



## Effectivity of Dexamethasone Fighting Cytokine Storm in Severe COVID-19 Patients; Does it still reliable used for COVID-19?

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**ABSTRACT:** Covid-19 has been declared a pandemic by WHO (World Health Organization) since March 2020. However, there is confusion about the therapy that should be used for covid-19. This virus enters the human body by binding to ACE-II receptors in the human body, causing an inflammatory response and a decrease in the body's immune response. The overproduction of pro-inflammatory cytokines relates to COVID-19's cytokine storm, also known as cytokine release syndrome (CRS). The aim of this article is to determine the effectiveness of dexamethasone in treating cytokine storms in severe COVID-19 patients using ventilator respiratory. This study used a narrative review journal from several leading platforms such as PubMed, NEJM, NCBI, and others, as well as from government websites, selected between 2019 and 2021 in the English language. Dexamethasone is a corticosteroid class of drugs that can act as anti-inflammatory and immunosuppressive. The drug inhibits the expression of genes that induce inflammatory proteins. In the case of severity covid-19, dexamethasone was used in patients who had decreased oxygen saturation. After being treated using this drug intravenously, the patient showed a positive increase in oxygen saturation levels. Dexamethasone therapy was effective and may have been acceptable in severe Covid-19 patients that actively ventilator respiratory. Then, a more rigorous investigation of the impact of dexamethasone is needed.

**Keywords:** SARS-CoV-2, Corticosteroids, Dexamethasone, Covid-19

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## INTRODUCTION

WHO (World Health Organization) has declared Covid-19 a pandemic since March 11, 2020. This case began with the first covid-19 infection in Wuhan Hubei province, China [1]. The transmission of this infection is reported to have originated from animals sold at South China's Huanan seafood market. This virus enters the body through mucosal cells, binds to ACE II receptors, and causes local respiratory system inflammation [2].

WHO highly recommends dexamethasone as therapy for patients with severe and critical Covid-19. However, WHO does not recommend corticosteroids to patients with non-severe covid-19 [3]. G. van den Bossche first claimed the crystal structure of dexamethasone after 13 years of discovering corticosteroids that have a design similar to the hormone cortisol produced by the adrenal glands as a regulation of body stress [4].

This drug has various indications for treating inflammatory and autoimmune diseases such as asthma, allergies, septic shock, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. However, this class is minimal in use because there are many side effects of this class of drugs such as osteoporosis, skin atrophy, diabetes, abdominal obesity, glaucoma, cataracts, necrosis and avascular infections, growth retardation, and hypertension [5]. Dexamethasone is not recommended for patients with systemic illness, hypersensitivity to dexamethasone, or cerebral malaria [6].

Dexamethasone acts in the body by binding glucocorticoid receptors type I and type II. Both receptors will change the endogenous substance, increasing the immune and inflammatory response [7]. Dexamethasone exerts a good effect on inflammatory factors and is quite widely used as an adjunct for viral pneumonia. This effect is about 25 times more active than other corticosteroid compounds [8].

In some cases, the use of dexamethasone in patients infected with non-severe Covid-19 has reportedly not provided therapeutic effectiveness. Improper use of dexamethasone can cause long-term side effects of blurred vision and dizziness (more than a week), headaches, and can even lead to arrhythmias. In patients with severe covid-19, the use of dexamethasone is claimed to reduce the danger in patients with hyper-inflammatory conditions, lung-related cytokines, and rapidly progressive pneumonia [8].

Anti-inflammatory medicines, such as corticosteroids, can be administered to minimize the lung damage caused by the cytokine storm in COVID-19 patients. Dexamethasone, a synthetic corticosteroid, is a broad-spectrum immunosuppressant with higher activity and a longer half-life than cortisone. It has a variety of mechanisms of action, and as a result, it can influence a variety of body systems [9].

Through a review of this journal, we will discuss the use of dexamethasone as a therapy in Covid-19 patients based on the severity, its advantages, and disadvantages, as well as proper therapy management.

