

## Convalescent Plasma and Dexamethasone: A Review of Effectiveness in Treating Critical COVID-19 Cases

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### ABSTRACT

Covid-19 is characterised by exaggerated immune response in patients who develop severe disease. 'SARS-CoV-2' differs from 'SARS-CoV-1' and 'MERS', showing high viral loads with some infiltrates in the lung fields at time of death. Convalescent plasma, antibody-rich (specifically IgG antibodies) are the blood sample or products which are collected from eligible donors like with active antibodies or who are the asymptomatic carriers or who have recovered from COVID-19). After the assessment of the donor, 200-600 mL plasma can be collected with apheresis devices. The process involves first clotting and then secondly centrifuging the blood sample from people who just got recovered from the disease so as to separate out the plasma containing serum antibodies it contained, then giving those antibodies to patients in critical emergency. These antibodies are injected into a sick's or covid-19 positive patient's body. The antibody then creates passive immunisation in the sick person. Corticosteroids like dexamethasone have broad effects on humoral and cell-mediated response and affect both innate and adaptive immunity. Adaptive immunity here plays an important role in to covid-19 immunoassays and immunopathology as severity of respiratory illness that is acute respiratory distress syndrome is associated temporally with the cell-mediated immunity and appearance of a specific antibody against SARS-CoV-2. Trials of Convalescent plasma and dexamethasone were conducted for treatment of critically ill COVID-19 patients. This article compiled the related information collected from various sources like 'MEDLINE', 'Web of science' 'Embase, Cochrane, COVID-19 Study Registers.

**KEY WORDS:** DEXAMETHASONE, CYTOKINE STORM, CORONAVIRUS, CONVALESCENT PLASMA, CRITICALLY -ILL, COVID-19.

### INTRODUCTION

"COVID-19 is defined as the disease which is caused by a novel coronavirus now called 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)' which was first identified after an outbreak of respiratory ailments cases in Wuhan City, Hubei Province, China". The outbreak has probably spread more widely than it might have given the recent uptick in domestic travel. COVID-19 is a

phased illness with an exaggerated immune response. The pathogenesis of 'SARS-CoV-2' differs in presentation from that of its previous types 'SARS-CoV-1' and 'MERS', for which adverse effects (co-morbidities) correlate with viraemia and high viral loads with some infiltrates in the lung fields at time of death.

(Cadejani et al., 2020) The Emergency Committee on the COVID-19 under the 'International Health Regulations (IHR 2005)' was redeliberated on 30 January. WHO declared the outbreak to be a pandemic which is of public health emergency of worldwide concern and activated the emergency preparedness responses. The wake up of 'Pandemic' with limited subsidies and substantial mortality has geared up the countries to double their fundamental and public health measures. Pandemic is a scientific challenge but also an act of character. People

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need to act in the interests of global solidarity and shared humanity.

Exponential spike of positive cases are a hallmark of pandemics. The spread of sars-cov-2 worldwide has followed such a curve inexorably. (Cadeiani et al., 2020) But it has a marginal effect on mortality, has accelerated the research point of view to understand and control the virus. More than 7,000 research papers and articles/publications the pandemic—covering everything from study of virology(microbiology) to epidemiology—have been appeared in the past three months. Around 20 % of people tested positive COVID-19 develop a severe form of SARS-COV2(critical illness), which is represented with rise to respiratory distress and multi-organ dysfunction syndrome. This condition demands for intensive care interventions. This results due to an exaggerated immune response ultimately damaging pulmonary alveoli, leading to a spiked lymphocytosis, cytokine and chemokine storm with systemic ill-effects.

(Cadeiani et al., 2020) WHO's 'Risk and emergency Communication Team' launched 'WHO Information Network for Epidemics (EPI-WIN)' portal which created a series of amplifiers for sharing customized information to the specific target groups. Meanwhile, researchers have escalated the process of testing the potential efficacy of many drugs in 'COVID-19 infection spectrum. WHO and many other researchers around the world and national authorities have done is put in place randomized control trials in order to test which drugs are effective. (Cadeiani et al., 2020) Various anti-virals and immunomodulators are being investigated and developed as the effective regimen. Searching for potential therapies for COVID-19 infection is a very tedious and complex procedure.

**Background:** Convalescent plasma and dexamethasone can be effective to reduce mortality in critically sick patients with respiratory distress due to viral infections and are piloted for treatment of COVID-19. (Stockman et al., 2006) The RECOVERY clinical trial revealed the effectiveness of dexamethasone and convalescent plasma therapy in the survival of critically ill patients. This review included epidemiological studies on convalescent plasma, hyperimmune immunoglobulin and corticosteroids therapy for people with COVID-19, Meta-analysis studies. (Stockman et al., 2006 and Li et al., 2020) The information portals like 'World Health Organization (WHO) COVID-19' MEDLINE', 'Web of science' Embase, Cochrane COVID-19 Study Register', 'Centers for Disease Control and Prevention COVID-19 Research Article Database', PubMed were accessed.

