

A comparative study of the efficacy and outcome of methylprednisolone and dexamethasone in moderate to severe COVID-19 disease



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Submission: 21-08-2021

Revision: 09-11-2021

Publication: 01-12-2021

ABSTRACT

Background: COVID-19 disease is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). In the first half of 2020 COVID-19 disease has already converted into a global pandemic. Many treatment options were explored through the world. **Aims and Objectives:** To compare the efficacy and outcome of methylprednisolone (MTP) and dexamethasone (DEXA) in moderate-to-severe COVID-19 disease. **Materials and Methods:** In this prospective study, a total of 140 moderate to severe COVID-19 patients were enrolled from 15 April to June 15, 2021. These patients were randomly allocated into two groups, 70 patients were received MTP 2 mg/kg/day for 3 days followed by 1.0 mg/kg/day for 3 days in divided doses while 70 patients received DEXA 8 mg/day in divided dose up to 10 days. **Results:** The mean age was 45.5 years in MTP group whereas 45.34 years in DEXA group. The clinical outcome in MTP group and DEXA group was assessed in terms of clinical improvement (92.85% vs. 81.42%), radiological improvement (82.85% vs. 68.57%), transfer to ICU (5.71 vs. 14.57%), needs of ventilatory support (2.85% vs. 8.57%) and mortality (7.14% vs. 18.57%) respectively. **Conclusion:** In this study, MTP demonstrated better outcome as compared to DEXA in COVID-19 patients.

Key words: COVID-19 disease; Dexamethasone; Methylprednisolone

Access this article online

Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v12i12.39294

E-ISSN: 2091-0576

P-ISSN: 2467-9100

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes coronavirus diseases (COVID-19) was first identified in December 2019 in Wuhan city, China, and later spread to many provinces in China¹ and has spread with great speed around the world.

On March 12, 2020, it was declared as global pandemic by the World health organization.² The first SARS-CoV-2 positive case in India was reported in the state of Kerala on January 30th, 2020.³

The COVID-19 primarily affects the lung resulting in inflammation and pneumonia. On the basis of clinical, biochemical, and radiological parameters it is divided into mild, moderate, and severe disease. In mild disease, there is fever and upper respiratory symptoms but no documented hypoxia or shortness of breath. In moderate disease, there is tachypnea >24/min, hypoxia (SpO₂ <93%), and in severe disease there is tachypnea >30/min, hypoxia (90%), and biochemical parameter suggest cytokine storm and patient can develop multiorgan failure.⁴

The relatively high infectivity, rapid progression of lung involvement, and absence of definite effective treatment

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all contribute to a need to design effective measures for the management of COVID-19 based on the disease pathogenesis. Although many types of research and studies have contributed to the understanding of the disease and various empirical therapeutic options have been introduced on several operational methods, including the existing and new generation of antivirals and traditional medicine. An effective therapeutic option has not been achieved for severe COVID-19 cases.⁵⁻⁸

Corticosteroids have been used previously in respiratory illnesses such as asthma, COPD, severe bacterial pneumonia, and acute respiratory distress syndrome. The use of corticosteroids on COVID-19 disease is still controversial.⁹ Some studies have shown a good response to steroids as they reduce inflammation,^{10,11} However corticosteroids suppress the patients immunity making him more prone to superadded infection.^{10,12} Recently, the recovery trial in the U.K. showed dexamethasone (DEXA) (corticosteroid) to be the only drug able to reduce mortality in severe COVID-19 disease.¹³

However, there is a paucity of literature on the use of methylprednisolone (MTP) in COVID-19. Hence, this study has been under taken to compare the role of DEXA with MTP in patients of COVID-19.

Aims and objectives

To compare the efficacy and outcome of MTP and DEXA in moderate to severe COVID-19 disease.

MATERIALS AND METHODS

The current study is a prospective study involving 140 patients diagnosed with moderate to severe COVID-19 disease admitted in Kaily Hospital Mahirshi Vashisth Autonomous State Medical College, Basti, U.P. from 15 April to 15 June 2021.

Inclusion criteria

- Age: 18–75 years.
- COVID-19 RT-PCR positive.
- Moderate-to-severe COVID-19 cases according to definition.
- Patients having oxygen saturation <93% on room air, regardless of chest X-ray infiltrates.
- Patients given informed consent.

