. Levels of inflammatory markers (C-reactive protein, D- dimer and lactate dehydrogenase), World Health Organization (WHO) ordinal scale scoring, symptomatic improvement in terms of fever, cough, shortness of breath, 6-minutes' walk test and SpO_2 levels on day of admission (D0), 3 days and 5 days after admission (D3 and D5), and 10 days overall outcome (determined as death, or discharge with or without Long Term Oxygenation Therapy) were collected and analyzed.

Results: Addition of remdesivir to dexamethasone in treating COVID 19 did not have any additional benefits. No additional role of remdesivir is seen in combating the disease except in case of 10 days outcome. However, the better 10-day outcome associated with the use of remdesivir was thought to be due to the patients who were on mechanical ventilation in the dexamethasone treated group at the time of inclusion.

Conclusions: Since a similar trend was seen in both groups, our study concluded no additional role of remdesivir in combating COVID-19.

Key words: COVID-19, dexamethasone, remdesivir.

J Infect Dev Ctries 2023; 17(7):953-960. doi:10.3855/jidc.17971

(Received 20 January 2023 – Accepted 10 March 2023)

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2), was first detected in Hubei province, China and was reported to the World Health Organisation (WHO) on December 31, 2019 [1]. Since the first case was reported to WHO, COVID-19 has spread to other countries and has resulted in mortality as never seen before. COVID-19 is characterized by cytokine storm and hyperinflammatory syndrome [2]. The two main processes that drive the progression of COVID-19 are the replication of SARS-CoV-2 and dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage [3]. Clinical manifestations usually occur within a week and consist of fever, cough, nasal congestion, fatigue and other signs of upper respiratory tract infections [4].

Initially, when there was no specific treatment for COVID-19 and many clinical trials were conducted for the treatment of COVID-19 using existing drugs. On 16th June it was reported that a randomized evaluation of COVID-19 therapy in UK conducted as a COVID 19 recovery trial revealed that when patients with severe COVID-19 were given 6 mg dexamethasone (DEXA) once daily, there was a 8-26% lower mortality than patients who were given the standard care [1]. The study reported a significant improvement in the outcome of COVID-19 patients who were under respiratory support [5]. Corticosteroids such as dexamethasone have broad effects on innate and adaptive immunity [2]. They work by inhibiting some cytokines like IL-12, IL-18, IL-1, TNF α, TNF γ, granulocyte- macrophage stimulating factor and reduce their destructive effects [6]. However, they can also reduce the function of T cells and present macrophage clearance of apoptised cells, increase viral load and lead to increased risk of secondary infections [5]. Initially, before the RECOVERY trials used systemic glucocorticoids, it was not recommended, and, in fact, was contraindicated [7]. But soon after several trials indicated positive effect of dexamethasone, the guidelines of all the countries, WHO and National

Institutes of Health (NIH) were updated to recommend its usage [8–10].

Dexamethasone is a glucocorticoid which is widely available globally at low price. It is a synthetic glucocorticoid with anti-inflammatory and immunosuppressant activity, and has 20 to 30 times the binding affinity for glucocorticoid receptors of endogenous cortisol [11].

Remdesivir is an experimental antiviral drug manufactured by Gilead Sciences, Foster City, California, United States that was granted approval for emergency use by the United States Food and Drug Administration (US-FDA) in May 2020 for hospitalized COVID 19 patients [12]. The clinical benefits of early treatment with remdesivir emerged from a randomized placebo-controlled trial in 2 hospitalized patients with COVID-19 with evidence of lower respiratory tract infection (LRTI) [13]. The preliminary data showed that remdesivir acts against coronavirus and therefore it inhibits COVID-19 infection [14].

Neither the large adaptive COVID-19 trials nor multinational phase 3 randomized control trials reported the efficacy of remdesivir in terms of shedding the viral load [15]. However initial trials reported that the 10-day course of remdesivir decreased the length of hospitalization, thus suggesting its usage [13].

The current study aims at ruling out the necessity of adding the antiviral remdesivir, to the steroid, dexamethasone for improving the outcomes of hospitalized COVID-19 patients.

