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Review Article

Consequenses on Consumption of Corticosteroid Drugs and It's Harmful Effect on Humans: A REVIEW

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Abstract

This article contains an over view Corticosteroids and especially Harmful effects of Corticosteroids on short term and long term use. Corticosteroids have numerous applications as, anti inflammatory, immune response, anti cancer agent, allergic response and for asthma like this. Along with the multipurpose use there are some adverse effects with chronic use. Minimum adverse effects are growth retardation in children, Hypertension, ImmunoSupression, Severe asthma, Inhibition of wound repair, hyper glycemia, Osteoporosis, Glucoma, Metabolic disturbance and Cataracts. Cognitive shortage following acute administration of CS (Corticosteroids) on humans. In serious Psychiatric disorder, insomnia, agitation Oral clefts to born babies when mother consumed CS during pregnancy of first trimester, Fetal deaths on some cases. The effect of CS is based on doses and period they are using. Risk factors are low when doses are mild and risk or adverse effects are high when prolonged periods or using high doses.

Keywords

Corticosteroids, Orofacial clefts, cardiovascular diseases, Asthma, Arthritis, Psychological disorders, Osteoporosis side effects.

Introduction

Natural steroids produced in humans these are used as proteins to build muscle tissues. Physiological response of steroids is reached by regulating the expression of specific genes in steroid hormones. Cortisol is a natural steroid produced by adrenal gland which response for stress. It is also responsible for blood pressure, sugar level in blood and prevents the inflammation on target tissues. This anti inflammation property makes it particularly used in medicine and in inhalers to treat asthmatic attack. It also used to control of swelling due to injuries and reduce inflammation raised by arthritis (1). Corticosteroids (CS) are used to treat allergic, to suppress undesirable immune system action as therapeutic agents (7).

Corticosteroids (glucocorticoids, Mineralocoticoids) are used to replacement of adrenal insufficient therapy for management of various pulmonary, ophthalmologic, dermatologic, gastrointestinal, hematologic disorder, parenchymal lung diseases (11). Osteophorosis is one of the serious complications of oral corticoid treatment. It decreases the bone mineral density. This effect relates to the doses consumed and occurs more rapidly in trabecular trancortical bone, vertebral fractures also observed (21).

Along with the uses of Corticosteroids there is also harmful effects to humans, declared basing on analytical data. The adverse effects of corticosteroids are on pregnant women is oral clefts for new born babies (Robert et al 1994, Czeize and Rockenbauer 1997,Martinez Frias 1998, Roderiguez Pinilla) and teratogen risk to fetus (Fraser and Sajoo 1995), limb deficiency , neural tube defects, psychological effects like psychological defects, psychosis, depression, mania, irritability, sleeping disorders, diabetes,

adrenal suppression and cardiovascular disorders. These effects impact on patience quality of life, which associated physical and psychological impairment (2, 6, 9).

Clinical investigations revealed that the deficiency of glucocorticoids leads to decrease in integration of sensory information, on resent investigations conclude that the pathophysiological effects on brain of elevated endogenous glucocorticoids level that is tests of cognition function and treatment resistant depressive illness (5).

Many synthetic compounds with activity of corticoids are synthesised and tested (1), the difference is pharmacological results conclude that basic nucleus of steroid structure and side chain or groups on it (18).

Classification of Steroids

• Corticosteroids

Corticoids contain Glucocorticoids and mineralocorticoids. Functioning of glucocorticoids is to regulate many metabolism and immune function. Mineralocorticoids helps to maintain blood volume and electrolysis renal excretion.

• Sex Steroids

These are the subset of sex hormones that differentiate sex or support reproduction. This type of steroids includes androgens, progesterones, and estrogens.

• Anabolic Steroids

It interacts with androgen receptors to raise muscle and bone synthesis. There are number of natural and synthetic anabolic steroids like testosterone.

•**Phytosterols** includes beta sterols, stigma sterols. Boosts cholesterol lowering potential.

•**Brassinosterols** contains campesterol. Used to plant growth and development of immunity (1).

Secretion

Corticosteroids synthesised by adrenal gland in circadian manner. Adrenal gland is regulated by hypothalamic pituitary adrenal (HPA). On stimulation of para ventricular nucleus (PVN) of HPA releases Corticotrophin and arginine Vasopressin (23). Corticoids further classified into glucocorticoids (GC) and mineralocorticoids. Major glucocorticoid is cortisoland mineralocorticoid is aldosterone and androgenic sex hormone (17).

Glucocorticoids and mineralocorticoids are synthesised in Zona Fasciculata and Zona glomerulosa. The biologically active glucocorticoid in humans is Cortisol (22). Production concentration of plasma Cortisol is peak level on morning (10-15µg/ml) and lowest during sleep. In adults at non stressed state releases 20mg daily. During physical and mental stress production of cortisol increases to 150-200mg (7).

