Case Series

Favourable outcome of severe COVID-19 patients in hyperinflammatory phase with high dose dexamethasone pulse therapy: A series of 10 cases

Swetalina Pradhan[1], Shyama Sharma[2], Anup Kumar[3], Prabhat Kumar Singh[4]

Departments of [1]Dermatology, [2]Medicine, [3]Orthopedics and [4]Anaesthesiology, All India Institute of Medical Sciences, Patna, Bihar, India

Abstract

The hyperinflammatory phase of COVID-19 occurring because of cytokine storm is the leading cause of mortality and morbidity in the affected patients. Various drugs with no definite cure are being tried to tackle the cytokine storm. Recently high dose corticosteroids are being used to arrest the surge of cytokines. In the current case series, we will be discussing the outcome of high dose dexamethasone pulse therapy in 10 cases of COVID-19 in hyperinflammatory phase who were cured of the disease along with improvement in laboratory parameters without any complications to the therapy.

Keywords: Case series, high dose dexamethasone pulse therapy, hyperinflammatory phase, outcome, severe COVID-19

Introduction

Globally, by 15 May 2021, there have been 161,513,458 confirmed cases of COVID-19, including 3,352,109 deaths, with 24,372,907 confirmed cases from India.[1] The disease course of COVID-19 has been divided into three phases: A first phase characterized by a viral infection in the respiratory tract; a secondary pulmonary phase characterized by lung infection with a non-hypoxic stage (phase IIA) and leads into a hypoxic stage (phase IIB); and a third hyper-inflammatory phase.[2] The third phase or hyperinflammatory phase occurs because of cytokine storm due to activation of both the innate and adaptive immune responses in the body is believed to be the cause of ARDS, MODs and even death.[3] Several inflammatory markers such as procalcitonin, C-reactive protein, neutrophils, interleukin (IL) 6, Lactate dehydrogenase (LDH) and ferritin have been found to be significantly elevated in severe COVID-19 cases indicating poor prognosis.[4-9] Clinically the disease severity has been classified into 3 categories, *mild:* Individuals with various signs and symptoms of COVID-19 but without breathlessness or hypoxia, *moderate:* Individuals with respiratory rate ≥24/min having an oxygen saturation (SpO_2) ≤93% on room air and *severe:* Individuals with respiratory rate >30/min and SpO_2 <90% on room air.[10]

Various drugs are being tried in COVID-19 include hydroxychloroquine, ivermectin, doxycycline, remdesivir, favipiravir, dexamethasone, tocilizumab, along with vitamin, zinc and other nutritional supplements.[11] Remdesivir is the only FDA approved drug for hospitalized COVID-19 patients on supplemental oxygen.[12] In many settings Tocilizumab (TCZ), a recombinant humanized anti-human IL-6 receptor monoclonal

Address for correspondence: Dr. Swetalina Pradhan, Department of Dermatology, All India Institute of Medical Sciences, Patna, Bihar, India.
E-mail: dr.swetalinapradhan@gmail.com

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antibody is used to tackle the cytokine storm in COVID patients, though found unsuccessful. [13] In addition, it is costly and has availability issues.[13] Systemic corticosteroids have been demonstrated to be effective in the treatment of severe COVID-19 in a number of recent investigations.[14] Recently high dose pulse methylprednisolone has been found beneficial in tackling the severe COVID-19.[3]

In this series we'd like to present our experience of using high-dose dexamethasone pulse treatment in 10 patients of COVID 19 with severe disease.

Cases

We are presenting here, 10 cases aged 31 to 62 years admitted in the general COVID ward of our institute. Table 1 shows the demographics, presenting signs/symptoms, concomitant co-morbidities, vitals, and oxygen need on the day of admission. Baseline routine haematological investigations and inflammatory marker levels (serum Lactate dehydrogenase LDH, C-reactive protein CRP, interleukin 6 IL 6 and ferritin) and Chest X-ray were done in all cases. The inflammatory markers were high, with infiltration affecting >50% of lung field in Chest X-ray of all the cases suggestive of hyperinflammatory phase [Figure 1a and 1b]. The patients received various treatments in the form of supplemental oxygen, injectable/oral antibiotics, oral dexamethasone, oral Ivermectin, injection Remdesivir, therapeutic subcutaneous low-molecular-weight heparin, cough syrup, steam inhalation, awake proning, multivitamins, paracetamol, zinc and vitamin C as per requirements and the institute protocol [Table 1]. Remdesivir was not given to case 3, 6 and 10 due to deranged liver enzymes. The patients with <15 lit oxygen demand to maintain saturation above 94 were put on non-rebreathing mask (NRM) and those not maintaining saturation on 15 lit NRM were put on high flow nasal canula (HFNC). Those requiring oxygen below 5 litres were put on nasal prong (NP).