Methodology

A retrospective observational case cohort study was carried out to compare the effects of dexamethasone (glucocorticoid) alone and dexamethasone plus remdesivir (anti-viral) in treating moderate and severe COVID-19 patients in terms of reducing the levels of viral markers (C-reactive protein (CRP), D-dimer and lactate dehydrogenase (LDH)), score value as per WHO ordinal scale, presence of symptoms (fever, cough and shortness of breath (SOB)), 6-minute walk test and SpO_2 levels. CRP was measured in terms of mg/L, D-dimer in µg/mL, and LDH in IU/L. The study period was divided into 3 time points: day of admission (D0), 3 days after admission (D3) and 5 days after the admission (D5). The population in each group was monitored on these time points for the above-mentioned factors. The group with significant reduction in the levels was considered as the most effective treatment method for COVID-19 patients with moderate and severe high resolution computed tomography (HRCT) chest score.

In order to measure the clinical improvement of hospitalized COVID-19 patients, a 9-point scale developed by WHO was deployed in the study.. According to the scale, uninfected patients are scored as 0, ambulatory patients with no limitations in activities as 1, ambulatory patients with limitations in activities as 2, hospitalized patients with mild symptoms and no oxygen requirements as 3, hospitalized patients requiring oxygen through a mask or nasal prongs as 4, hospitalized patients with severe symptoms and requiring non-invasive ventilation or high flow oxygen as 5, patients with intubation or mechanical ventilation as 6, and patients requiring ventilation and additional oxygen support - pressors/renal replacement therapy/extra corporeal membrane oxygenation (ECMO) as 7, and patients who died were scored as 8 [16].

Selection of subjects

Data from MRD (medical records department) between 1st July 2020 and 30th June 2021 was used in the study. All the patients with real time polymerase chain reaction (RT-PCR) confirmed COVID-19 and HRCT chest score indicating moderate or severe symptoms were considered and divided into two groups depending upon the medications prescribed. The patients who received only dexamethasone were categorised into group 1 and those who received dexamethasone along with remdesivir were categorised into group 2.

The inclusion criteria were: patients who tested positive with SARS-CoV-2 RT-PCR, HRCT showing moderate and severe symptoms, age ≥ 12 years, any gender, and those who presented to the hospital within the study duration.

The exclusion criteria were: pregnant and lactating women, immunosuppressed patients, those who were already receiving steroids for other medical conditions, and patients who received investigational therapies like tocilizumab, plasma therapy, etc.

Procedure

A total of 413 patients were included; group 1 (dexamethasone only) included 141 patients and group 2 (dexamethasone + remdesivir) included 272 patients.

All the patients were given standard of care (SoC) which included oxygen support to maintain $SpO_2 \geq 93\%$, doxycycline (100 mg twice daily for 7 days) or azithromycin (500 mg for 5 days) at physician's discretion when a bacterial infection was suspected, prophylactic anticoagulation therapy with Low Molecular Weight Heparin/Unfractionated Heparin,

dose adjusted according to the body weight and renal function of the individual patient, along with symptomatic treatment that included antitussives, antihistamines, antipyretics, etc. and either dexamethasone (0.1-0.2 mg/kg/day), or remdesivir (200 mg stat dose followed by 100 mg once daily for 4 days to a cumulative dose of 600 mg given in 5 days).

All the subjects were screened for levels of inflammatory markers, clinical presentations, SpO_2 levels in room air, and 6-minute walk test on D0, D3 and D5, and given with a score based on the WHO ordinal scale.

The 6-minute walk test was conducted in accordance with the American Thoracic Society guidelines by marking a straight, flat and hard surfaced area of a distance of 30 m using bright coloured tapes. Two chairs were kept on either side of the 30 m walkway. Each patient was asked to walk to and forth in that 30 m walkway for 6 minutes. Laps are recorded as 60m/1 lap and the total distance walked in 6 minutes was calculated [17]. The patients who walked a distance of about 400-700 m were considered to be of normal functional exercise capacity [18] and were considered to be negative for the 6-minute walk test. The patients who are unable to walk a minimum distance of 400 m

Table 1. Detailed summary of the study variables.