Exclusion criteria

- Pregnant or lactating females.
- Immunocompromised conditions such as HIV or long-term use of immunosuppressant for any chronic illness.

Study

We enrolled 140 patients admitted in Kaily hospital Mahirshi Vashisth Autonomous state Medical College, Basti U.P. who fulfilled the inclusion criteria and signed informed consent.

After admission, Baseline oxygen saturation and clinical findings were noted. Chest X-ray was done on admission and laboratory tests were performed such as haemogram, liver function test, kidney function test, C-reactive protein (CRP), Serum ferritin (S. ferritin), lactate dehydrogenase (LDH), and D-dimer. Low molecular weight heparin (Enoxaparin) was prescribed to all patients to prevent thromboembolism and antibiotics also during their hospital stay.

Patients were divided into two groups. Group A (n=70) and Group B (n=70). Group A received intravenous methylprednisolone (MTP) 2.0 mg/kg bodyweight for 3 days followed by 1.0 mg/kg for 3 days in the divided dose and Group B received DEXA 8 mg/day intravenously daily in divided dose up to 10 days. Oxygen saturation was recorded daily and laboratory investigations such as CRP, LDH, S. ferritin, and repeat chest X-ray were performed after 5 days and also after 10 days. Patients were given oxygen by nasal cannula, face mask, and non-rebreathing mask. Patients were shifted to ICU if clinical condition deteriorated and/or mechanical ventilation was needed.

We compared outcomes on the basis of clinical, radiological, biochemical parameters and mortality of patients on day 0 that is admission day, 5th and 10th days between both drugs.

Data were analyzed using SPSS 26.0 mean and standard deviation was computed for quantitative variables whereas frequency and percentage were calculated for other category variables.

RESULTS

A total of 140 patients of COVID-19 having moderate to severe COVID-19 disease and admitted to Kaily Hospital, MVASMC Basti fulfilling inclusion criteria were recruited in the study. Out of 140, 70 patients received MTP (Group-A) and the other 70 patients received DEXA (Group-B).

The mean age in MTP group was found to be 45.5 years and 45.34 years in DEXA group (Table 1).

Both groups were compared for underlying diseases such as diabetes, hypertension, COPD, renal disease, and hypothyroidism. There was no statistically significant

difference between both groups but hypertension was found in 16 patients in group A while in group B hypertension was found in 26 patients ($P<0.05$).

On completion of 10 days of treatment with parental corticosteroids, the biochemical markers of severity improved significantly in MTP as well as DEXA group (Table 2).

Patients were evaluated on day 0, 5, and 10. There was a significant clinical improvement in the MTP group as compared to the DEXA group (92.85% vs. 81.42%, $P<0.05$).

Radiological improvement was statistically significant in the MTP group when compared to the DEXA group (82.8% vs. 68.5%, $P<0.05$).

Transfer to intensive care unit and ventilator requirement was lower in the group that received MTP (5.71% vs. 14.28%) and (2.85% vs. 8.57%), respectively (Table 3).

Hyperglycemia was more frequent in the DEXA group (18.57%) as compared to the MTP group (7.14%) ($P<0.05$). In terms of mortality, group B reported 13 cases (18.5%) while in group A five patients died (7.14%). The difference was statistically significant ($P<0.05$).

Z test for proportion (one-tailed) is carried out to see if there any proportion difference between two drug groups for variables under study. P-value (for one-tailed alternative) showing there is significantly more clinically improved and radiologically improved patients are in MTP group and also for hyperglycemia and mortality, there is significantly lesser proportion of patients in MTP group.

Table 1: Socio-demographic and clinical characteristics of hospitalized patients with COVID-19 pneumonia, according to treatment group

S. No.	Variable	MTP (Group-A) n=70	DEXA (Group-B) n=70	Total n=140	P-value
1.	Age (years)	Mean age 45.50	Mean age 45.34		0.949
2.	Sex				
	Male	46 (65.71%)	50 (71.42%)	96 (68.57%)	0.466
	Female	24 (34.28%)	20 (28.57%)	44 (31.42%)	
3.	Diabetes mellitus	16 (22.85%)	19 (27.14%)	35 (25.0%)	0.612
4.	CKD	06 (8.57%)	07 (10.0%)	13 (9.28%)	0.781
5.	Hypertension	16 (22.85%)	26 (37.14%)	42 (30.0%)	0.048
6.	COPD	09 (12.85%)	06 (8.57%)	15 (10.71%)	0.438
7.	Hypothyroidism	06 (8.57%)	04 (5.71%)	10 (7.14%)	0.527
8.	Heart disease	03 (4.28%)	03 (4.28%)	06 (4.28%)	1.0
9.	Obesity	07 (10.0%)	06 (8.57%)	13 (9.28%)	0.781
10.	Malignancy	02 (2.85%)	01 (1.42%)	03 (2.14%)	0.563