## **METHODOLOGY**

We made a Narrative Review by collecting several scientific journals from several leading platforms such as PubMed, NEJM, NCBI, and others and government websites like WHO. The journals we selected ranged from 2019 to 2021 with keywords such as Coronavirus, SARS-Cov-2, Severe Covid-19, Dexamethasone usage, and report cases.

## **DISCUSSION**

### **Spreading of Covid-19 around the world**

The first Covid-19 case was found in Hubei, China, in December 2019. Five patients were hospitalized with a diagnosis of acute respiratory distress syndrome from December 18 to December 29, 2019, one of the five people was declared dead. They are alleged to have consumed wild animal food purchased from the local market there. Researchers who have worked since the emergence of Covid-19 stated that this virus is not transmitted from only one person and then spreads to many people. However, this virus is transmitted from an infected group in one area [10].

Based on WHO data, updated on August 5, 2021, worldwide, there are still 202,146,929 cases worldwide, including 4,264,641 newly confirmed cases and 65,472 deaths in the last seven days. As the spread of Covid in China [11].

### **Pathophysiology of covid-19**

This virus is transmitted by an infected person who is either causing symptoms or who is asymptomatic. The person secretes the virus, entering other people through the respiratory tract and even through the human eye. This method of transmission can be said as direct transmission. This virus can also be infected through indirect transmission when touching the surface of an object that the virus has contaminated. This virus can survive on the surface of things for several days in a temperature and atmosphere that supports it, but it can be destroyed in just a short time, less than a minute, by disinfectants such as hydrogen peroxide, and sodium hypochlorite [12].

The SARS-CoV-2 virus enters the nasal cavity by binding to epithelial cells with the most common type of receptor, ACE-2 [13]. Angiotensin-converting enzyme 2 (ACE2) is an enzyme that attaches to the membrane of the cells of the organs of the lungs, heart, intestines, and kidneys [14]. Therefore, the symptoms caused attack the respiratory organs and these organs (including the lungs). In addition, this virus also attacks the digestive tract because ACE-2 receptors are also found on intestinal epithelial cells, which act as carriers of nutrients into the intestine so that the symptoms related to the digestive tract include abdominal pain, diarrhea, and others [15], [16].

## **Cytokine Storm**

Cytokine is the general name of several antibody compounds found in human organs. This compound is produced by several types of white blood cells, including neutrophils, monocytes, and macrophages which recognize pathogens and then destroy these pathogens through phagocytosis as a body Defense when pathogens enter the human body. Besides these three cells, dendritic cells, gamma-delta T cells, and natural killer (NK) cells increase immune cells by recognizing and responding to various foreign microbes by producing cytokines [17].

In patients with severe cases of COVID-19 experiencing Cytokine release syndrome (CRS) or known as cytokine storm, is a condition in which the body experiences an uncontrolled increase in the number of cytokines caused by several cells that produce cytokines, such as macrophages are tissue-resident cells that are frequently made from circulating monocytes. They have a variety of roles, including engulfing senescent cells, tissue repair and immunoregulation, and antigen presentation. Macrophages become activated and secrete excessive levels of cytokines in various types of cytokine storms, resulting in severe tissue damage and organ failure. In some kinds of cytokine storms, NK cells' cytolytic function is impaired, resulting in extended antigenic stimulation and trouble resolving inflammation [17].

Figure 1. The mechanism of cytokine storm in covid-19 patients; in more detail, cytokine storm is caused by the process in which virus-infected cells are destroyed by the innate immune system (NK cells) and adaptive immunity (CD8 positive cytolytic T cells). However, this destruction process does not work correctly due to impaired lymphocyte cytolytic activity due to genetic problems or acquired conditions, then causes innate and adaptive immune cells to work continuously so that TNF, interferon- $\gamma$ , IL-1, IL-6, IL-18, and IL-33 are among the pro-inflammatory cytokines released unrestrainedly [18].