Total study population: 413 with 311 males (75.3%) and 102 females (24.7%)							
Factor	**Measure**	**Group 1**			**Group 2**		
		D0	**D3**	**D5**	**D0**	**D3**	**D5**
Study population	N, (% population)		141, (34.14)			272, (65.86)	
Males	N, (% population)		104, (73.76)			207, (76.10)	
Females	N, (% population)		37, (26.24)			65, (23.9)	
Adolescence (13-18)							
Males	N		2			2	
Females	N		1			1	
Adults (19-59)							
Males	N		71			148	
Females	N		18			48	
Geriatric (> 60)							
Males	N		31			57	
Females	N		18			16	
World Health Organisation (WHO) ordinal scale score							
3	% population	36.17	29.79	31.91	47.06	50.37	54.78
4	% population	27.66	25.53	29.08	30.88	25.74	22.79
5	% population	32.62	40.43	31.21	22.06	23.16	19.85
6	% population	3.55	4.25	7.80	0.00	0.37	2.20
7	% population	0.00	0.00	0.00	0.00	0.00	0.00
8	% population	0.00	0.00	0.00	0.00	0.37	0.37
	p value		0.35			0.82	
Inflammatory markers							
C-reactive protein (CRP)	Mean ± SD	33.71 ± 20.77	27.09 ± 18.89	23.33 ± 20.4	39.92 ± 21.26	29.73 ± 18.45	24.6 ± 18.91
	95% CI	30.25, 37.16	23.94, 30.23	19.93, 26.72	37.38, 42.46	27.53, 31.93	22.35, 26.84
	p value		0.000075			< 0.00001	
D- dimer	Mean ± SD	416.63 ± 287.71	376.9 ± 249.76	356.42 ± 319.33	360.62 ± 217.26	361.86 ± 192.09	389.02 ± 245.30
	95% CI	365.71, 461.53	335.32, 418.49	303.26, 409.60	334.68, 386.55	338.93, 384.80	359.74, 418.30
	p value		0.24			0.23	
Lactate Dehydrogenase (LDH)	Mean ± SD	446.78 ± 205.98	353.08 ± 182.16	252.86 ± 169.92	431.55 ± 195.79	353.72 ± 162.24	301.21 ± 162.38
	95% CI	412.48, 481.07	322.75, 383.41	224.57, 281.16	408.18, 454.92	334.35, 373.08	281.83, 320.60
	p value		< 0.00001			< 0.00001	
Clinical presentations							
Cough	% population	78.01	12.77	10.64	83.09	30.88	20.96
Fever	% population	82.98	2.13	1.42	93.75	3.68	0.00
Shortness of Breath (SOB)	% population	65.96	50.35	39.72	56.99	35.66	26.47
6 minutes walk test							
Positive	% population	65.96	50.35	43.97	44.49	32.72	25.00
Hypoxia							
Spo_2 < 93%	% population	45.39	50.35	43.26	29.78	27.57	25.00
10 days outcome							
Death	% population		29.79			13.24	
	OR			2.78			
	95% CI			1.68, 4.6			
Discharge with Long Term	% population		10.64%			12.13%	
Oxygenation Therapy (LTOT)	OR			0.86			
	95% CI			0.45, 1.65			
Discharge without Long Term	% population		59.57%			74.63%	
Oxygenation Therapy (LTOT)	OR			0.5			
	95% CI			0.32, 0.77			

in 6 minutes were considered as positive for the test. The patients who were on non-invasive ventilation (NIV)/mechanical ventilation (MV) and those who were unable to get off the bed were considered as positive for the test.

Oxygen saturation levels were checked using a pulse-oximeter. Patients who were maintaining $SpO_2 \geq 94\%$ in room air were not given oxygen support. Patients requiring oxygen support to maintain $SpO_2 \geq 94\%$ were considered hypoxic.

Measure of outcome

Outcome of the treatment plan was measured based on decrease in the levels of inflammatory markers (CRP, D-dimer, LDH) over time points, improvement in WHO ordinal scale score; disease regression in terms of clinical presentations, 6-minutes-walk test and hypoxia; and 10 days outcome in terms of death or discharge with and without long term oxygenation therapy (LTOT).

Statistical analysis

All the above-mentioned measures of outcome were recorded in both the groups on all the time points of the study. The difference in the numerical data was tested for any statistically significant difference using appropriate statistical tests.

The levels of inflammatory markers were presented as mean ± standard deviation (SD) with 95% confidence interval (CI) at each time point in both the groups followed by an appropriate statistical test to measure the significant reduction over time points in individual group.

The values of WHO ordinal scale score and the levels of inflammatory markers (CRP, D-dimer and LDH) in each group were tested for any statistically significant reduction over the time period using ANOVA single factor assay. A p value < 0.05 was considered significant.