## DISCUSSION

**Convalescent Plasma:** Till date there are no proven pre or post prophylaxis for covid-19 patients. Convalescent plasma, antibody-rich (specifically igG antibodies) are the blood sample or products which are collected from eligible donors like with active antibodies or who are the asymptomatic carriers or who have recovered from

COVID-19). After the assessment of the donor, 200-600 mL plasma can be collected with apheresis devices. The process involved first clotting and then secondly centrifuging the blood sample from people who just got recovered from the disease so as to separate out the plasma containing serum antibodies it contained, then giving those antibodies to patients in critical emergency. These antibodies are injected into a sick's or covid-19 positive patient's body. The antibody then creates passive immunisation in the sick person.

Since then the 'antibody-rich "convalescent plasma" (cp)' is being used as an adjunctive treatment for many critical ill cases including cases of SARS, MERS and the pandemic 'h1n1' and 'h5n1' influenza. Now covid-19 pandemic is also chipped in. CP may be used as an adjunctive treatment to combination the anti-viral therapy and immunomodulators. The positive effect of CP can be continued for weeks and months. Convalescent plasma proved to be a safer option. Passive antibodies administration through convalescent plasma transfusion has sought to prove a short term strategy to confer immediate immunity. (Wood et al., 2021) The mechanism is inferred to be direct neutralization of the virus by the neutral Abs and control of the an overactive immune system (i.e. Cytokine and chemokine storm, surge of TH1/TH17 ratio and activation of complement system pathway).

Plasma transfusion in 'high-risk' patients with detrimental and deleterious effects was seen has sought to reduce the mortality in some. Some studies conducted in which some patients with laboratory confirmed severe acute respiratory syndrome who were reported to be critically ill (severe pneumonia or respiratory distress and rapid progression and continuous high viral load despite antiviral treatment and on mechanical ventilation). CP transfusion was done in these patients. After 12 following plasma transfusion, significant changes were seen. Body temperatures were normalized within 3-4 days in some patients, SOFA scores decreased within 20 days. (Biju et al., 2020, Franco et al., 2019, Mahase et al., 2020 and Chai et al., 2020) PaO<sub>2</sub>/FiO<sub>2</sub> increased within 20 days. 'SARS-COVID-2' Specific ELISA and neutralizing antibody titers were increased. ARDS was resolved within days.

**Complications:** However, broad immune dysregulation is the highlighted concern for the horrendous and fatal picture covid-19, including the 'cytokine storm syndrome'— this is due to exaggerated immune-inflammatory response to infection resulting in TARGET ORGAN DAMAGE and increased oxidative stress. The choice for the timing of treatment with convalescent plasma transfusion as passive immunity is a sensitive issue. If it is given at the wrong time during a patient's covid-19 illness period, immune plasma could be ineffective, could worsen the immune-mediated tissue damage even accelerate or induce a chemokine or cytokine storm syndrome. Other general risks include "transfusion-related circulatory overload (TACO), Transfusion-related acute lung injury (TRALI)". Also kidney

injury and immune-mediated tissue damage via antibody-dependent enhancement have been mentioned in many research studies. (Garraud et al., 2020) Authorities and scientific research associations including the 'Food and Drug Administration (FDA)' and 'European Union Agency for Medicines and Health Products (EMA)', and scientific associations such as the 'International Society of Blood Transfusion (ISBT)' and the 'European Blood Alliance (EBA)', have provided protocols and guidance for the selection of donors and recipients.

**Dexamethasone:** Dexamethasone exerts its effects on humoral and cell-mediated responses thereby influencing the innate and adaptive immunity. Adaptive immunity plays a key role in COVID-19 severity of respiratory illness associated temporally with the cell-mediated immunity. The RECOVERY TRIAL has shown that corticosteroids such as dexamethasone or methyl prednisolone had lower mortality rates than patients not receiving any corticosteroids. The corticosteroid therapy increased 28-day survival in COVID-19 patients on ventilator support. (Horby et al., 2020) The RECOVERY trial has shown that dexamethasone has modulated the inflammatory-mediated lung injury, decreased mortality in patients who land on respiratory failure requiring mechanical ventilation or supplemental oxygen.

Dexamethasone (DECADRON) is a synthetic glucocorticoid steroid roughly 25 times more potent than hydrocortisone and devoid of mineralocorticoid "sodium retaining" properties. Therefore, it is primarily used for anti-inflammatory properties. However, it is seen that it only potentially improved the survival of critically ill patients and thus decreasing the detrimental effects. THE IMMUNOLOGICAL impacts shall be further discussed.