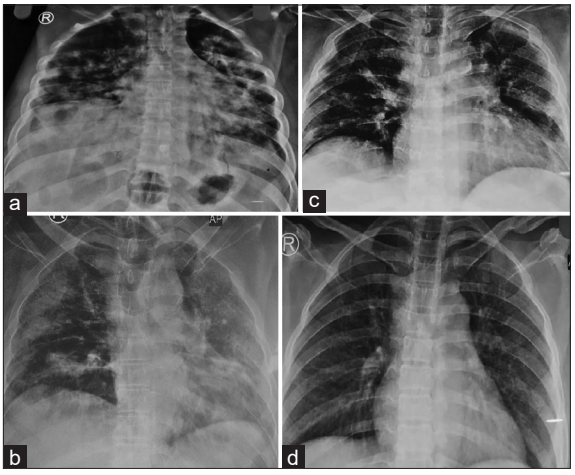

Figure 1: (a and b) Chest X-ray showing infiltrations in >50% lung field. (c and d) Improvement in opacities post dexamethasone pulse therapy

On the second or third day of hospitalisation, despite sufficient oxygen support and standard treatment, all the patients worsened, with increasing respiratory distress and oxygen requirement. Based on clinical deterioration and high inflammatory markers, patients were prescribed high dose dexamethasone pulse therapy (HDDPT) –100 mg Dexamethasone in 500 ml of 5% dextrose solution (D5) slow IV (45 drops/min) for three consecutive days. In patients of diabetes mellitus 8 Unit regular insulin was added to D5 solution. Before giving dexamethasone pulse normal serum electrolytes and ECG were ensured in all patients. Breathlessness and oxygen requirement decreased in all cases after dexamethasone pulse. The duration required to maintain saturation on room air from the day of initiation of high dose dexamethasone pulse ranged from 5 to 18 days. The total duration of hospital stay ranged from 9 to 22 days [Table 2]. Subjective improvement was achieved in all cases post dexamethasone pulse [Table 2]. The inflammatory marker levels and amount of opacities in chest X-ray also improved with dexamethasone pulse [Table 3] [Figure 1c and 1d]. Except transient rise in blood sugar level in cases 2, 3, and 7 no other side effect were found in any of the patient. Raised blood sugar was managed with a basal-bolus regimen of insulin therapy.

Discussion

Glucocorticoids are being used widely nowadays in COVID patients because of their immunosuppressive and anti-inflammatory properties. Immunosuppressive effects are exhibited through transactivation, and induction of gene transcription and protein synthesis of NF-κB inhibitors and lipocortin-1. Inhibition of NF-κB signalling, results in downregulation of IL-1, IL-6, granulocyte-macrophage colony-stimulating factor, and inducible cyclooxygenase-2 production.[15,16] GCs also inhibit the Th1 and macrophage-based pro-inflammatory cytokines IL-1β, IL-2, IL-6, TNF-α, and IL-17. Because of the above effects GCs are thought to be useful in combating the hyperinflammatory phase of COVID-19. Recently studies have found beneficial effects of systemic corticosteroids on mortality of COVID-19 patients.[17,18] Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest benefit observed in patients who require mechanical ventilation.[14] Recently in a prospective observational study, high-dose corticosteroid pulse therapy (HDCPT) using methylprednisolone or dexamethasone equivalent was found to increase COVID-19 survival rates in patients at risk of developing a COVID-19 hyper-inflammatory response.[3] In another multicentre retrospective cohort study high dose corticosteroid (methylprednisolone) pulse was found to reduce mortality significantly in severe COVID-19 patients.[19]

In the current series all severe COVID patients were in hyperinflammatory phase. Despite receiving all the authorised medications in accordance with protocol and receiving

Table 1: Patient demographic details, presenting complaints, oxygen requirement and treatment details on the day of admission

