



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.3996143>Available online at: <http://www.iajps.com>

Review Article

**CORTICOSTEROID- TRIAL STATUS, BENEFITS AND
PITFALLS OF DEXAMETHASONE
IN SITUATION OF COVID-19 PANDEMIC****Bhuvanesh R. Thakare***

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Article Received: June 2020**Accepted:** July 2020**Published:** August 2020**Abstract:**

The main focus of our article is that benefits and pitfalls of corticosteroid. Dexamethasone is the steroid drug which classify in corticosteroid class. It was introduced for medical use in 1958 which relieves inflammation in various part of body. Now a day there is worst situation in world about covid-19 pandemic. Whole world suffered from covid-19 pandemic. In this situation government of all countries are busy in discovery of vaccines. Many drugs are used in trial of prevent corona virus. Dexamethasone is the drug is also used in this situation. Use of this drug is benefits in some patients but side effect of this drug is more to know and its harm to patients. That's why Food and Drug Administration (FDA) does not approve trial of Dexamethasone in covid-19 disease. The present article tells us the significance of drug repurposing, Mechanism of action of Dexamethasone against covid-19, Trial report of Dexamethasone about improve survival rate in covid patients which receiving oxygen or on a ventilation.

Key words: Corticosteroid, Dexamethasone, Drug repurposing, Covid-19, Inflammation, FDA, Ventilation.

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Please cite this article in press Bhuvanesh R. Thakare, *Corticosteroid- trial status, benefits and pitfalls of dexamethasone in situation of covid-19 pandemic.*, Indo Am. J. P. Sci, 2020; 07(08).

INTRODUCTION:

The covid-19 pandemic spread from Wuhan city, china in December 2019. Wuhan is the 7th most populated city. This virus spread all over the china and its 67 territories. First case was found in outside china on 13 January 2020 in Bangkok (Thailand). Then spreading of virus exported to growing number of country. There are difficult to calculate cases worldwide because cases are more in number globally. This virus spread in about 188 countries. Now a days situation is worst due to COVID according to WHO report, the number of cases globally in last 24 hour (18 June 2020) was 8,242,999 and number of death occurred 4, 45,535. In India 3, 80,532 cases were confirmed and 12,573 cases was death as per report. All countries do their best to save cases from this pandemic. A many number of drug are developed and use to treat patients suffer from COVID-19 but those drug are used to treat covid trail are somewhat harm to suspect body which produce side effect to his/her body that's why those drug are use in trail are not use fixed in vaccine preparation in covid infection. First covid vaccine in china to be ready for clinical trial at the end of April. Further chloroquine and hydrochloroquine / plaquenil drug are approved by US FDA. Such a way flaviravil which is anti-viral drug by china, fusogenix drug which is proteo-lipid vehicle by Entos pharmaceutical, ChAdOx1 nCoV19 which is adenovirus vaccine by the University of Oxford, Gimsilumab, TZLS-501 are monoclonal antibodies targeted drug also developed to took trail, TJM2, AT-100, OYA1, BPI-002, INO-4800, NP-120(Ifenprodil), Mrna-1273 vaccine, IBV vaccine, TNX-1800, Brilacidin, BXT-25, Remdesivir, Blood plasma therapy and many more medications are developed on trail bases to treat COVID infection.

(J D Almeida, D M Berry, C H Cunnigham, D Hamre, M S Hofstad, L Mullucci and D A J Tyrrell) who was the person which first indentified corona virus. They published their work in 1986 to the journal natural. The published journal virologist called that virus named Corona virus to recall the characteristics of these virus are identified in electron microscope. The word 'Corona' has so many different meaning. The appearance of virus is seen like sun in eclipse, this fact had in mind of virologist when chose name of virus. They compare characteristics fringe of projection on the surface of virus with sun in eclipse. Corona virus is the single stranded RNA virus. They are involved in mutation and recombination. Corona virus has about 120 nanometer in diameter. They have so many varieties about 40 and they get affected human and non human mammals, birds. They present most in bats and spread other mammal through it. This virus first present in bats then in snakes after in pangolins and finally in human hence that's way COVID-19 spread