CKD: Chronic kidney disease, MTP: Methylprednisolone, DEXA: Dexamethasone, COPD: Chronic obstructive pulmonary disease. T-test is performed to see if there any mean age difference between MTP and DEXA group, P value is coming out to be greater than 0.05, means there is no mean age difference. Chi-square test is carried out to see if there any association between two groups of drug for variable under consideration. There is a significant association between hypertension and two groups of drug. For other variable, P value is coming out to be more than 0.05, showing there is no significant association

Table 2: Comparison of intervention between two groups

Medicine or treatment	Variable	Mean±SD MTP (Group-A)	Mean±SD DEXA (Group-B)	P-value
On day 0	SPO ₂	89.91±2.05	90±1.91	0.799
	CRP	112.49±46.91	110.62±48.37	0.816
	S.Ferritin	186.85±167.96	190.20±94.40	0.885
	LDH	315.63±184.36	318.40±131.23	0.9187
Day 5	SPO ₂	91.90±1.05	91.00±2.70	0.013
	CRP	58.62±39.001	75.52±50.014	0.032
	S.Ferritin	134.14±123.135	142.95±101.215	0.655
	LDH	272.29±151.83	282.40±163.16	0.713
Day 10	SPO ₂	94.48±81	93.60±5.411	0.204
	CRP	28.00±7.605	31.30±8.934	0.032
	S. Ferritin	88.56±42.82	93.54±47.14	0.544
	LDH	188.49±47.22	190.28±39.119	0.823
		Greenhouse- Geisser (P=0.00)	Greenhouse- Geisser (P=0.00)	

CRP: C-reactive protein; S. Ferritin: Serum ferritin; LDH: Lactate Dehydrogenase. Greenhouse-Geisser (P-value) showing there is a significant difference over time within a group for all variables under study. T-test is carried out to see if there any mean difference for variables under consideration for drug A and B. At 0 day, there is no significant difference between drug group A and B for all variables. ($P>0.05$) At day 5, S. ferritin and LDH showing no difference in drug group A and B. While in SPO₂ and CRP there is significant mean difference for the drug. At day 10, only CRP is showing significant mean difference for the two drug group

Table 3: Clinical outcome of hospitalized patients with COVID-19 pneumonia according to the treatment group

Variables	MTP (Group-A) n=70	DEXA (Group-B) n=70	Total patients n=140	P-value
Clinically improved	65 (92.85%)	57 (81.42%)	122 (87.14%)	0.0433
Radiologically improved	58 (82.85%)	48 (68.57%)	106 (75.71%)	0.0487
Hyperglycemia	05 (7.14%)	13 (18.57%)	18 (12.85%)	0.046
ICU transfer	04 (5.71%)	10 (14.28%)	14 (10.0%)	0.090
Ventilator need	02 (2.85%)	06 (8.57%)	08 (5.71%)	0.145
Hyperglycemic coma/DKA	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	0
Superadded infection	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	0
Mortality	05 (7.14%)	13 (18.57%)	18 (12.85%)	0.0433

CKD: Chronic kidney disease, MTP: Methylprednisolone, DEXA: Dexamethasone

For other variables, the result is coming not out to be significant.

DISCUSSION

COVID-19 disease is caused by SARS-CoV-2 has emerged as a major threat globally. The novelty of disease and its undesirably high morbidity and mortality have lead physicians to explore new dimensions of treatment.

ARDS and cytokine release syndrome are dreadful complications of COVID-19, both characterized by increased levels of Tumor necrosis factor Alfa, Interleukin (IL) 1B, IL-2, IL-6, IL-8, IL-10, and Interferon-gamma which causes dysregulated auto-inflammatory response, severe tissue inflammation and ultimately death.¹⁴ Due to its anti-inflammatory properties corticosteroids have been used in the treatment of COVID-19. We performed a comprehensive comparison of MTP and DEXA in the treatment of moderate to severe COVID-19 disease.

