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The Adverse Effects of Corticosteroids

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ABSTRACT

Background: *Corticosteroids (cortisone-like medicines) are used to give comfort for inflamed areas or different portion of the human body. They lessen swelling of body, redness in the body, itching, and allergic reactions. They are used as procedure of the treatment for a numerous different disease, like as acute allergies or dermatological problems, which are very common, problem in breathing, or arthritis. There are two main division of corticosteroids, one is glucocorticoids and another is mineralocorticoids, which are included in lots of range of physiological processes, it creates stress response and immune response in the person, and regulation of inflammation, carbohydrate and protein catabolism, electrolyte levels in the blood, psychological behavior. The corticosteroids have two types of mechanism of action one is Genomic and another is Nongenomic actions. It is administered in three different ways in the body.*

Objective: *To observe the adverse effect of corticosteroids. I try to find the different physiological response of the body for different doses of corticosteroids. Corticosteroid drugs-includes cortisone, hydrocortisone and prednisone. However, these drugs also carry a high risk of serious physiological side effects. Therefore, I try to find different effects of corticosteroids in the human body.*

Methodology: *Systematic data collected from the electric database. I also used qualitative methods and gather some data. Content analysis method is used.*

Main findings: *Osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome, psychiatric disturbances and immunosuppression are among the more serious side effects noted with systemic corticosteroid therapy, particularly when used at high doses for prolonged periods. Glucocorticoids cause Osteoporosis is one of the commonly known and destructive adverse effects glucocorticoids for long-term use. Systemic glucocorticoids cause a dose- dependent grow in fasting glucose levels and a more significant increase in postprandial worth in patients without preexisting diabetes mellitus. Moderate to high dose use of glucocorticoids poses a significant risk of infections in the human body. Including common mild infections as well as very serious life-threatening infections. Mineralocorticoid effects in Cardiovascular, especially as seen with cortisol and cortisone, can lead to fluid retention in the body, edema, weight gain, hypertension, and arrhythmias by increasing renal excretion of potassium, calcium, and phosphate. Several cutaneous adverse effects can take place even at a low dose use of glucocorticoids, although the risk may increases linearly with the increasing dose and duration of glucocorticoid therapy. The risk of cataract disease is significantly high in patients taking prednisone dose more than 10 mg daily for more than one year it is an ophthalmologic disorders. Glucocorticoids expand the risk of adverse gastrointestinal effects, such as gastritis, gastric ulcer formation, an internal bleeding. Patients who takes glucocorticoids often feels an improved sense of well-being within several days of starting the taking of glucocorticoids; mild euphoria or anxiety may also happen. Hypomanic reactions and activated states are more common thing in early therapy than depression. Therefore, these are the main findings of the adverse effect of corticosteroids.*

Conclusion: *So I find Corticosteroids are hormone mediators produced by the cortex of adrenal glands of the human body that are further classified into glucocorticoids (e.g. in human body is cortisol), mineralocorticoid (produced in the body is aldosterone), and androgenic sex hormones.*

Glucocorticoids are a group of drug structurally and pharmacologically similar to the endogenous hormone cortisol with various outcomes like anti-inflammatory, immunosuppressive, anti-proliferative, and vaso-constrictive effects. These are mainly used for the treatment of various medical conditions. We also find the use of corticosteroids in different diseases. Along with their positive effects, there are many adverse effects of corticosteroids. We aimed to further evaluate the different adverse effects of corticosteroids like Musculoskeletal adverse effects, Metabolic and endocrine adverse effects, Infections, Cardiovascular effects, Dermatologic adverse effects, Opthalmogic adverse effect, adverse effects, Neuropsychiatric adverse effects.

