



## A Review on the Use of Dexamethasone in COVID-19

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### ABSTRACT

Initiated from the sea food market, Hubei province, Wuhan of China in December 2019, COVID-19 trapped various countries around the globe very rapidly. Hence, it was declared a global health emergency on 30th January 2020 and a global pandemic by WHO on March 11, 2020. COVID-19 is a contagious viral disease caused by a member of beta coronaviruses- Severe acute respiratory syndrome corona virus 2. A patient of COVID-19 initially presents with the symptoms of fever, cough, headache, fatigue when the disease is mild but in later stages leads to acute respiratory distress syndrome (ARDS) and multiple organ failure. Numerous trials are being conducted around the globe to find a standard treatment or vaccine. Currently used treatment options involve oxygen support and supportive therapy. Most COVID-19 positive patients have mild symptoms but few experiences an uncontrolled cytokine production which is referred to as cytokine storm. It results in development of an autoimmune response leading to destruction of alveoli causing respiratory depression. According to a report released by the RECOVERY trial dexamethasone has shown to be beneficial and decrease mortality rate by one-fifth in patients on mechanical ventilation and by one-third in patients on oxygen support. No benefits were seen in the mild cases. Lack of evidences and immunosuppressive activity of dexamethasone puts a question Mark on utility of dexamethasone.

**Keywords:** COVID-19, SARS-CoV 2, dexamethasone, cytokine storm.

### INTRODUCTION

COVID-19, now a global pandemic has resulted in more than 500000 deaths (As per the data available till 1 July 2020 from the WHO coronavirus dashboard) across the world and the number is hyping up day by day.<sup>1</sup> It is a life threatening disease which initially showed up in the form of fever, cough, fatigue, headache in the initial stages and turn into acute respiratory distress syndrome (ARDS) and multiple organ failure in the later stages ultimately causing death.<sup>2,3</sup> COVID-19 is caused by a virus - severe acute respiratory syndrome corona virus 2.<sup>4,5</sup> WHO declared it a global health emergency on 30 January 2020 and a global pandemic on march 11, 2020.<sup>6,7,8</sup> COVID-19 is associated with high morbidity and mortality rates.<sup>3</sup> The mortality rate for COVID-19 was noted to be 3.7% while 6.3% being the fatality rate.<sup>7</sup> Across the globe, more than 2200 clinical trials and researches are being carried out for finding a vaccine or treatment effective against SARS-COV 2.<sup>10</sup>

### DEXAMETHASONE

Dexamethasone, is a well-known corticosteroid, easily available across the world, is a drug with powerful anti-inflammatory properties.

Corticosteroids are basically classified into two groups – glucocorticoids and mineralocorticoids. On one hand glucocorticoids have anti-inflammatory properties

whereas on the other hand the electrolyte and water balance of body is maintained by mineralocorticoids. Out of the two classes, dexamethasone lies in the glucocorticoid group. Before information about the use of dexamethasone in COVID-19, it has been significantly used in treatment of arthritis, immune system disorders, and allergic reactions of skin, eyes and many more.<sup>11</sup>

### CYTOKINE STORM

When the regulatory control over pro-inflammatory cytokine production and release in response to any infection or stimuli is lost at both, internal and external levels, it is defined as cytokine storm.<sup>12</sup> Infection is a term used to expound a condition of the pathogen's effect and inflammation together. Body's immune response to an invading pathogen is described as inflammation. To clear the pathogens that have already invaded the body, inflammation is pivotal.<sup>11</sup>

Cytokine storm results in vasodilation, increased capillary permeability, leukocyte migration

And release of oxygen reactive species resulting in destruction of alveoli.<sup>19</sup> Another condition which has a hand in increasing mortality rate but is under recognised sHLH- secondary hemophagocytic Lymph histiocytosis. It is a hyperinflammatory syndrome with multiple organ failure.<sup>13</sup>