all over the world from china meal market. Corona like appearance of corona virus has crown means spikes of glycoprotein's which are useful for enter of virus in any host cell. The spike having two subunits, first unit is attached to surface of host cell and second unit is attached to cell membrane. When virus is susceptible with enzymes (ACE then it enters into the cell, inside cell virus release from endosome by acidification. When corona virus found in humans it called as 229E and OC43. It is the family of virus which causes illness such as respiratory disease and gastrointestinal disease. Coronaviridae is the family name of virus which take on the bases of two subfamilies 'Letovirinae' and 'coronaviriae'. This virus has also different genera Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. There are seven corona viruses are affected to humans. Corona virus is zoonotic means that the virus is transmitted in humans and animals. The virus that cause COVID-19 infection to all group, however two group has high risk in older people (age about above 60) and people those already suffered from other diseases. This virus spread via respiratory droplets, direct and indirect contact with suspect.

- **Significance of drug repurposing in against any pandemic spread level disease:**

Drug repurposing is the work for identifying new use of approved meditational drug that are outside the scope of original medication. Drug repurposing or repositioning are expanding in area of rare and neglected disease. This is the process of validating of new therapeutic indication for developmental drug. The repositioning of drug is important because of finding new scope of drug, problem in productivity and worldwide pressure on increasing prices and improve role of drug which already exists. The old method of developing drug is more expensive, time consuming and complex hence drug repurposing is significantly approaches the reduce time and price of drug which is use in pandemic level disease. The power towards resistant drug and side effect limits the value of developed drug targeting the viral protein and host factor hence repurposing drug approaches to finding new indication of drug which accelerate the process of targeting the drug protein to resist virus. The drug repurposing is very important to fight the battle against the spreading deadly diseases. The drug which are developed by DR approach are quickly enter in clinical trial, mostly disease which required less treatment but drug repositioning having ability for formulation setup in larger scale productivity. Drug repurposing is the best solution for reduce the risk way of drug discovery. Drug repurposing pathway required about 4 – 12 year.

