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

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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 (SpO₂) ≤93% on room air and severe: Individuals with respiratory rate >30/min and SpO₂ <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
antibody is used to tackle the cytokine storm in COVID patients, though found unsuccessful. In addition, it is costly and has availability issues. Systemic corticosteroids have been demonstrated to be effective in the treatment of severe COVID-19 in a number of recent investigations. Recently high dose pulse methylprednisolone has been found beneficial in tackling the severe COVID-19.

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).

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. 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. 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. 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. In another multicentre retrospective cohort study high dose corticosteroid (methylprednisolone) pulse was found to reduce mortality significantly in severe COVID-19 patients.

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          | Case 6          | 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           | Fever           | Fever           | Fever           | Cough           | Fever           | Fever           | Dysnea          | Dysnea          | Dysnea          |
| Dysnea                            | Myalgia         | Myalgia         | Rhinorrhea      | Anosmia         | Dysnea          | Cough           | Dysnea          | Dysnea          | Dysnea          | Dysnea          |
| Myalgia                           | Headache        | Rhinorrhea      | Rhinorrhea      | Anosmia         | Cough           | Anosmia         | Anosmia         | Anosmia         | Anosmia         | Anosmia         |
| Vital signs                       | RR‑32/min       | RR‑38/min       | RR‑33/min       | RR‑35/min       | RR‑41/min       | RR‑36/min       | RR‑31/min       | RR‑30/min       | RR‑36/min       | RR‑40/min       |
|                                  | PR‑123/min      | PR‑120/min      | PR‑118/min      | PR‑121/min      | PR‑112/min      | PR‑116/min      | PR‑110/min      | PR‑109/min      | PR‑109/min      | PR‑112/min      |
|                                  | BP‑122/78 mmHg  | BP‑132/86 mmHg  | BP‑114/80 mmHg  | BP‑128/82 mmHg  | BP‑110/78 mmHg  | BP‑130/84 mmHg  | BP‑126/86 mmHg  | BP‑110/78 mmHg  | BP‑120/78 mmHg  | BP‑116/84 mmHg  |
| Oxygen Requirement on day of admission (litres) | 10              | 15              | 9               | 10              | 15              | 15              | 10              | 10              | 8               | 15              |
| Known Co-morbidities             | NO              | HTN Hypothyroid | NO              | NO              | No              | NO              | Diabetes        | NO              | NO              | NO              |
| Drugs History                    | NO              | Amlodipine 10 mg| NO              | NO              | Metformin 500 mgOD Glimepiride 1 mg | NO | NO | NO | NO |

| Drugs given for COVID            | All received IV Antibiotics, Enoxaparin sc (therapeutic dose), Zinc, Vit C, PCM |
|----------------------------------|---------------------------------------------------------------------------------|
| Dexa 6 mg                        | Remdesivir, Ivermectin, Cough syp, Dexamethasone, Zinc, Vit C, Remdesivir, Dexamethasone 6 mg |
| DEXA 6 mg OD                     | Remdesivir, Ivermectin, Dexamethasone, Zinc, Vit C, Remdesivir, Cough syp |
| Remdesivir, Ivermectin, Cough syp| Remdesivir, Ivermectin, Dexamethasone, Zinc, Vit C, Remdesivir, Dexamethasone 6 mg |
| Remdesivir, Ivermectin, Dexamethasone 6 mg | Remdesivir, Ivermectin, Dexamethasone, Zinc, Vit C, Remdesivir, Cough syp |

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 leukocytosis 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).
| Parameters                                      | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 |
|------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| O₂ requirement on the DOA                      | 8 lit  | 15 lit | 7 lit  | 6 lit  | 13 lit | 10 lit | 10 lit | 8 lit  | 9 lit  | 12 lit  |
| Day of starting dexona pulse from DOA          | NRM    | HFNC   | 2lit   | NRM    | NRM    | NRM    | NRM    | NRM    | NRM    | NRM     |
| O₂ req.                                        | 10     | 20 lit | 9      | 10     | 15     | 15     | 10     | 10     | 9      | 15      |
| 1ˢᵗ day post DP O₂                             | 4      | 15     | 5      | 10     | 15     | 10     | 10     | 7      | 8      |
| 5ᵗʰ day                                       | RA     | 6      | NRM    | 6      | NRM    | 5      | 4      | 6      | 2      |
| Of post DP O₂                                  |        |        | NRM    |        |        |        |        |        |        |
| Subjective Improvement                         |        |        |        |        |        |        |        |        |
| D1 post DP                                    | Able to eat comfortably | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min | able to eat comfortably off O₂ for 5 to 7 min |
| D5 post DP                                    |        |        |        |        |        |        |        |        |
| Days required to maintain saturation in room air from DP (without O₂) (days) | 5      | 13     | 5      | 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    | Raised RBS | Nil    | Nil    |
| Outcome                                       | Cured  | Cured  | Cured  | Cured  | Cured  | Cured  | Cured  | Cured  | Cured  | Cured   |