### How inflammation occurs and use of Dexamethasone

With the help of enzyme phospholipase A2, arachidonic acid is secreted by the phospholipid membrane of the cells. because of the enzyme cyclo-oxygenase, arachidonic acid is converted to inflammatory mediators (cytokines, prostaglandins, leukotrienes). These mediators are responsible to fight the infection.<sup>11</sup> Dexamethasone is a drug for which nearly all cells in the body expresses receptors. When there is a complex formation between dexamethasone and its receptors, inhibition of phospholipase A2 takes place and there is no production of inflammatory mediators and as a consequence of this process there is no inflammation.<sup>11</sup>

Dexamethasone even decreases the vasodilation, capillary permeability and leukocyte migration, hence preventing deterioration of the condition.<sup>19</sup>

### DEXAMETHASONE IN COVID-19

Being aware of the anti-inflammatory activity of the dexamethasone, it is also a well-known immunosuppressant. It broadly affects both innate as well as adaptive immunity.<sup>26</sup> Immunosuppressant property of dexamethasone is a major drawback for its use in COVID-19. When the person is infected with SARS-COV2 the number of T- lymphocytes are already less in blood and strength of the body to fight against the infection is decreased and dexamethasone further lower downs the number as well as protective function of T-lymphocytes in blood. Therefore, viral load consequently increases in the blood after patient survives SARS.<sup>11</sup> It not only affects the function of T-lymphocytes but also blocks the macrophages from cleaning up the secondary nosocomial infections from the body. Apart from this, dexamethasone blocks the beta- cells, inhibiting the production of antibodies, increasing plasma viral load.<sup>12</sup>

Now declared a global pandemic, COVID-19 was initially presented as pneumonia of unknown etiology.<sup>14</sup> More than 2200 trials are going on around the world to find a vaccine or treatment for COVID-19, but till now no rock solid treatment option is available and the patients are managed by giving supportive therapy.<sup>10,13,18</sup> Our body fights against any infection by producing immune response through activating t-cells and producing specific antibodies.<sup>3</sup>

In the gravely ill patients of COVID -19, the immune responds develops uncontrollably, producing a rush of proteins called cytokine and this uncontrolled release of cytokines is termed as Cytokine storm.<sup>11,12</sup> These cytokines along with fighting the infection also aggressively attack the body cells and tissues leading to an autoimmune response and damaging lung. In time, edema of alveoli in lungs develop causing shortness of breath and

with time converting to a condition called acute respiratory distress syndrome (ARDS).<sup>3,11,12,14,15</sup>

ARDS is The leading cause of death in COVID-19 patients.<sup>19</sup>It is further responsible for deterioration of the

condition of the patient.<sup>16</sup> Hence to decrease the mortality rate for COVID-19 suppression of the cytokine storm is key.<sup>17</sup> The pivotal point in today's hour for treatment of Covid-19 is stuck on dexamethasone, a drug claimed to reduce mortality by one third in patients on mechanical ventilation and one fifth in patients on oxygen support.<sup>10,11,20</sup>

According to the randomised evaluation of COVID-19 therapy – RECOVERY, dexamethasone has turned out to be a turning point. It diminishes the inflammation when it becomes too antagonistic for the body.<sup>11</sup> The RECOVERY trial, initiated in March, is one of the enormous randomized trials intended to find treatment for COVID-19. In the trial, the patients received 6mg of dexamethasone per day for 10 days.<sup>18</sup>

In the trial, 2104 patients were administered dexamethasone and the results were compared with the results of 4321 patients subjected to usual care. The trial was for 28 days. Within these 28 days, 454 (21.6%) patients out of 2104, receiving dexamethasone and 1065 (24.6%) patients receiving usual care died.<sup>26</sup>

The mean age of patients in study was 66.1 years out of which 36% patients were female. History of diabetes was present in 24%. 27% had history of heart disease, 21% had suffered from chronic liver disease. 56% of the patients had at-least one or more comorbid conditions.<sup>21</sup> The trial depicted that dexamethasone was found to be effective only in severely ill patients not the ones having mild symptoms. This was explained by the fact that

inflammation occurs only in critically ill COVID-19 patients who are on mechanical ventilation or oxygen support.<sup>11</sup> Dexamethasone will have a massive global impact- the RECOVERY study announced.<sup>18</sup> the major adverse effect associated with dexamethasone is hyperglycaemia which needs to be monitored.<sup>25</sup>