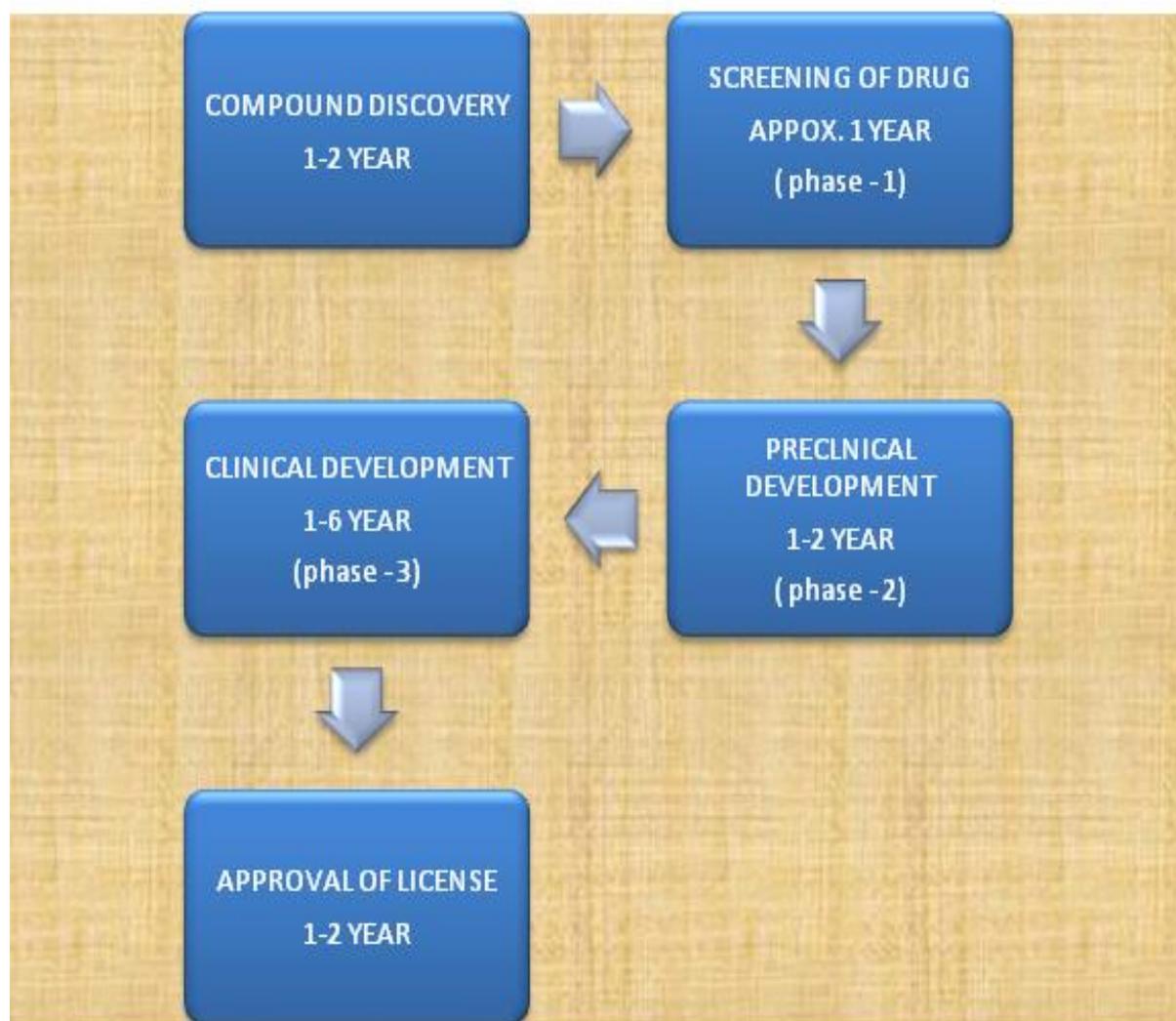


Fig. 1 Drug Repurposing Pathway

- **Introduction of Dexamethasone drug:**

Dexamethasone is the anti-inflammatory and corticosteroid medication which reduces inflammation in various parts of the body. It is used to treat many conditions such as rheumatoid arthritis, skin disease, some allergies, asthma, chronic obstructive lung disease, brain swelling, eye disease, cancer, sore throat, nausea and vomiting, high altitude illness, pregnancy. In tuberculosis treatment dexamethasone is taken with antibiotics. Dexamethasone metabolism occurs in the liver. It is excreted through urine about 65%. The elimination half-life of dexamethasone drug is 190 minutes (3.2 hours). The availability of this steroid is 80-90%. It has many trade names such as Dextenza, Ozurdex, Decadron and Dexasone. Dexamethasone was first made by Philip Showalter Hench in 1957 and approved for medical use in 1958. It is the drug mentioned in WHO's list of essential medicines. It was the most common prescribed medicine in the United States. Dexamethasone is a synthetic corticosteroid which affects the function of many cells within the body and

suppresses the immune system. The available brand name for dexamethasone is 'DEXPAK'. It is also available as generic medicine. Dexamethasone with known drug interactions includes barbiturates, phenytoin, and rifampicin, which can reduce the half-life of this steroid drug. This steroid has a co-treatment with oral contraceptives, which increases the volume of distribution. Dexamethasone is an agonist of the glucocorticoid receptor. It does not have mineralocorticoid activity. The absorption of dexamethasone is between a few minutes and several hours, depending on the indication and route of administration. Dexamethasone has non-medical uses (illegal). It is used in Bangladesh brothels to prostitute women not yet of legal age, to gain weight and make them appear older and healthier to customers and police, due to its steroid effect. The drug is taken orally as a tablet or elixir, as an injection into the vein and muscle, i.e. intravenously and intramuscularly, respectively. This drug is available in combination with morbofloxacin and clotrimazole, which is useful for treating infections on dogs. On the other hand, it also

combined with Trichloromethazide to treat swelling of limb and brushing of horses. The exact incident of adverse effect of dexamethasone is not available but some are available with corticosteroids such as hypertension, dyspepsia, malaise, cataract but this occurs when long term of treatment takes to any patient. Dexamethasone is not so expensive. In India it is about US\$0.50 for treatment of preterm labor. This drug is available all over the world. Anti-inflammatory and immune-suppressive effect of this steroid is more potent than cortisol. Now a days dexamethasone has received some popularity in market because it could be taken once a day drug. Some time it takes two times in day when replacement with cortisol. Dexamethasone is about 77% protein bound in plasma. Mostly protein binding occurs with albumin and serum. This drug is not significantly bind with corticosteroid binding protein. Dexamethasone is the drug s taken with food because it reduces irritation and avoid with alcohol it is hazardous to body.