O₂ - 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                     | Pre DP-WNL | 10,200 | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    |
|                         | DP-WNL | N-89%  | N-91%  | N-76%  | N-78%  | N-78%  | N-78%  | N-78%  | N-78%  | N-78%  |
|                         | D1 post DP-WNL | 14,000 | TLC-WNL | TLC-10,700 | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    |
|                         | TLC-11,820 | N-86%  | N-82%  | N-74%  | N-82%  | N-82%  | N-82%  | N-82%  | N-82%  | N-82%  |
|                         | D5 post DP-WNL | 17,200 | TLC-WNL | TLC-11,200 | TLC-10,100 | TLC-10,600 | 12,100 | TLC-10,500 | TLC-10,600 | WNL |
|                         | WNL    | N-96%  | N-88%  | N-80%  | N-95.5% | N-95%  | N-95%  | N-87%  | N-79%  | N-79%  |
| LFT                     | Pre DP-WNL | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    |
|                         | SGOT-256.2 | 74.68  | SGOT-73.3 | SGOT-58.9 | SGOT-150.2 | SGOT-29.1 | SGOT-48.1 | WNL    | WNL    | WNL    |
|                         | SGPT-38.3 | 91.56  | SGPT-15.1 | SGPT-88.5 | SGPT-124 | SGPT-102.3 | SGPT-120.1 | WNL    | WNL    | WNL    |
|                         | SGPT-212.3 | 102.28 | SGPT-36 | SGPT-60 | SGPT-135 | SGPT-78.9 | SGPT-88.1 | WNL    | WNL    | WNL    |
|                         | SGPT-37  | 157.1  | SGPT-112 | SGPT-96.8 | SGPT-54.2 | SGPT-66  | SGPT-234.1 | WNL    | WNL    | WNL    |
|                         | SGPT-157.1 | 345.7  | SGPT-27 | SGPT-59 | SGPT-59.7 | WNL    | WNL    | WNL    | WNL    | WNL    |
|                         | SGPT-59  | 240    | 197    | 598    | 741.6  | 1518.6 | 966    | 1207   | 1234.5 | 1247   |
|                         | SGPT-27  | 1044   | 598    | 741.6  | 1518.6 | 966    | 1207   | 1234.5 | 1247   |        |
|                         | RBS     | Pre DP-WNL | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    | WNL    |
|                         | D1 post DP-WNL | 1070   | 567    | 580    | 270.3  | 1353.1 | 561.3  | 991.3  | 838.8  | 1141.7 |
|                         | D5 post DP-WNL | 641.7  | 341.4  | 432.8  | 221    | 785.4  | 480    | 540.1  | 347.3  | 543.2  |
|                         | Discharge-WNL | 345.7  | 241.6  | 297.5  | 211.5  | 431.9  | 368.3  | 442.7  | 321.8  | 410.4  |
|                         | CRP (mg/l) Pre DP-2648.98 | 345.7  | 241.6  | 297.5  | 211.5  | 431.9  | 368.3  | 442.7  | 321.8  | 410.4  |
|                         | Ref range (230-460) | 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-12.33 | 6.8    | 2.8    | 3.5    | 2.1    | 7.3    | 5.9    | 6.3    | 11.7   | 2.8    |
|                         | Discharge-CRP | 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   |
|                         | Ref range (0-5) | 12.9   | 3.1    | 2.8    | 5.8    | 6.1    | 5.3    | 5.6    | 7.4    | 2.8    |
|                         | D1 post DP-7.4 | 2.8    | <2.8   | <2.8   | <2.8   | <2.8   | <2.8   | <2.8   | <2.8   | <2.8   |
|                         | D5 post IL6 | 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 | D1 | 1.7 | 0.42 | 0.69 | 0.5 | 1.60 | 0.63 | 2.02 | 0.88 |
|                         | Post DP-0.2 | 0.6 | <0.2 | 0.3 | 0.5 | 0.61 | <0.2 | 0.81 | 0.37 | 0.40 |
|                         | D5 post DP-0.2 | <0.2 | 0.3 | <0.2 | 0.32 | 0.41 | <0.2 | 0.65 | <0.2 | 0.3 |
|                         | Discharge <0.2 | 0.3 | <0.2 | 0.3 | 0.32 | 0.41 | <0.2 | 0.65 | <0.2 | 0.3 |

CvC - Complete blood count. TLC- total leucocyte 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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