**Mechanism of Action:** Dexamethasone, it is a classic Glucocorticoid, they are bound to the intracellular glucocorticoid receptors (GRs). They need not be recruited to various genomic sites without directly binding to DNA, they are lipid soluble which are transported by certain proteins called transcortin via protein-protein interactions. These are ligand-dependent transcription molecular proteins which are expressed by most cells of the body. Liganded GRs translocate from the cytosol to the nucleus to mediate a host of cellular responses reactions. They regulate the genes and these genes activate nuclear factor NF kappa B. The genomic effects occur through direct bound glucocorticoid response elements in target genetic proteins. (Franco et al., 2019) These Liganded GRs which activates the genes which in turn activates the mRNA. Some rapid effects occur independent of the cytosolic GR. Glucocorticoids reflect cell type-specific changes in the transcription. (Franco et al., 2019) In B cells, glucocorticoids bind to certain receptors which downregulate and upregulate certain genes. Glucocorticoids bind on T cells to inhibit T cell receptor signalling transduction and cytokine expression.

During the early incubation (prodromal) stage, subjects remain generally asymptomatic as viral replication is inhibited by the type I interferon response. With eventual

mutation the disease is progressed from mild to moderate symptoms (including sore throat, cough, fever and muscle aches) that arise from cell-mediated immunity response which cause reversible damage or irreversible damage of the respiratory tract membrane due to hyperplasia of mast cells and infiltration of inflammatory markers and cells and antiviral activity of the adaptive immune system which causes cell-mediated immunity response which in turn secretes T cells. T helper cells mediate CD4+ T cells (MHC II restricted: master regulators which is 1st line of defence), cytotoxic T cells activate CD8+ T cells (MHC I restricted). It is considered 2nd line of defence, secretes interferon- $\gamma$ . In most people contracting COVID-19, mild or moderate symptoms are successfully resolved through a coordinated antiviral immune response. (Horby et al., 2020 and Parwe et al., 2020) Therefore, most people with immune competence remain asymptomatic.

COVID-19 is pictured as a biphasic disease: in the early phase, virus pathology comes into play; and in the later phase, immunopathology causes the disease. (Mahase et al., 2020) Ironically, (Kute et al., 2020, Lohi et al., 2020, Lohiya et al., 2020, Madhu et al., 2020, Parveen et al., 2020, Khatib et al., 2020 and Nibudey et al.) Dexamethasone has no role in patients in the RECOVERY trial whose disease had not progressed to the critical state requiring respiratory support/ventilation; the immunomodulatory effects of glucocorticoids are beneficial, perhaps by breaking the inflammatory feedforward loop, at least in some patients. Few of the related studies on COVID-19 were reviewed. Reviews of (Prasad et al., 2020, Patel et al., 2020, Pate et al., 2020, Pasari et al., 2020 and Nibudey et al., 2020) reflected on key issues and preparations for COVID-19 in different healthcare specialities.

The main breakthrough of the treatment with the dexamethasone in the RECOVERY trial is the low-dose treatment which recommended 6mg once a day. A 6mg per day dexamethasone is a fairly low-dose therapy with chances of minimal side effects. Most importantly, it prevents glucocorticoid resistance. It is reported that people with continuous high-dose therapy renders insensitivity to the treatment. (Stockman et al., 2006, Mahase et al., 2020 and Horby et al., 2020) It is suspected that the low-dose dexamethasone can complement endogenous cortisol activity which will be helpful to suppress COVID-19-associated immunopathology.

## CONCLUSION

Dexamethasone and other synthetic glucocorticoids could prove to be a potential option for treating COVID-19 and similar diseases considering the recommended adaptations to dose and frequency of administration.

## REFERENCES

- Biju, M.P., 2020. CONVALESCENT PLASMA AS A POTENTIAL THERAPY FOR TREATING COVID-19 PATIENTS. *Journal of American Medical Association*.  
 Cadegiani, F.A., 2020. Repurposing existing drugs for COVID-19: an endocrinology perspective. *BMC*