• **Chemistry of Dexamethasone:**

Dexamethasone is the synthetic pregnane corticosteroid. The chemical formula of

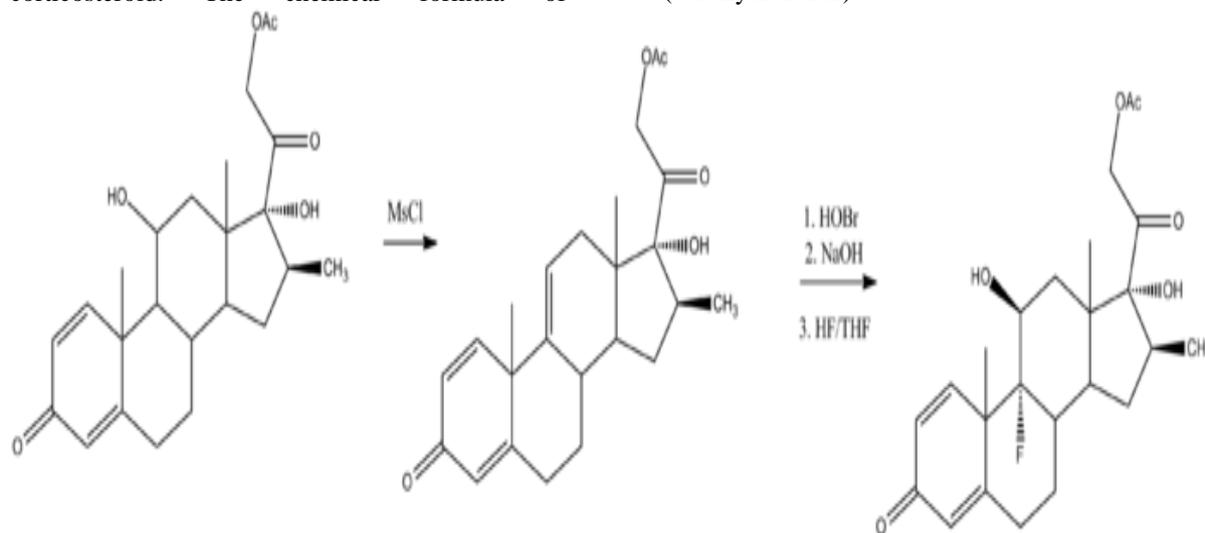


Fig.2 Reaction- Synthesis of Dexamethasone

CHEMICAL TAXONOMY:

- DESCRIPTION: Dexamethasone belongs to class known as 21-hydroxysteroid. This steroid class s present at the 21 position of steroid skeletal.
- KINGDOM: Organic compound
- SUPER CLASS: Lipid and lipid like molecules.
- CLASS: Steroid and steroid derivatives.
- SUB CLASS: Hydroxysteroid.

dexamethasone is 9-fluoro-11 β , 17-dihydroxy-16 α -methyl-21- (phosphonooxy) pregna-1, 4-diene-3, 20-dione disodium salt. (Fig.2) or 1-dehydro-9 α -fluoro-16 α -methylhydrocortisone. The molecular and crystal structure of dexamethasone has been determined by X-ray crystallography. The compound of dexamethasone is described in chemistry word is anti-inflammatory 9-fluoro-glucocorticoid. Chemical formula of dexamethasone is C₂₂ H₂₉ FO₅. Average molecular mass of dexamethasone is about 392.461 g/mol and monoisotopic mass is about 392,200 g/mol.

SYNTHESIS:

To synthesize dexamethasone first obtained 16 β – methylprednisolone acetate, which is considered as most potent steroid anti-inflammatory agents dehydrated to the 9,11-dehydro derivative which will be converted into 9 α bromo - 11 β hydrin derivative with the source of hypobromite, such as basic N-bromosuccinimide which will determine the epoxide ring closure and formation of dexasone (dexamethasone) is made secondary to a ring opening reaction with hydrogen fluoride in THF (tetrahydrofuran).