***Future perspectives:** In Future we can further research on different demography. We can try to find is there any different effects present in hill area's people compare to normal area's people. We can also find the effects of corticosteroids in athletic population. We also find the difference of adverse effect in children and adult. Therefore, these are some future perspectives of this study.*

INTRODUCTION

Adverse effects of corticosteroids

Corticosteroids are hormone mediators that are produced by the cortex of adrenal glands of the human body that are further categorized into glucocorticoids and mineralocorticoid. The main glucocorticoid produced by the human is cortisol. The prime mineralocorticoid produced in the human body is aldosterone, and androgenic sex hormones. Endogenous cortisone was first segregate in the year of 1935 and synthesized in the year of 1944. In the year of 1948, Dr. Philip S Hench produced administered cortisone to a young woman who was bed-ridden for active rheumatoid arthritis. The person was able to walk after three days of proper treatment (Figure 1).

This case was published in 1949 [1].

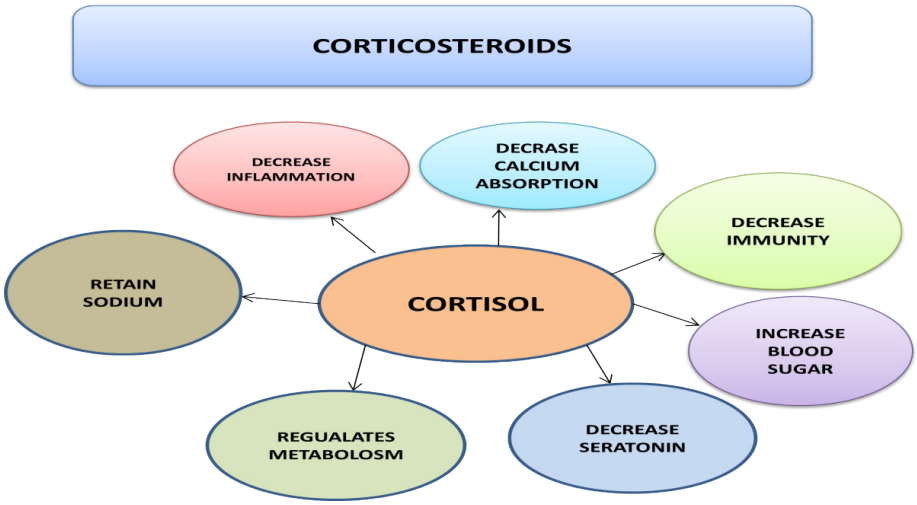

Figure 1. Types of Cortisol

Glucocorticoids are a group of drugs, which are arrangementally and pharmacologically similar to the endogenous human hormone cortisol with various purposes like anti-inflammatory, immunosuppressive, vaso-constrictive effects. Their effects are used medically for the treatment of various conditions indicated below. I have categorized and mentioned the most important and broad-spectrum of indication below.

As a Substitute Therapy**:** It is used as

- Adrenocortical insufficiency or addison disease in the human
- Congenital Adrenal Hyperplasia (CAH) disease

Methodical Symptomatic Treatment

Severe Effect: Severe effects are mentioned below

- In Allergic reactions and anaphylactic shock, it shows the vasoconstrictive effectsto the body
- In Asthmatic patient it use as a bronchodilator
- It has an Antiemetic effect it prevents the nausea and vomiting
- It is often used in person who suffers from Chronic Obstructive Pulmonary Disease (COPD) it also help to decrease the inflammation of the lung

Long-Term Effect: In long-term treatment, it has a major role

- It used in Chronic, inflammatory diseases like asthma, COPD, inflammatorybowel disease
- Graves' ophthalmopathy it is tested and used

After watching the uses of glucocorticoides lets discuss about Mineralocorticoids. Mineralocorticoids are connected in the regulation of electrolyte and water balance by adjusting ion transport in the epithelial cells of the collecting ducts of the kidney. The use of mineralocorticoid drugs is restricted to their replacement therapy in severe adrenal crisis and Addison disease.

Due to lots of roles played by corticosteroids in the human body, we see extensive use in medical practice for the treatment of various diseases. As a result, their adverse-effects become another significant medical issue requiring special attention.