## **The severity of Covid -19**

Patients with SARS-COV-2 were divided into several clinical manifestations, from patients with no symptoms to patients with critical conditions. Asymptomatic or Pre-symptomatic Infection: People infected with SARS-Cov-2. But only mild symptoms, do not develop into a clinical disease, and even some do not experience symptoms, mild illness, an infected person experiences symptoms of fever, sore throat, cough, fatigue, muscle aches, cough, vomiting, diarrhoea, headache, and loss of smell. Elderly patients under these criteria are potentially at greater risk; Severe Illness, a person infected with covid then has a SpO<sub>2</sub> of less than 94%, is classified as a severe disease. Therapy in this severity level is given oxygen support using a breathing apparatus [19].

Some comorbidities that can increase the severity of SARS-Cov-2 infection include chronic kidney disease, cancer, chronic lung diseases, including COPD (chronic obstructive pulmonary disease), asthma (moderate-

to-severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension, fatigue (quickly tired), diabetes type 1 and type 2 Down syndrome, heart conditions, HIV infection, immunocompromised state (weak immune system), alcohol, obesity, sickle cell or thalassemia, cardiovascular disease, and substance use disorders (for example, patients who use alcohol, opioids or cocaine substances) [20].

### **Mechanism of dexamethasone**

The pharmacological effects of dexamethasone are initiated at the encounter of this drug with intracellular glucocorticoid receptors (GR). These receptors are in the cytoplasm of human cells. After binding to the corticosteroid group, the Glucocorticoid receptor in the cytoplasm changes shape (activates) to hyperphosphorylation (P), breaks down from a multi-protein complex, and moves to the nucleus, where gene expression begins. The glucocorticoid receptor binds to the GRE (glucocorticoid responsive element) binding site for transcription of the target gene. In addition to this method, these receptors can also bind directly to other transcription factors. Most of the gene expression that occurs due to glucocorticoid receptors is specific. Each tissue is activated differently in a fraction of genes only [5]. Based on an in-silico study conducted by Zhang et al., dexamethasone can prevent the binding of the virus to its receptor in the body, namely ACE2-Receptors [21].

Dexamethasone also decreases IL-6, which is particularly problematic in critically ill individuals, which patients in a decline of IL-6 can cause cardiomyopathy who have severe Cytokine Release Syndrome (CRS). During SARS-CoV-2 infection, high levels of IL-6 activate C-Reactive Protein (CRP), another inflammatory factor linked to COVID-19-related various systemic diseases and pneumonia. Corticosteroids decrease inflammation by non-genomic processes such as binding to membrane-associated glucocorticoid receptors on T cells, causing receptor signalling and immune response to be disrupted. These medications also interact with the calcium-sodium exchange across the cell membrane, resulting in a rapid reduction in inflammation [22], [23].

### **Case and management Dexamethasone on Covid-19**

A study with dexamethasone conducted by researchers from Oxford University in 2,104 patients who were given 6mg of dexamethasone once a day for ten days showed that it reduced 28-day mortality by 25% when compared with 4,321 patients who were not given dexamethasone therapy [8].

Corticosteroid drugs have been widely used in respiratory syndromes associated with SARS-CoV-2, including MERS (Middle East Respiratory Syndrome), severe influenza, SARS, and community-acquired pneumonia. Based on a case study by Hassan, E.M et al., In ICU, patients with severe covid-19 simultaneously experienced ARDS (acute respiratory distress syndrome), and other comorbidities who have been given dexamethasone therapy intravenously showed significant results after five days and discharged from

the ICU. Another study found that severe systemic infection is characterized by a mix of variables, including high levels of IL-6, IL-2, IL-10, and TNF-, low levels of CD4+ and CD8+ T cells, and lymphopenia [24][25]. Furthermore, dexamethasone can reduce several mediator inflammations, including IL-6.

## CONCLUSION AND RECOMMENDATIONS

SARS-CoV-2 has caused dangerous complications, especially in the elderly. The use of dexamethasone, which is included in the corticosteroid class as an anti-inflammatory and immunosuppressive, can relieve symptoms of covid-19, especially in the case of patients with cytokine storm in severity covid-19. This finding adds to previous studies and can provide a more straightforward path to the future treatment of COVID-19.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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