Non-numerical or categorical data were presented as percent population in each group at each time point. 10 days outcome was presented as odds ratio (OR) with 95% CI for each outcome along with the percent population.

Table 1 presents the details of the study outcomes comparing both the groups.

Results

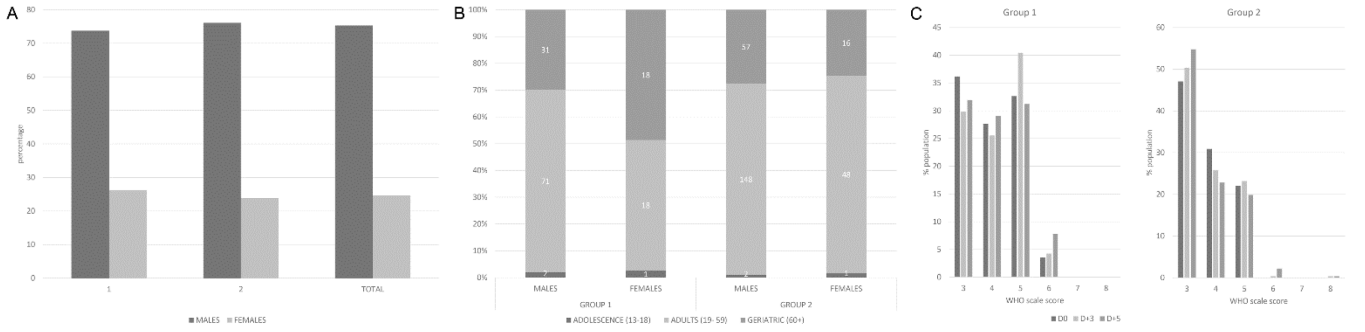
The study included a total of 413 patients, 311 males (75.3%) and 102 females (24.7%). Out of the total of 413 patients, 141 (34.14%) were grouped into group 1, 104 males (73.76%) and 37 females (26.24%); and 272 (65.86%) were grouped into group 2, 207 males (76.1%) and 65 females (23.9%). Figure 1A represents the percent population of each gender in both the groups.

Group 1 included, 2 males and 1 female of adolescence age group (13-18 years), 71 males and 18 females of adults age group (19-59 years), 31 males and 18 females of geriatric age group (≥ 60 years). Group 2 included 2 males and 1 female of adolescence age group, 148 males and 48 females of adult age group, 57 males and 16 females of geriatric age group. Figure 1B represents age distribution of our study population.

On D0, 36.17%, 27.66%, 32.62% and 3.55% of group 1 population had a WHO score of 3, 4, 5 and 6 respectively. On D3, 29.79%, 25.53%, 40.43% and 4.25% of group 1 population had WHO scores of 3, 4, 5 and 6 respectively. On D5, 31.91%, 29.08%, 31.21% and 7.80% of group 1 population WHO scores of 3, 4, 5 and 6 respectively (Figure 1C). ANOVA single factor assay conducted across the time points reported a p value of 0.35, indicating no statistically significant difference in score across the time points.

Only 3.55% (5 patients) population in group 1 were intubated and receiving mechanical ventilation (MV) on D0 and continued with the same till D5. None of the patients were on non- invasive ventilation (NIV).

Figure 1. Percentage population of **A:** males and females in each group, along with **B:** age wise distribution.



On D0, 47.06%, 30.88%, and 22.06% of group 2 population had a WHO score of 3, 4 and 5 respectively. On D3, 50.37%, 25.74%, 23.16%, 0.37% and 0.37% of group 2 population had a WHO score of 3, 4, 5, 6 and 8 respectively. On D5, 54.78%, 22.79%, 19.85%, 2.20% and 0.37% of group 2 population had a WHO score of 3, 4, 5, 6 and 8 respectively (Figure 1C). ANOVA single factor assay conducted across the time points reported a *p* value of 0.82 indicating no statistically significant difference in the WHO ordinal scale score across the time points.

None of the patients in group 2 were on NIV/MV on D0.