MECHANISM OF ACTION OFCORTICOSTEROIDS

Glucocorticoids

The anti-inflammatory and immunosuppressive response of glucocorticoids is conditional on dose. The pharmacological anti-inflammatory and immunosuppressive response of glucocorticoids are huge scale and can be the genomic or non-genomic mechanisms. Most effects of the glucocorticoids are via the genomic mechanisms, which take a time, while instant effects *via* the non-genomic mechanisms can occur with high doses of glucocorticoids. Clinically, it is not feasible to separate these effects.

Genomic mechanisms of Glucocorticoids

Being very small, lipophilic substances, glucocorticoids easily pass the cell membrane by diffusion methods and enter the cytoplasm of the target cells, where the main action is conciliate by binding to the intra-cytoplasmic glucocorticoid receptors in the cell. α, and β are the two Glucocorticoid receptors, glucocorticoids bind to the α-isoform. Glucocorticoid resistance in some person has been partially ascribed to higher levels of the β-isoform in these people [2]. Binding of the glucocorticoid to the glucocorticoid receptor in the cell of human body results in shedding of heat-shock proteins. In the nucleus of the marked cells, this complex reversibly binds to a lots of specific DNA sites resulting in stimulation and suppression of a numerous variety of gene transcription.

Non-Genomic mechanisms

The immediate effects of high dose-glucocorticoids are mediated *via* non-genomic mechanisms. At high doses, glucocorticoids bind the membrane-associated glucocorticoid receptors on target cells like as T-lymphocytes.

The effects of glucocorticoids are-Reduced proliferation of fibroblast, reduced phagocytosis and antigen presentation by macrophages, Decreased cytokine production by macrophages and lymphocytes in the human body.

Mineralocorticoid Effects

Glucocorticoids bind to Mineralocorticoid Receptors (MRs) and create their mineralocorticoid response, but only when used at the high amount and for the extended period of time.

ADMINISTRATION

Many preparations of glucocorticoids are available in the market, each with varying there efficacy. Dexamethasone and betamethasone are long acting with the highest glucocorticoid efficacy with a biological half-life of 36 to 54 hours (Figure 2).

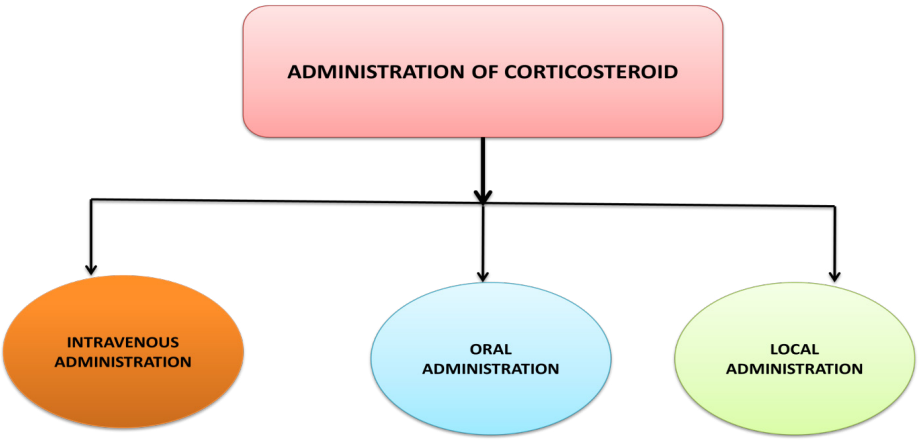

Figure 2. Administration of Corticosteroid

Intravenous Administration

Parenteral intravenous delivering of high amount of glucocorticoids may be warranted in emergency situation, such as septic shock, COPD exacerbation, and severe acute asthma.

Oral Administration

Oral compound those are usually effective in both severe and chronic indications. For acute exacerbations of underlying persistant illness (such as respiratory problems, Orthopedic disease Systemic Lupus Erythematosus (SLE), etc.), short duration of moderate to high ammount of oral corticosteroids is usually efficacious in treating the flare.