Other Application of Dexamethasone:

- ✓ Application of dexamethasone enhances bone morphogenetic –
Dexamethasone application increased the bone volume and osteoblast number of the ectopic bone nodules with untreated controls. Ectopic bone formation was induced in control and dexamethasone treated by application of BMP-7 into hamstring muscles. After 20 days treatment each ectopic nodule was analyzed by contact radiography, tomography and histomorphometry. Mice are the subjects for histomorphometric analyses of their lumbar vertebrae and proximal tibiae to assess the

effect of dexamethasone treatment on bone metabolism.

- ✓ Application of dexamethasone in the masseter muscle during surgical removal of lower third molar –

The doctor or physician group received 8 mg of dexamethasone which was applied on masseter muscle immediately after surgery. 7 and 15 days after surgery, the patient were assess in relation to their level of pain, trismus and edema. Hence it is concluded that the application of dexamethasone in masseter muscle effectively reduces edema and trismus but does not affect pain.

- ✓ Application of dexamethasone for aged eyes-
The risk of eyes problem has been found increase with age. Particularly in the age 50 to 60 of life. Cataracts, dry eye, neo-vascular age-related muscular degeneration, diabetic retinopathy, retinal vein occlusion are the very common age-related problems with reduces the quality of life. The corticosteroids to treat anterior and posterior ocular segment diseases are driven by inflammation. Dexamethasone is the most powerful corticosteroid medication available, is widely use for topical or intravitreal administration. Topical dexamethasone has efficacy for management of postoperative inflammation in the anterior segment after cataract surgery and symptoms relief in dry – eye disease. A new sustained release 700 µg dexamethasone intravitreal implant (DEX) was recently approved for the treatment of macular edema like RVO, diabetic macular edema or noninfectious uveitis. Dexamethasone drug use is increases when another therapeutic agent failed in action. The most common side effect is increased i.e. intraocular pressure and cataract formation. The potency of dexamethasone, alone or in combination with other drug, agent makes dexamethasone a better option for treatment of several retinal diseases.

- ✓ Application of dexamethasone in patient having high grade glioma –
Patient having primary brain tumours which develops vasogenic edema and increase intracranial pressure. The corticosteroid therapy improves those symptoms which develop by brain tumour in generally within 48 hours. Corticosteroid therapy is more important to embraking on radiotherapy after surgery, particular in patient whose brain tumour exert significant mass effect. Dexamethasone is the corticosteroid of choice because of its minimal mineralocorticoid activity, long half-life and high potency. Hence the few prospective clinical trial has set out to determine its optimal dose and schedule in patient with primary brain tumors. Dexamethasone work on CNS and suppress the high grade of glioma.

- ✓ Application of dexamethasone for suppression test –

Dexamethasone drug which is steroid changes the level of the hormone cortisol in the blood. This is the test for condition in which large amount of cortisol are produce by the adrenal gland. Normally when the pituitary gland makes less adrenocorticotrophic hormone (ACTH), the adrenal gland makes less cortisol. Dexamethasone which is like cortisol, lower the amount of ACTH release by the pituitary gland. After the use of dexamethasone, cortisol level stays very high in people whose have Cushing's syndrome. Sometimes other condition also keep cortisol level high , example such as major depression , alcohol use disorder, stress , obesity , kidney failure, pregnancy and uncontrolled diabetes.

The night before blood test, you will take dexamethasone pill. The next morning, the cortisol level will be measured in your blood, if your blood cortisol level is high, Cushing's syndrome may be the cause. Sometimes ACTH test also done at the same time as the cortisol test. This is the application of dexamethasone for suppression test.

- ✓ Application of dexamethasone in prevent postoperative nausea and vomiting –

Postoperative nausea and vomiting is common experience after surgery. The overall incident of PONV in adult is 20-30 % , incident in high risk patient is very high up to 70-80 % , the children are not expected to attacking this much but rate n children above age 3 is more than 40 % . The incident slowly reduces after puberty. Dexamethasone is effective in children as well as in adults. Comparing with other medication dexamethasone having more efficacy in reducing incident of PONV and has advantage of low cost and longer effectiveness. The action of dexamethasone is not fully understood, animal studies have confirmed that vomiting centre in the brain stem plays a central role. The combination of dexamethasone with other antiemetic is more effective than any single drug effect. The use of dexamethasone to prevent nausea and vomiting triggered by intravenous or epidural morphine for pain control can also having good therapeutic effect. Dexamethasone can reduce local inflammation after surgery this may reduce by afferent stimulation of parasympathetic nervous system to the vomiting centre, and reduce PONV.