Detail parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case6	Case 7	Case 8	Case 9	Case 10
Age/sex	38/M	58/F	55/M	62/M	39/M	48/M	62/M	57/M	43/F	39/M
Symptoms	Fever Cough Dysnea Myalgia Headache	Fever Dysnea Myalgia Rhinorrhoea	Fever Anosmia	Fever Dysnea	Cough Dysnea Myalgia, Rhinorrhoea	Fever Cough Dysnea Ageusia	Fever Myalgia Dysnea	Dysnea Myalgia	Dysnea Headache Myalgia Anosmia	Dysnea Myalgia
Vital signs	RR- 32/ min PR-123/ min BP- 122/78 mmHg	RR-38/min PR-120/ min BP-132/86	RR-33/min PR-118/ min BP-114/80 mmHg	RR-35/min PR-121/min BP-128/82 mm Hg	RR-41/min PR-112/ min BP-110/78 mm Hg	RR-36/ min PR-116/ min BP-130/84 mm Hg	RR-31/ min PR-110/ min BP-126/86 mm Hg	RR-30/ min PR-109/ min BP-110/78 mm Hg	RR-36/min PR-109/ min BP- 120/78 mm Hg	RR-40/ min PR-112/ min BP-116/84 mm Hg
Oxygen Requirement on day of admission (litres)	10 NRM	15 NRM	9 NRM	10 NRM	15 NRM	15 NRM	10 NRM	10 NRM	8 NRM	15 NRM
Known Co-morbidities	NO	HTN Hypothyroid	Diabetes	NO	NO	NO	Diabetes HTN	NO	NO	NO
Drugs History	NO	Amlodipine 10 mg	Metformin 500 mg OD Glimepiride 1 mg	NO	NO	NO	Telmisartan 40 Amlodipine 5 Metformin 500 mg	NO	NO	NO
Drugs given for COVID	**All received IV Antibiotics, Enoxaparin sc (therapeutic dose), Zinc, Vit C, PCM**									
	Dexa 6 mg	**Ivermectin,**	**Dexa 6 mg OD,**	**Remdesivir, Zinc, Vit C**	**Dexa 6 mg**	**Dexa 6 mg**	**Dexa 6 mg**	**Dexa 6 mg**	**Remdesivir,**	**Doxy,**
	Remdesivir Cough syp	Dexa 6 mg Remdesivir,			Remdesivir Cough syp	Cough syp	Remdesivir	Remdesivir,	Dexa 6 mg	Ivermectin, Dexa 6 mg

Drug dosing details: Dexa (dexamethasone) 6 mg oral OD, Injection Remdesivir (200 IV on day 1 followed by 100 mg IV OD for next 4 days), PCM (paracetamol) 650 mg TID, Vitamin C 100 mg/day till discharge, oral Ivermectin (200 mcg/Kg) once a day for 5 days, Enoxaparin Subcutaneous 60 mg BD till discharge. BP- blood pressure, PR-pulse rate, RR-respiratory rate, NRM-Non-rebreathing mask, HTN- hypertension

appropriate oxygen support, the patients' condition worsened, clinically warranting high dose dexamethasone pulse. There was objective improvement in clinical parameters in the form of relief in respiratory distress and decreased oxygen demand post pulse therapy. The patients maintained saturation on room air within 5 to 18 days of pulse therapy. All the patients were cured of severe COVID-19 with hospital stay duration ranging from 9 to 22 days. Subjective improvement in the capacity to eat comfortably and go to the bathroom without oxygen was seen in all post-pulse treated patients. The inflammatory markers also started decreasing after first dose of 100 mg dexamethasone and came down to normal/ lower side 5 days post pulse therapy. Three cases had transient elevation in blood sugar level which was managed with insulin. All cases had a transient increase in leukocyte counts with neutrophilia after receiving high dosage dexamethasone, since corticosteroids are known to produce leucocytosis with neutrophilia.[20] Corticosteroids can cause hypernatremia and hypokalaemia with volume expansion due to mineralocorticoid action.[21]

Among all the corticosteroids dexamethasone is long acting, highly potent steroid with minimal mineralocorticoid action. Hence chances of dyselectrolytemia are minimal with dexamethasone and it is usually reserved for short term use in severe acute conditions.[21] We verified appropriate electrolyte levels in all our patients before administering high-dose dexamethasone pulse and none of them developed dyselectrolytemia post dexamethasone pulse.

Conclusion

High-dose dexamethasone pulse therapy for three days can be a safer and less expensive way to treat COVID-19 hyper-inflammatory phase and prevent the illness from progressing further. This medication is a good alternative for treating severe COVID patients and will be helpful for the physicians to tackle the cases of severe COVID-19 in a resource-constrained setting with a limited number of beds in intensive care units (ICU).