Local Administration

Glucocorticoid administration can be *via* different non-systemic routes, including intra- articular joint injections for joint inflammation, inhalational for asthma, topical for dermatological problems, ocular drops for eye conditions, and intra-nasal for seasonal rhinitis [2].

ADVERSE EFFECTS

Factors influencing the adverse effects of glucocorticoids

For the diversity in the mechanism of action of glucocorticoids, they can create a wide array of adverse effects ranging from mild to severe. Of all the factors affect the adverse effects of glucocorticoids, dose, and time span of therapy are the most significant individualistic and well-documented risk factors. It is usually at "supra-physiologic" doses of corticosteroid administration where multiple and especially severe adverse effects of glucocorticoids occur, ranging from mild suppression of hypothalamic-pituitary axis to severe, life-threatening infections [3]. However, long-term use of low to moderate doses of glucocorticoids can lead to a lots of serious adverse effects as well [4,5]. Adverse effects of corticosteroids are both dose and time-dependent [6]. Some adverse effects follow a linear dose-response pattern where the incidence increases with an increase in the dose it cause ecchymosis, cushingoid features, parchment-like skin, leg edema, and sleep disturbance.

Musculoskeletal adverse effects

Glucocorticoids cause Osteoporosis is one of the commonly known and destructive adverse effects glucocorticoids for long term use Up to 40% of patients on long-term glucocorticoids grow bone loss leading to fractures [7]. Steroid-induced myopathy, which is a reversible painless myopathy and is a direct result of muscle breakdown, can occur in both the upper and lower extremities of the body, usually with high-dose long-term use of glucocorticoids. Muscle enzymes Creatin kinase and Aldolase are normal, and findings on EMG are non-specific. Muscle biopsy tells that Type-II muscle fiber atrophy without inflammation. Abolitaion of glucocorticoids and exercises usually results in resolution of the myopathy. It characteristically presents with a severe, diffuse, proximal, and distal weakness that develops over several weeks. Osteonecrosis can be seen especially with long-term use of prednisone dose more than 20 mg daily basis. Patients who have SLE and the children are at higher risk. Hips and knees are the most commonly

involved joints in the human body with less common involvement of shoulders and ankles joints. Pain is the initial sign, which may eventually become severe and debilitating. MRI is the most delicate medical test, especially for early detection of the disease. Plain radiographs may have no effect initially but can be useful for follow-up.