According to another case study involving 21 COVID-19 positive patients stated that dexamethasone was well tolerated in patients for a short term and level of c-reactive protein decreased significantly (77.98% reduction). No patient was needed to shift to ICU or subjected to mechanical ventilation. C- reactive protein is an inflammatory marker and increased levels are associated with high morbidity and mortality.<sup>19</sup>

In some cases, it may prove to be fatal for the patient.<sup>12</sup> Being an immunosuppressant, it further lowers downs the number and protective function of T- lymphocytes, B – lymphocytes, macrophages resulting in decreased tendency of the body to fight against the infection. Consequently, viral load increases after the patient survives SARS. After putting light on these points, it puts a question-mark on administration of dexamethasone.<sup>3</sup> According to the recovery trial, on calculating the risk benefit ratio, the benefit of using corticosteroids to treat COVID-19 outweighed the harm.<sup>18</sup> For the benefit of the patient, it is advisable to opt for the pulse of iv dexamethasone followed by nebulized triamcinolone



which is a glucocorticoid so that it is concentrated in the lungs only and not acting systemically. Mast cells are the precursors of pro-inflammatory cytokines like IL-1B, IL-6 and TNF.<sup>22</sup> Therefore, inhibition of mast cells play an important role in controlling symptoms and hence treat COVID-19. Addition of natural flavonoid luteolin, a mast cell inhibitor, to it seems to be beneficial because of its anti-viral and anti-inflammatory properties.

After the relief of symptoms, when the patient is being discharged from hospital, anti-cytokines may be prescribed like anti-IL6 or inhibitors of other IL-1 family members.<sup>11</sup> After months of encounter with COVID-19, before the RECOVERY study data, anti-viral drug remdesivir is only other drug which has shown benefits. Remdesivir decreased the hospitalisation span but had no effects on number of deaths happening<sup>26</sup> and the other point to be considered is its administration, which is somewhat complex. It is administered by injection over a time period of several days whereas dexamethasone having easy administration as it is available in multiple dosage forms.<sup>18</sup>

The other treatment options that are under testing in the RECOVERY trial are-

- Lopinavir- ritonavir (commonly used to treat HIV)
- Tocilizumab (commonly used antibiotic)
- Convalescent plasma (it is the collection of plasma from a recovered COVID-19 patient as it contains antibodies against SARS-COV2).<sup>20</sup>

Convalescent plasma has also some some benefits.<sup>27</sup>

In severe COVID-19 patients, the cytokine status is similar to that of sHLH i.e increased interleukin -IL2, IL -7, GSF, interferon gamma, induce protein 10, monocyte chemo attractant protein, macrophage inflammatory protein and tnf-alpha.<sup>27</sup>

The human race has previously encountered the MERS and SARS, in the treatment use of corticosteroids was not supported and some studies say that it might amplify the lung injury associated to COVID-19 .<sup>18,23</sup>

### Management of COVID-19 in Pregnant Women

In obstetrics, corticosteroids have been proved to be significantly important in premature cases for lung maturity. In certain studies, it has been clearly indicated that lowest gestations are the most benefited from use of corticosteroids, but with no clarity and evidences, it is recommended that use of corticosteroids should be limited to less than 32 weeks in women tested COVID-19 positive. Even tocolytics should not be used in women, who are COVID-19 positive and in whom corticosteroids are not used. Hence the decision to use or not to used is made after checking the risk benefit ratio for the mother as well as foetus.<sup>24</sup>

### CONCLUSION

Dexamethasone is a corticosteroid, which has been claimed by the RECOVERY trials to be beneficial in COVID-19. WHO recommended not to use corticosteroids for the treatment of COVID-19. Because it suppresses the immune response, resulting in increased plasma viral load after the patient survives COVID-19. Many countries have been used steroids from the beginning. But till date, there is no clarity about the use of dexamethasone.

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