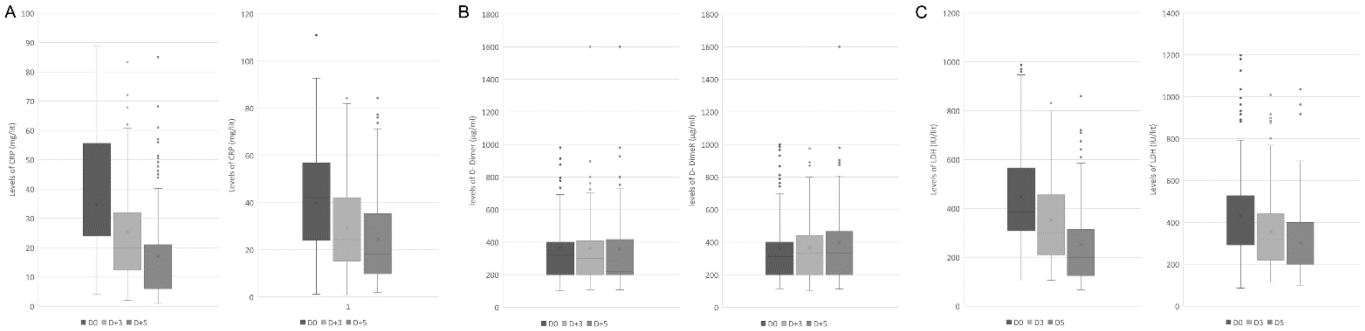
The mean ± SD of CRP of patients in group 1 on D0 was 33.71 ± 20.77 with 95% CI of 30.25, 37.16. On D3 the mean decreased to 27.09 ± 18.89 with 95% CI of 23.94, 30.23 and on D5 to 23.33 ± 20.4 with 95% CI of 19.93, 26.72. The overall decrease in the mean CRP of patients in group 1 across time points was statistically significant with *p* value 0.000075, tested using ANOVA single factor assay. On the other hand, mean ± SD of CRP of patients of group 2 on D0 was 39.92 ± 21.26 with 95% CI of 37.38, 42.46. On D3 and D5 the values were 29.73 ± 18.45 with 95% CI of 27.53, 31.93 and 24.6 ± 18.91 with 95% CI of 22.35, 26.84 respectively. The statistical significance of the difference between the values of CRP in group 2 across the time points as tested using ANOVA single factor assay and a *p* value of < 0.00001 indicated a significant difference. Figure 2A represents the range of CRP values on different time points in group 1 and group 2 respectively.

Mean ± SD of D-dimer in group 1 patients on D0, D3 and D5 were 413.63 ± 287.71 (95% CI 365.72, 461.53), 376.90 ± 249.76 (95% CI 335.32, 418.49), and 356.42 ± 319.33 (95% CI 303.26, 409.60) respectively. The decrease in the mean D-dimer levels across the time points in group 1 was analyzed using ANOVA single factor assay. A *p* value of 0.24, indicated no significant difference. On the other hand, mean ± SD of D-dimer of patients in group 2 at D0, D3 and D5 were 360.62 ± 217.26 (95% CI 334.68, 386.55), 361.86 ± 192.09 (95% CI of 338.93, 384.80) and 389.02 ± 245.30 (95% CI 359.74, 418.30) respectively. Using the same ANOVA single factor assay, it was determined that there was no significant difference between the three time points (*p* = 0.23). However, dispersion of values around the mean is large in both the groups. Figure 2B presents the range of D- dimer at the three time points in group 1 and group 2.

The other inflammatory marker of the study was LDH. The mean ± SD of LDH of patients in group 1 on D0, D3 and D5 were 446.78 ± 205.98 (95% CI 412.48, 481.07), 353.08 ± 182.16 (95% CI 322.75, 383.41) and 252.86 ± 169.92 (95% CI 224.57, 281.16) respectively. ANOVA single factor analysis indicated that there was statistically significant difference in the values across time points (≤ 0.00001). The mean ± SD LDH of patients in group 2 on D0, D3 and D5 were 431.55 ± 195.79 (95% CI 408.18, 454.92), 353.72 ± 162.24 (95% CI 334.35, 373.08) and 301.21 ± 162.38 (95% CI 281.83, 320.60) respectively. ANOVA single factor analysis indicated a statistically significant difference across time points (*p* < 0.00001). Although in this case, dispersion of values around the mean was larger, there was a significant difference between the time points. Figure 2C represents the levels of LDH of patients in groups 1 and group 2.