Table 2: Hospital course with clinical parameters pre and post High dose dexamethasone pulse therapy

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
O_2 requirement on the DOA	8 lit NRM	15 lit HFNC	7 lit	6 lit NRM	13 lit NRM	10 lit NRM	10 lit NRM	8 lit NRM	9 lit NRM	12 lit NRM
Day of starting dexona pulse from DOA	3rd	2nd	3rd	3rd	2nd	2nd	3rd	2nd	3rd	2nd
O_2 req. Before DP (litres)	10 NRM	20 lit HFNC	9 NRM	10 NRM	15 HFNC	15 HFNC	10 NRM	10 NRM	9 NRM	15 HFNC
1st day post DP O_2	4 NP	15 HFNC	5 NRM	10 NRM	15 HFNC	12 HFNC	10 NRM	10 NRM	7 NRM	8 NRM
5th day Of post DP O_2	RA	6 NRM	RA	6 NRM	5 NRM	4 NP	6 NRM	6 NRM	2 NP	8 NRM
Subjective Improvement D1 post DP	Able To eat comfortably Off O_2 for 10 to 15 mins	Frequent Use of O_2 while Eating, Unable to go bathroom Off O_2	Able to Eat comfortably off O_2, Able to bathroom Self-off O_2	Able to Eat comfortably off O_2 for 5 to 7 min	NO	Able to Eat comfortably off O_2 for 5 to 7 min	NO	Able to Eat comfortably off O_2 for 5 to 7 min	Able To eat comfortably Off O_2 for 10 to 15 mins, Able to bathroom off O_2	Able to eat comfortably for 5 mins off O_2
Subjective improvement D5 post DP	Able to eat off mask comfortably Able go to bathroom off O_2	Able to Eat comfortably off O_2, Able to go bathroom off O_2	Able to Eat comfortably off O_2, Able to bathroom off O_2	Able To eat comfortably Off O_2 for 10 to 15 mins, Able to bathroom off O_2	Able To eat comfortably Off O_2 for 10 to 15 mins, Able to go bathroom off O_2	Able To eat comfortably Off O_2 for 10 to 15 mins, Able to go bathroom off O_2	Able to Eat comfortably off O_2 for 5 to 7 min,	Able To eat comfortably Off O_2 for 10 to 15 mins, Able to go bathroom off O_2	Able to eat off mask comfortably Able go to bathroom off O_2	Able to eat comfortably for 10 mins off O_2
Days required to maintain saturation in room air from DP (without O_2) (days)	5	13	5	13	13	14	15	13	9	18
Total Duration of hospital Stay (days)	9	17	10	18	17	18	18	17	12	22
Complications to DP	Nil	Single Episode Raised RBS	Nil	Raised RBS	Nil	Nil	Raised RBS	Nil	Nil	Nil
Outcome	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured

O_2 - oxygen, NRM - Non-rebreathing mask, HFNC - High flow nasal canula, NP - Nasal prong, DOA - day of admission, DP- dexamethasone pulse

Table 3: Routine investigations and Inflammatory markers pre and post high dose dexamethasone pulse therapy