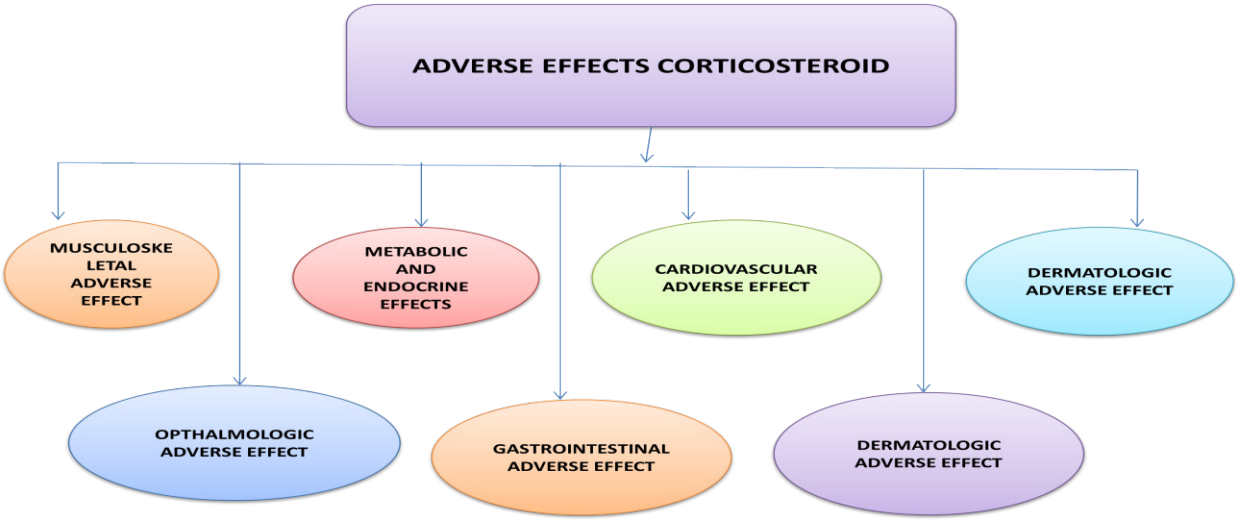

Figure 3. Adverse Effects of Corticosteroids

Metabolic and endocrine adverse effects

Systemic glucocorticoids cause a dose-dependent grow in fasting glucose levels and a more significant increase in postprandial worth in patients without preexisting diabetes mellitus, but the development of de novo diabetes in a patient who has initially normal glucose tolerance is uncommon. Risk factors for new-onset hyperglycemia during glucocorticoid therapy appear to be the same as those for other patients. However, patients with diabetes mellitus or glucose intolerance exhibit higher blood glucose levels while taking glucocorticoids, leading to increased difficulty with glycemic control [8].

Administration of glucocorticoids can conceal the Hypothalamic-Pituitary-Adrenal (HPA) axis decreasing the level of corticotropin-releasing hormone from the hypothalamus, adrenocorticotropic hormone from the anterior pituitary gland and endogenous cortisol.

Prolonged ACTH suppression can cause atrophy of adrenal glands. The clinical presentation of adrenal suppression is variable. Many of the signs and symptoms are not properly specific and can be mistaken for symptoms of intercurrent illness Adrenal suppression is the common cause of adrenal insufficiency in children and is associated with higher mortality over the pediatric population. In adults human, the symptoms of adrenal suppression are not specific; therefore, the condition may go not recognise until exposure to the physiological stress, resulting in an adrenal crisis. Children who suffereds with adrenal crisis secondary to adrenal suppression may present with hypotension, shock, decreased consciousness, lethargy, unexplained hypoglycemia, seizures, and sometime even death.

Infections

Moderate to high dose use of glucocorticoids poses a significant risk of infections in the human body. Including common mild infections as well as very serious life-threatening infections. There is a linear increase in the risk with dose and the time span of the therapy. Especially with common bacterial, viral, and fungal pathogens are responsible.

Accompanying use of other immunosuppressive agents and the elderly People further increases the risk of infections [9,10]. Prednisone dose of less than 10 mg daily pose minimal to no risk of infection in the human body. Patients who take glucocorticoids may not obvious common signs and symptoms of infection as clearly, due to the inhibition of cytokine release and the reduction in inflammatory and febrile responses leading to a failure in premature identification of infection.

Cardiovascular adverse effects

Mineralocorticoid effects in Cardiovascular, especially as seen with cortisol and cortisone, can lead to fluid

retention in the body, edema, weight gain, hypertension, and arrhythmias by increasing renal excretion of potassium, calcium, and phosphate. Hypertension usually occurs with higher doses only [11]. Long-term use of medium-high dose of glucocorticoids has implications in premature atherosclerosis in a dose-dependent pattern [12].

Dermatologic adverse effects

Several cutaneous adverse effects can take place even at a low dose use of glucocorticoids, although the risk may increases linearly with the increasing dose and duration of glucocorticoid therapy. Although cutaneous adverse effects appear to be clinically significant by physicians, they are usually of most concern to the patients [13]. These adverse effects include ecchymosis, skin thinning and atrophy, acne, mild hirsutism, facial erythema, stria, impaired wound healing, thinning of hair, and perioral dermatitis.