Clinical presentations of patients in group 1 on D0 included cough in 78.01% patients, fever in 83.98% patients and SOB in 65.96% patients. The percentage of population presenting cough decreased gradually to 12.77% on D3 and 10.64% on D5. Fever resolved to a greater extent by D3 with 2.13% population presenting fever and 1.42% population on D5. SOB showed a slow recovery in comparison with other two clinical presentations with 50.35% and 39.72% population presenting SOB on D3 and D5 respectively. A similar

Figure 2. Levels of inflammatory markers in both the groups at different time points. **A:** C-Reactive Protein (CRP); **B:** D-dimer; **C:** Lactate Dehydrogenase (LDH).



trend was seen in group 2 with 83.09%, 30.88% and 20.96% population presenting cough on D0, D3 and D5 respectively. 93.75%, 3.68% and 0% population presented fever on D0, D3 and D5 respectively. 56.99%, 35.66% and 26.47% population presented SOB on D0, D3 and D5 respectively.

Among the patients who could perform 6 minutes' walk test, in group 1, 65.96%, 50.35% and 43.97% population reported positive test study. On the other hand, in group 2, 44.49%, 32.72% and 25% population were positive for the test. A steady decrease in % population with positive test result was observed in both the groups.

The proportion of patients who were hypoxic in group 1 and group 2 remained almost unchanged across the time period. In group 1, 45.39%, 50.35% and 43.26% were hypoxic on D0, D3 and D5 respectively. Parallelly, in group 2, 29.78%, 27.57% and 25 % were hypoxic on D0, D3 and D5 respectively. The percent population hypoxic in group 1 and group 2 over the time points is presented in Figure 3A as a funnel graph.

After 10 days 29.79%, 10.64% and 59.57% population in group 1 died and were discharged with and without LTOT respectively. In the case of group 2, 13.24%, 12.13% and 74.63% population died, and were discharged with and without LTOT respectively. Odds Ratio (OR) for death was 2.78 with 95% CI of 1.68, 4.6, indicating that there were 2.78 time more deaths in group 1. OR for discharge with LTOT was 0.86 with 0.45, 1.65 as 95% CI, indicating that discharge with LTOT in group 1 was just 0.86 times more than that in group 2. OR for discharge without LTOT was 0.50 with 95% CI of 0.32, 0.77, indicating the discharge without LTOT in group 1 was half of that in group 2. Figure 3B represents the 10 days outcome of both the study groups.

The increased deaths seen in group 1 is related to the patients who were on MV at D0 and no such patients were included in group 2.

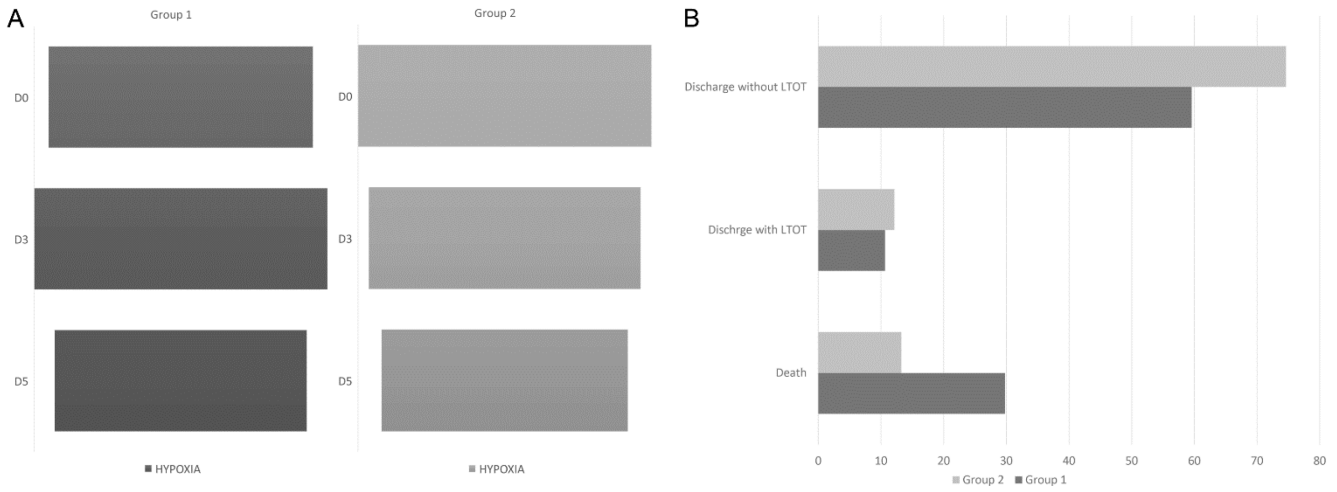
Causes of death in both the groups were similar: acute respiratory distress syndrome (ARDS), bilateral viral pneumonia, type 2 respiratory failure, sepsis, multiple organ dysfunctional syndrome, heart failure, and cardio- pulmonary arrest.