- ✓ Application of dexamethasone in adults with bacterial meningitis –

Mortality and morbidity rate is high in adults with acute bacterial meningitis, especially those with pneumococcal meningitis. In studies of bacterial meningitis in animal adjuvant treatment with corticosteroid has beneficial effect. The test of treatment is with dexamethasone as compare with

placebo. Dexamethasone or placebo was administered 15-20 min before the dose of first antibiotic and gives every 6 hours for 4 days. The treatment with dexamethasone is reduced in mortality rate among patients those with pneumococcal meningitis. Early treatment with dexamethasone improve the effectiveness in adults with bacterial meningitis, does not increase the risk of gastrin. The beneficial effect occurred in patient those who have pneumococcal meningitis so hence physician recommended dexamethasone for patient who has acute bacterial meningitis.

✓ Application of dexamethasone in prevent sever kidney injury following heart surgery- Acute kidney injury (AKI) is one of the devastating complications following cardiac surgery. Approximately 1% patient of cardiac surgery requires dialysis to treat severe AKI that arises after surgery, and incident is higher in patient with pre-operative chronic kidney disease. Heart surgery initiates with inflammatory reaction, and dexamethasone has anti-inflammatory drug property, which could decrease the risk of severe AKI following cardiac surgery. Patient who received the drug had 2.5 times lower risk of development of sever AKI. The effect of dexamethasone were particularly patient who already had pre – existing kidney disease, the single dose of dexamethasone is inexpensive, straightforward, painless and safe for patient during operation of heart following sever acute kidney disease.

Mechanism of action of Dexamethasone against covid-19:

Dexamethasone is the corticosteroids drug is a class of steroid hormones released by the adrenal cortex which includes glucocorticoids and mineralocorticoids. Glucocorticoids regulate diverse cellular functions including development, homeostasis, metabolism, cognition, and inflammation. Due to profound immune modulatory action glucocorticoid is prescribed drug in worldwide market for estimated to be worth more than USD 10 billion per year. The therapeutic benefits of glucocorticoids are limited by the adverse side effect that is associated with high dose and long-term use. Furthermore, patients on long

term glucocorticoid therapy also develop tissue specific glucocorticoid resistance.

GENOMIC ACTION OF GLUCOCORTICOID:

Glucocorticoid signal are through genomic and non-genomic pathways. The gnomonic pathway of glucocorticoid are classify on action of glucocorticoid receptors (GR). GR resides in the cytoplasm of cell as a part of large multi protein complex that includes some protein and immunophilin. Multiprotein complex are maintain affinity of binding.

Dexamethasone molecules (DM) bind to glucocorticoid receptors (GR) this DM+GR complex passes through membrane. Through cell membrane corticoid binding proteins (CBP) attached to DM+GR complex with target enzymes such as histone deacetylases2 (HDAC2). In this process CBP increases gene expression and increases inflammation directly. This increase gene expression which further divide into some actions i.e. 1) Decreased formation of cytokines which are small secreted proteins produce by helper T cells. [Interleukin (ILs), TNF alpha] which leads to decreased in airway inflammation, decreased airway hyperactivity. This leads to decreased wheezing, coughing, and excessive bronchoconstriction. 2) Increase gene expression reduces the activation of eosinophil by apoptosis. This leads to decreased fibrosis and release of cytokines further leads to reduced collagen deposition to the membrane of airway and this makes to decreased in wheezing, coughing and excessive bronchoconstriction and inflammation. 3)Increased in gene expression leads to increase in Beta2 receptors leads to decreased in mucus secretion which helpful to decreased in wheezing, coughing, excessive bronchoconstriction and inflammation. 4) sometimes increased in gene expression leads to make decreased in activation of inflammatory cells such as T – lymphocytes (cytokines), Mast cells, Dendritic cell (cytokines), Macrophages this all events lead to reduced bronchospasm which leads to decreased wheezing, coughing, excessive bronchoconstriction and inflammation.