Ophthalmologic adverse effects

The risk of cataract disease is significantly high in patients taking prednisone dose more than 10 mg daily for more than one year. However, a greter risk of cataracts has been reported even with low-dose of glucocorticoids [14]. Cataracts are usually bilateral and progress as a lizserly pace [15]. Increased intraocular pressure is seen in patients receiving intraocular glucocorticoids, and high dose systemic glucocorticoids [16]. Glaucoma is painless and can lead to Blindness, optic disc cupping, and optic nerve atrophy. After the discontinuation of the systemic therapy, the elevation in intraocular pressure of the eye usually resolves within a few weeks, but the damage to the optic nerve is permanent.

Separation of the retina from its underlying photoreceptors may occur. This condition manifests as central visual blur and reduced visual acuity of the person [17,18]

Gastrointestinal (GI) adverse effects

Glucocorticoids expand the risk of adverse gastrointestinal effects, such as gastritis, gastric ulcer formation, and internal bleeding [19]. The use of NSAIDs drugs and glucocorticoids is associated with a 4-fold increased risk of a GI adverse effect compared with the use ofeither drug alone. Other complications associated with glucocorticoid use include pancreatitis, visceral perforation, and hepatic steatosis that can lead to systemic fat embolism or cirrhosis.

Neuropsychiatric adverse effects

Patients who takes glucocorticoids often feels an improved sense of well-being within several days of starting the taking of glucocorticoids; mild euphoria or anxiety may also happen. Hypomanic reactions and activated states are more common thing in early therapy than depression. Disturbance in sleep are reported by many patients. Motor restlessness is a very common glucocorticoids side effect in the human body. The possibility of developing a given neuropsychiatric disorder following glucocorticoid therapy may increase among the patients with a history of the condition. A very rare condition of pseudotumor cerebri have also correlated with glucocorticoid use [20].

There is specific documentation of neuropsychiatric adverse effects with glucocorticoid therapy in children with acute lymphoblastic leukemia or blooddisorder taking dexamethasone or prednisone for the induction and maintenance of treatment [21]. The risk is little bit higher in preschool children, and the symptoms is present during the first week of glucocorticoid therapy [22,23]. Glucocorticoid-create acute neuropsychiatric impairment may present with a lots of behavioral symptoms. Which includes euphoria, aggression, insomnia, mood fluctuations, depression and manic behavior [24]. Although these psychiatric problems tend to wear off with time on stop of glucocorticoid therapy, a small amount of the patients may face persistent symptoms even after notcontinuation of the drug.

TOXICITY

Acute psychosis can develop in patients who receiving high-dose glucocorticoids in their body. Immediate stop of the drug on the appearance of symptoms is the first step. Although a lots of drugs, including antipsychotics, antidepressants, benzodiazepines, and hydrocortisone have been tried with variable success in the human body, in recent days, there is no consensus on the ideal therapeutic remedy to stop and reverse the corticosteroid- induced neuropsychiatric adverse effects in adults or children. Their specific adverse effects further limit the use of the medications mentioned above.

CONCLUSION

So I find Corticosteroids are hormone mediators produced by the cortex of adrenal glands of the human body that are further classified into glucocorticoids (e.g. in human body is cortisol), mineralocorticoid (produced in the body is aldosterone), and androgenic sex hormones.

Glucocorticoids are a group of drug structurally and pharmacologically similar to the endogenous hormone cortisol with various outcomes like anti-inflammatory, immunosuppressive, anti-proliferative, and vaso-constrictive effects. These are mainly used for the treatment of various medical conditions. We also find the use of corticosteroids in different diseases. Along with their positive effects, there are many adverse effects of corticosteroids. We aimed to further evaluate the different adverse effects of corticosteroids like Musculoskeletal adverse effects, Metabolic and endocrine adverse effects, Infections, Cardiovascular effects, Dermatologic adverse effects, Opthalmogic adverse effect, adverse effects, Neuropsychiatric adverse effects.

FUTURE PERSPECTIVES

In Future we can further research on different demography. We can try to find is there any different effects present in hill area's people compare to normal area's people. We can also find the effects of corticosteroids in athletic population. We also find the difference of adverse effect in children and adult. Therefore, these are some future perspectives of this study.

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