Investigation Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
CBC TLC-4000-1000/microlit	Pre DP-WNL N-86%	10,200 N-89%	WNL N-79%	WNL N-91%	WNL N-76%	WNL N-78%	WNL	TLC-10,700 N-84%	WNL N-84%	WNL N-71%
	D1 post DP-TLC-11,820	14,000 N-90%	TLC-13,900 N-88%	TLC-10,700 N-82%	WNL N-74%	WNL N-82%	11,300 N-88%	TLC-11,960 N-92%	TLC-WNL N-83%	WNL N-69%
	D5 post DP-WNL	17,200 N-96%	TLC-14,200 N-90%	TLC-11,2200 N-88%	TLC-10,100 N-80%	TLC-10,600 N-95.5%	12,100 N-95%	TLC-10,500	TLC-10,600 N-87%	WNL N-79%
	Discharge WNL	WNL N-69%	WNL N-71%	WNL N-73%	WNL N-64%	WNL N-80%	WNL N-59%	WNL N-71%	WNL N-73%	WNL N-60%
LFT SGOT <37 U/L SGPT 13-40 U/L	Pre DP-WNL	WNL	SGOT-256.2 SGPT-38.3	SGOT-73.3 SGPT-15.1	SGOT-58.9 SGPT-88.5	SGOT-150.2 SGPT-124	SGOT-29.1 SGPT-102.3	SGOT-48.1 SGPT-120.1	WNL	SGOT-75.6 SGPT-297.2
	D1 post DP-WNL	WNL	SGOT-212.3 SGPT-37	SGOT-36 SGPT-14.7	SGOT-60 SGPT-112	SGOT-135 SGPT-98.6	SGPT-78.9 SGOT-WNL	SGOT-WNL SGPT-88.1	WNL	SGOT-91.6 SGPT-321.5
	D5 post DP-WNL	WNL	SGOT-157.1 SGPT-27	WNL	SGOT-39.1 SGPT-56	SGOT-WNL SGPT-59.7	SGPT-54.2 SGOT-WNL	SGOT-WNL SGPT-51	WNL	SGOT-66 SGPT-234.1
	Discharge-WNL	WNL	SGOT-59 SGPT-WNL	WNL	WNL	WNL	WNL	WNL	WNL	SGOT-43 SGPT-123.2
RFT	Pre DP-WNL	WNL	WNL	WNL	WNL	Na+-133.5	WNL	WNL	WNL	WNL
	D1 post DP	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	D5 post DP-	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	Discharge	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
RBS	Pre DP-WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	D1 post DP-WNL	WNL	WNL	498	WNL	WNL	542	WNL	WNL	WNL
	D5 post DP-WNL	240	WNL	349	WNL	WNL	431	WNL	WNL	WNL
	Discharge-WNL	WNL	WNL	197	WNL	WNL	160	WNL	WNL	WNL
LDH (U/L) Ref range (230-460)	Pre DP-2648.98	Pre DP-1357	1044	598	741.6	1518.6	966	1207	1234.5	1247
	D1 post DP-1618	1070	567	580	270.3	1353.1	561.3	991.3	838.8	1141.7
	D5 post DP-	641.7	341.4	432.8	221	785.4	480	540.1	347.3	543.2
	Discharge	345.7	241.6	297.5	211.5	431.9	368.3	442.7	321.8	410.4
CRP (mg/l) Ref range (0-5)	Pre DP-74.68	Pre DP-91.56	102.28	82	98.76	96.8	169	270	80.99	113.9
	D1 post DP-12.33	58	9.4	9.1	7.5	23.1	21.4	60.12	63.9	6.7
	D5 post DP-	6.8	2.8	3.5	2.1	7.3	5.9	6.3	11.7	2.8
	Discharge-	3.1	2.8	2.8	2.1	3.6	3.7	2.9	4.2	2.8
IL6 (pg/ml)	Pre DP-32	49.5	17.8	27.6	43.5	39.4	67.8	51	58.2	24.2
	D1 post DP-7.4	12.9	3.1	2.8	5.8	6.1	5.3	5.6	7.4	2.8
	D5 post DP- 2.7	2.8	<2.8	<2.8	<2.8	3.9	<2.8	<2.8	<2.8	<2.8
	Discharge-0.8	1.6	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8

Contd...

Table 3: Contd...

Investigation Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Ferritin (ng/ml)	Pre DP->1650	1487.6	1098.3	1256.8	1079	>1650	1570.4	1607.3	1478.9	>1650
Ref range (22-322)	D1 post DP-763	759	232.4	457.8	407	1231.2	1163.8	1143.1	1231.6	1231.6
	D5 post DP- 345.6	297.1	223.7	315.9	326.8	647.1	597.8	645.1	594.8	843.9
	Discharge-WNL	89.7	227.6	189.5	227	421.8	379.6	387.5	431.6	541.4
D-dimer <0.2 microgram/ml	Pre DP-0.32	2.36	0.42	0.69	0.5	1.60	0.63	2.02	0.88	0.65
	D1 Post DP-0.2	1.7	0.3	0.6	0.64	1.02	0.42	1.87	0.65	0.71
	D5 post DP-<0.2	0.6	<0.2	0.3	0.5	0.61	<0.2	0.81	0.37	0.40
	Discharge <0.2	0.3	<0.2	<0.2	0.32	0.41	<0.2	0.65	<0.2	0.3

CBC - Complete blood count, TLC - total leukocyte count, LFT - liver function test, RFT - renal function test, DP - Dexamethasone pulse, CRP - C-reactive protein, LDH - Lactate dehydrogenase, IL-6 - interleukin 6, RBS - random blood sugar, WNL - Within normal limit

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Conflicts of interest

There are no conflicts of interest.

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