In the current study, we included 140 patients with moderate to severe COVID-19 disease, they were randomly allocated to two groups, i.e., Group A (MTP group) and group B (DEXA group). Both groups were matched regarding their demographic profile (Table 1).

In MTP group, a more significant decrease in inflammatory response was observed than in DEXA group leading to decrease in CRP, LDH, and S. ferritin. This is consistent to the finding of Pinzón et al.¹⁵

In a randomized clinical trial performed by Edalatifard et al., the efficacy of intravenous MTP pulse was compared with standard care. In the mentioned study, patients with clinical improvement were higher in MTP group than in the standard care group (94.1% vs. 57.1%). The clinical improvement was noted in terms of increase in oxygen saturation and alleviation of myalgia, chest pain, cough,

fever, and gastrointestinal symptoms.¹⁶ These findings were in line with our study. The present study showed a significant clinical improvement (92.8% vs. 81.4%) as well radiological improvement on (82.8% vs. 68.5%) in MTP group when compared with DEXA group (Table 2).

As per study performed by Pinzon et al., patients in DEXA group developed severe ARDS in higher proportion than the MTP group, and transfer to the intensive care unit was less in the MTP group which is related to less clinical deterioration and less progress to critical illness with the administration of high dose of MTP,¹⁵ this was in corroboration with the finding of our study where transfer to ICU was 5.7% in MTP group as compared to 14.2% in DEXA group.

In a retrospective cohort study conducted by Wang et al., in the evaluation of treatment of patients suffering from COVID-19 with low dose of MTP (1–2 mg/kg/day) for 5–7 days had shorter hospital stay and less requirement of mechanical ventilation.¹⁰ These findings were in accordance to the current study (2.8% in MTP group vs. 8.5% in DEXA group).

Treatment of COVID-19 patients with corticosteroids may have some complications like superimposed infection, immunosuppression, and hyperglycemia. Hyperglycemia was more frequent in DEXA group (18.57%) when compared to MTP (7.14%). The hyperglycemia was managed effectively with insulin and none of the patients developed serious complications such as ketoacidosis or hyperosmolar coma. In some studies, it was found that hyperglycemia was more frequent in those who received MTP, managed without substantial complication.^{10,16,17}

None of our patients developed superadded bacterial pneumonia as determined by pro-calcitonin levels and serial chest X-ray for new opacities. This could be explained by short period of corticosteroid use (i.e. 5 days). This is similar to the study performed by Fatima et al.¹⁸

The recovery trial showed significantly less mortality in DEXA group as compared to standard care group.¹³ However, the recovery trial did not study the effects of MTP.

Wang et al., conducted a retrospective cohort study of MTP therapy in severe patients of COVID-19 pneumonia and found that there was a significant reduction in morbidity and mortality with MTP.¹⁰

KO et al., concluded that therapeutic benefits of corticosteroids are not limited to DEXA only. The higher anti-inflammatory potency of MTP had greater mortality benefits in COVID-19 patients requiring mechanical ventilation.¹⁹

In the present study, there was a significant reduction of mortality in the MTP group as compared to DEXA group (7.14% vs. 18.5%; $P < 0.05$). This is similar to the Edalatifard et al., who showed lower mortality rate in MTP group (5.9% vs. 42.9%, $P < 0.0001$).¹⁶

Limitations of the study

To the best of our knowledge, this was the first study in eastern Uttar Pradesh, India comparing the efficacy of MTP with DEXA.

However, major limitations of this study are sample size is small and there was no follow-up of patients after discharge.

CONCLUSION

In this study, the severity markers of COVID-19 pneumonia such as CRP, LDH, and S. ferritin are significantly reduced by administration of both MTP as well as DEXA. However, the outcome in the terms of clinical improvement, radiological improvement, reduction in mechanical ventilation requirement, and decrease in mortality was found to be better in MTP group when compared with DEXA group.

ACKNOWLEDGMENT

We are thankful to Mr. Pawan Kumar biostatistician for helping in statistical analysis.

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Authors Contribution:

PBG- Concept and design of the study; prepared first draft of manuscript; **AK-** Statistically analysed and interpreted the result; **BLK-** reviewed the literature and manuscript preparation; **RC-** preparation of manuscript and revision of the manuscript

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Source of Funding: None, **Conflicts of Interest:** None.