- Endocrine Disorders, 20(1), pp.1-19.
- Chai, K.L., Valk, S.J., Piechotta, V., Kimber, C., Monsef, I., Doree, C., Wood, E.M., Lamikanra, A.A., Roberts, D.J., McQuilten, Z. and So-Osman, C., 2020. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews*, (10).
- Franco, L.M., Gadkari, M., Howe, K.N., Sun, J., Kardava, L., Kumar, P., Kumari, S., Hu, Z., Fraser, I.D., Moir, S. and Tsang, J.S., 2019. Immune regulation by glucocorticoids can be linked to cell type-dependent transcriptional responses. *Journal of Experimental Medicine*, 216(2), pp.384-406.
- Garraud, O., 2020. Passive immunotherapy with convalescent plasma against COVID-19? What about the evidence base and clinical trials?. *Transfusion and Apheresis Science*, 59(4).
- Horby, P., Mafham, M., Linsell, L., Bell, J.L., Staplin, N., Emberson, J.R., Wiselka, M., Ustianowski, A., Elmahi, E., Prudon, B. and Whitehouse, A., 2020. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. *MedRxiv*.
- Khatib, M.N., Gaidhane, S., Khatib, M., Ahmed, M., Gaidhane, A. and Syed, Z.Q., 2020. SARS-CoV and SARS-CoV-2: Similar viruses with different trajectories. *Wutan Huatan Jisuan Jishu*, 16(5).
- Kute, V., Guleria, S., Prakash, J., Shroff, S., Prasad, N., Agarwal, S.K., Varughese, S., Gupta, S., Gokhale, A.G.K., Sahay, M. and Sharma, A., 2020. NOTTO transplant specific guidelines with reference to COVID-19. *Indian Journal of Nephrology*, 30(4), p.215.
- Latchoumi, T.P., Ezhilarasi, T.P. and Balamurugan, K., 2019. Bio-inspired weighed quantum particle swarm optimization and smooth support vector machine ensembles for identification of abnormalities in medical data. *SN Applied Sciences*, 1(10), pp.1-10.
- Li, H., Chen, C., Hu, F., Wang, J., Zhao, Q., Gale, R.P. and Liang, Y., 2020. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. *Leukemia*, 34(6), pp.1503-1511.
- Lohi, A.S. and Sawarkar, G., 2020. Management of diet during Covid-19 pandemic.
- Lohiya, S.B., Damke, S. and Chaudhary, R., 2020. Coronavirus Disease (COVID) 2019 in Children—A Short Review. *International Journal of Current Research and Review*, 12, pp.172-77.
- Madhu, P.P., Patil, Y., Shinde, A.R., Kumar, S. and Phansopkar, P., 2020. The great awakening-digitalization in dental healthcare during the pandemic covid19. *International Journal of Research in Pharmaceutical Sciences*, 11(Special Issue 1).
- Mahase, E., 2020. Covid-19: Low dose steroid cuts death in ventilated patients by one third, trial finds.
- Nibudey, A. and Baliga, S.V., Preparing Hospitals in India for Covid-19 Pandemic. *International Journal of Research in Pharmaceutical Sciences*, 11, pp.333-41.
- Nibudey, A.R., Baliga, V.S. and Dhadse, P.V., 2020. To Keep COVID-19 Out of Hospitals in India--Are We Prepared?. *Journal of Evolution of Medical and Dental Sciences*, 9(37), pp.2751-2755.
- Parveen, S. and Jain, S., 2020. Pathophysiologic Enigma of COVID-19 Pandemic with Clinical Correlates. *International Journal of Current Research and Review*, 12, pp.33-37.
- Parwe, S.D., Nisargandha, M.A. and Thakre, R., 2020. Role of convalescent plasma therapy in new Coronavirus disease (nCOVID-19): A review. *International Journal of Research in Pharmaceutical Sciences*, 11(Special Issue 1).
- Pasari, A.S., Bhawane, A., Balwani, M.R., Tolani, P., Ramteke, V. and Deshpande, N., 2020. Knowledge about COVID-19 and Practices among Hemodialysis Technicians in the COVID-19 Pandemic Era. *International journal of nephrology*, 2020.
- Pate, B.S., Yeola, M.E., Gawande, A., Singh, A.K. and Tayade, H.A., 2020. Best Practices for Endoscopic Procedures in Covid-19 Pandemic. *Journal of Evolution of Medical and Dental Sciences*, 9(49), pp.3760-3767.
- Patel, M.P., Kute, V.B., Goswami, J. and Balwani, M.R., 2020. Hospitals may Become "Disease Hotspots" for COVID-19 amid Shortage of Personal Protective Equipment. *Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine*, 24(11), p.1145.
- Prasad, N., Bhatt, M., Agarwal, S.K., Kohli, H.S., Gopalakrishnan, N., Fernando, E., Sahay, M., Rajapurkar, M., Chowdhary, A.R., Rathi, M. and Jeloka, T., 2020. The adverse effect of COVID pandemic on the care of patients with kidney diseases in India. *Kidney international reports*, 5(9), pp.1545-1550.
- Stockman, L.J., Bellamy, R. and Garner, P., 2006. SARS: systematic review of treatment effects. *PLoS med*, 3(9), p.e343.
- Wood, E.M., Estcourt, L.J. and McQuilten, Z.K., 2021. How should we use convalescent plasma therapies for the management of COVID-19?. *Blood, The Journal of the American Society of Hematology*, 137(12), pp.1573-1581.