Discussion

Our study demonstrated no additional benefits of adding remdesivir to dexamethasone since the measures of outcome of our study were similar in both the groups. Our results were similar to those published from the randomized evaluation of COVID 19 therapy (RECOVERY) trial of remdesivir in treating COVID 19 [8,13]. However, the OR/ HR and 95% CI cannot be directly compared since in the RECOVERY trial drugs were compared against placebo groups, whereas, our study compared two approved drugs.

A randomized, double blinded, placebo controlled, multi-center study conducted by Yeming Wang MD *et al*. reported no statistically significant difference between the remdesivir treated and placebo-controlled group based on 28 days mortality with 14% mortality in remdesivir treated group and 13% in placebo-controlled group. Even the clinical improvement that was seen numerically was not statistically significant. However, the study had restrictions in terms of the number of patients enrolled in the study, availability of beds in the hospital leading to the patients coming to the hospital in later course of the disease and presenting in a severe stage [19].

Figure 3. Percent population with each score value as per World Health Organization ordinal scale at **A:** different time points; **B:** hypoxic in both the groups at different time points; along with **C:** 10-days outcome.



A study on compassionate use of remdesivir in treating severe COVID-19 patients by Jonathan Grein, *et al*., reported a mortality of only 13% and clinical improvement in 68% population which was not in agreement with other ongoing clinical trials of that time but is in line with the current study. However, this study was limited in size, had short duration of follow up and lacked a control group [20].

11 days outcome of clinical improvement was seen after 5-day course of remdesivir upon comparing with standard of care and was statistically significant (p = 0.02). However, the same study reported no statistically significant difference in the clinical improvement by day 11 between 10-day course of remdesivir and standard of care [21]. Our study finds the similiarity in terms of significant improvement in inflammatory markers with 5 day course of remdesivir.

RECOVERY collaborative study reported that the effect of dexamethasone was not seen in patients who were on non-invasive or invasive ventilation. The patients who were on MV in the dexamethasone treated group of our study progressed into death, further strengthening the results of RECOVERY collaborative study [8]. The patients who were on oxygen therapy and were receiving dexamethasone had a lower risk of progressing into invasive or non-invasive ventilation. Since a similar percentage population in both the groups of our study had progressed further into NIV/MV, our study conclusion that remdesivir has no additional benefits in lowering the risk supplements the above conclusion [22].

The results of our study are in agreement to previous studies conducted on individual drugs (as detailed in the discussion section). The results of our study, including the clinical improvement in terms of WHO ordinal scale score, clinical presentations, levels of inflammatory markers and 10 days outcome were very similar in the dexamethasone and dexamethasone + remdesivir treated groups. The results are in good agreement with the previously published results on the effect of dexamethasone alone in treating hospitalised COVID 19 patients, further strengthening the effect of dexamethasone without any addition of antiviral in treating hospitalized COVID 19 patients.

Conclusions

Adding remdesivir to the corticosteroid (dexamethasone) in treating moderate to severe COVID-19 disease did not result in additional benefits. No additional role of remdesivir was seen in combating the disease except in case of 10 days outcome. However, the better 10-day outcome associated with the use of remdesivir as seen in our study was due to absence of patients with MV at the time of admission in group 2.

Acknowledgements

We convey our sincere thanks to the managing director of the Medisys hospital Dr. Chandrashekar Reddy for allowing us to conduct the project, and to Dr. Chandrashekara Rao Baru, Principal, Chilkur Balaji College of Pharmacy, for allowing students to participate in our project as clinical research associates.

Authors' contribution

NS: protocol preparation, statistical analysis, first draft of manuscript; SG, SS: protocol evaluation, manuscript revision and finalization; VA, SRG: data collection, literature review, first draft of manuscript.

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Conflict of interests: No conflict of interests is declared.