This is mechanism of action of corticosteroid (dexamethasone) against COVID-19.

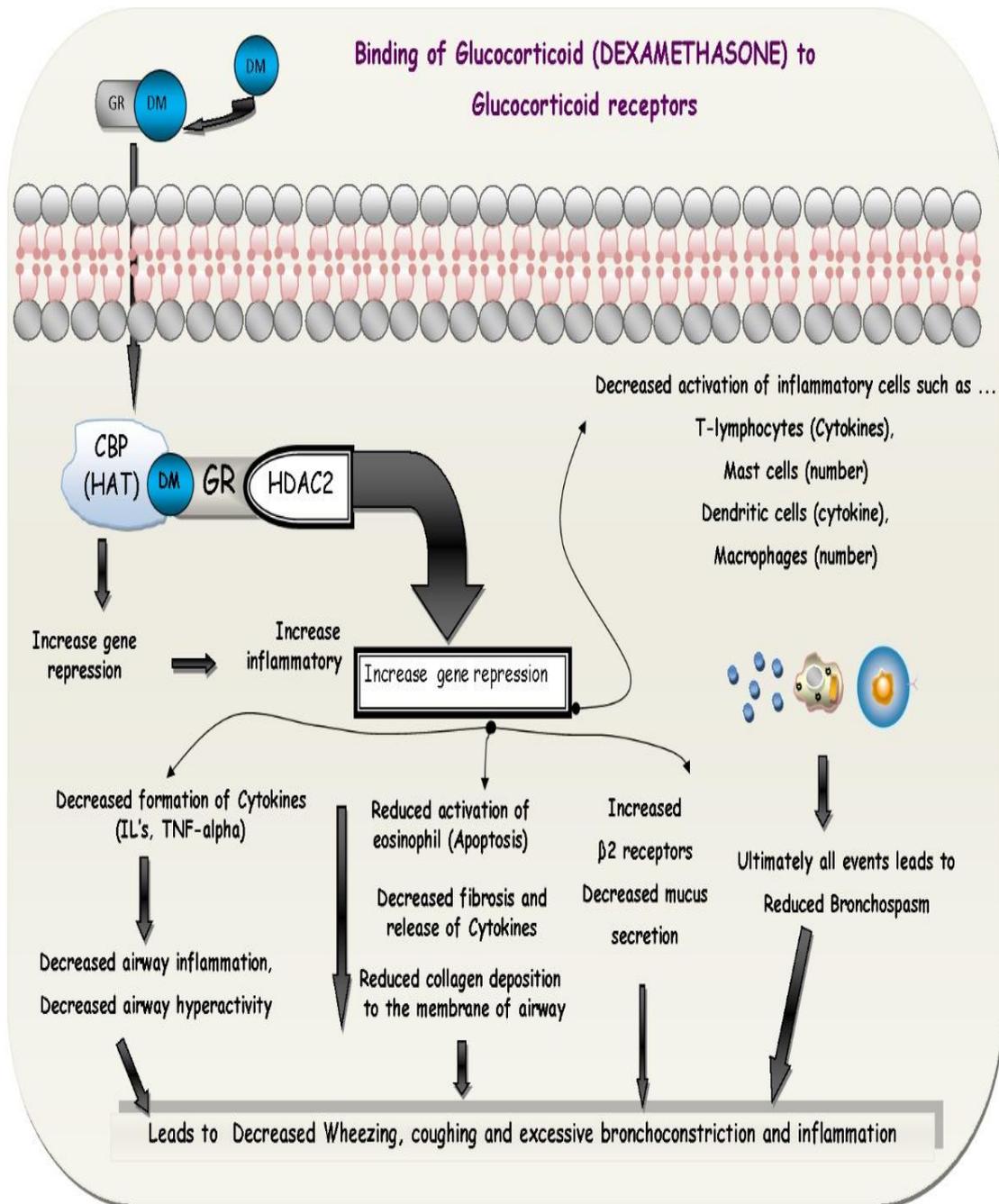


Fig.3 Mechanism of action of Dexamethasone against COVID-19

Side effect and Contraindication of Dexamethasone:

Side effect:

1. Acne
2. Weight gain
3. Impaired wound healing
4. Hypertension
5. Depression
6. Diabetes
7. Confusion
8. Nausea
9. Malaise
10. Headaches
11. Cataracts
12. Raised intraocular pressure
13. Insomnia
14. Increased risk of infection
15. Dyspepsia
16. Stomach pain and cramping
17. Drying and thinning of skin
18. Change in the menstrual cycle
19. Vision change

20. Weight gain

Contraindication:

1. Allergic response to dexamethasone
2. Cerebral malaria
3. Systemic fungal infection such as aspergillosis, blastomycosis, cryptococcosis
4. Treatment of smallpox vaccine, concurrently with dexamethasone
5. Liver disease
6. Thyroid disorders
7. Osteoporosis
8. Diabetes
9. Muscle disorder
10. Ocular herpes
11. Cataracts
12. Ulcerative colitis
13. Congestive heart failure
14. Depression or mental disorders
15. High blood pressure

Dexamethasone should not be used in cases where individuals have above certain infections. (Contraindication)

Preclinical Trial and Clinical Trial Status of Dexamethasone:

HOW DOES DEXAMETHASONE WORK IN COVID-19?

Dexamethasone is not an anticancer drug but it is used in certain tumors. It is not an anti-tuberculosis drug but it is used in certain TB. Similarly, it is not an antiviral drug. It does not kill or prevent corona virus. But the action is similar for all these diseases i.e. it is anti-inflammatory. Covid-19 is viral illness initially has high viral load when amount of virus in the body is high and immune response is low. Dexamethasone helps tone down this immune response gone bad stage.

WHAT DID THE STATUS FIND REGARDING TRIAL OF DEXAMETHASONE IN COVID-19?

6 mg of dexamethasone is administered per day to 2,104 patients for 10 days while 4,321 patients were providing standard care without dexamethasone. The death rate at 28 days was compared between these two groups of patients.

Result- This drug reduces the death rate by one – third in ventilated patient and by one – fifth in other extra care patient receiving oxygen only. 1 death would be preventing around 8 patients on ventilator, while 1 death would be prevent by treating 25 patients who receiving oxygen support. There is no benefit in patient who does not require any respiratory support.

The good part of dexamethasone; it is cheap, generic drug, with side effect known to doctors who have experience using it. It is useful addition to against covid-19. The bad part is various known side effects of steroid including increased vulnerability to fungal infection, tuberculosis, muscle weakness, psychiatric disturbance, increase blood sugar, brittle bones, fractures; it is lengthy list of disadvantages of dexamethasone. Early dexamethasone use can be harmful and life threatening. The dexamethasone arm was stopped early because of overwhelming benefit based on the rule called Haybittle Peto boundary. Due to side effect of steroid, use of steroid in covid-19 before recovery trial announcement was restricted to proven indication like asthma, chronic obstructive pulmonary disease and shock (low blood pressure).

CONCLUSION:

The overall study of this corticosteroid teaches us drug having its side effects but it also helpful in emergency pandemic level disease. In summary, the lack of substantial beneficial evidence for the use of steroid in general COVID-19 patient and data against their use during the past corona virus epidemics has led the WHO to state that routine steroid use should be avoided except in specific cases such as management of asthma and chronic obstructive pulmonary disease exacerbation, septic shock, acute respiratory failure. Recovery trial found a significantly better outcome with Dexamethasone, in some cases. More studies are needed to replicate the outcome shown in recovery trial. This drug shows long term side effect. Hence due to overwhelming benefits and adverse effect of this corticosteroid to patients, this drug not approved for trial in COVID-19 pandemic.

The main reason of this review is to introduce the role of corticosteroid like Dexamethasone drug, its trial status, benefits and pitfalls in COVID-19 pandemic.

ABBREVIATIONS:

FDA: food and drug administration; ACE: Angiotension converting enzyme; BMP-7 Bone morphogenetic protein; RVO: Retinal vein occlusion; CNS: central nervous system; ACTH: adrenocorticotrophic hormone; PONV: postoperative nausea and vomiting; AKI: Acute kidney injury; GR: Glucocorticoid receptor; DM: Dexamethasone molecules; CBP: corticoid binding protein; HDAC2: Histone deacetylases2; IL: Interleukin.

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