Drug Action/ Mechanism of Action

Corticosteroids (GCS and MCS) are metabolic substrates for cytochrome 3A4 iso enzyme. So, the increase or decrease of corticosteroids is depends on 3A4 (7). The clinical effect of corticosteroids is as, by either enhancement or suppression of transcription of inflammatory responsive genes. GC inhibits the synthesis of inflammatory cytokines, molecules (IL – 1, IL – 2, IL – 6, IL – 8) inflammatory eicosanaids, tumor necrosis factor and cyclo oxygenase affects the post translational events. The administration of GC results neutrophilic leukocytosis, transient minor reduction of monocytes and reduction in circulating eosinophils, basophils and total lymphocytes (11, 18).

Once released from adrenal gland into blood circulation glucocorticoids access the target tissues to regulate myriad of physiological process including skeletal growth, metabolism, cardiovascular function, immune function, cognition and reproduction. Due to it's liophilic nature, this steroid is not pre – synthesised and stored in adrenal gland, but it should be synthesised rapidly (23).

Receptor Types

There are eight corticosteroids according to 2017 analysis for inhalation. In which pro drugs that converted into their active forms by converting into esterase in the lungs and other tissues are ciclesonide, beclomethasone dipropionate. Main characteristics of inhaled corticosteroids (ICS) is receptor binding affinity. Receptors in body is similar at lungs to bind corticosteroids, so exhibits high affinity of systemic receptors. Both lung and gastrointestinal track contribute bio availability (7). Glucocorticoids is a single gene but multiple isoforms developed by alternative splicing and translation initiation site. Glucocorticoid receptors (GR) alteration is happen by post translational modifications including, acetylation, phosphorylation, ubiquitination and sumoylation. GR protein comprises three domains NTD, DBD, LBD that is N – terminal transactive domain DNA – binding domain and C – terminal ligand binding domain. NTD for post translational modifications IBD targets the glucocorticoid receptor. LBD for ligand dependent interacts with co regulators (22).

Corticosteroid hormone bind to it's receptor to induce a conformational change in receptor. This leads to dissociation of the receptor from attached protein (8). Dimerisation happens due to activation of

specific nuclear translation signals. The receptor dimer binds to hormone of the nuclear DNA. Although slow genomic action of corticosteroids reported the occurrence of rapid effect during uptake into cell corticosteroids are metabolised and interacted with membrane of receptor protein. This process effects the membrane characteristics (82) or transmitter responses (1 1 1). Both type I and II corticosteroid receptors have cloned and shown as product of different genes, also they share some DNA binding domain (3, 81, 126). Type I receptors in humans have peak affinity for corticosterone, aldosterone. Whereas Type II have some lower affinity (5).

Uses of corticosteroids

As anti cancer agent since 1940's, anti inflammatory, gout and immune response, allergic response, by alteration of cellular transaction, protein synthesis. Including breast cancer, prostate cancer, tumours, lymphoid, hematologic malignancies and multiple myeloma.

Non Hodgkin: in 1996, New Com reports on treatment of lymphocolic, lymphoma with prednisone, patients improved within three weeks.

For breast cancer: On front line hormonal therapy 9 women of 65 years old by estrogens, tamoxifen for a period of one month. In which 14% patients give objective response and 21% shows stable disease for at least 6 months.

As anti inflammatory: This corticosteroids are used to various diseases like inflammation, arthritis to psoriasis and asthma also. Using of this steroids have most powerful effects both good and bad. Dexamethasone is a corticosteroid which is also used as anti inflammatory and to decrease wound pain after oral surgery and also PONV, PDNV (Post Operative Nausea and Vomiting, Post Discharge Nausea and Vomiting). Corticosteriods also used to inhibit the production of prostagladins, to inhibit the ectopic discharge from injured sensor nerves. Epidural steroids injections work on the above manner to treat back pain, spine pathologies, spinal stenosis, radiculopathy, disk space narrowing spondylosis, annular tears, vertebral fractures (4, 9). The related corticosteroids are methyl prednisolone containing lidocaine (or) triamainolone (1, 12).

Endodontic: Patients who have severe pain and teeth with pulpal necrosis, chronic inflammatory suggested to corticoids combine with antibiotics (1,7).

Asthma: Inhaled Corticosteroids (ICS) are more effective therapy to control asthma through anti inflammatory effect. ICS reduces mortality and morbidity due to asthma (7).
These are also used as augmenting vascular tone by potentiating the action of vasoconstrictor hormone, and by action on vascular smooth muscles those are independent of vasoconstrictor hormones (24). After isolation of cortisone by Edward Kendall in 1930, Philip Hench first used on 1948 to treat rheumatoid arthritis. Later it become the corner stone of therapy for respiratory, neurologic, renal, endocrine, gastrointestinal, haematology, neuroplastic, dermatology, ophthalmic and allergy (4).

Types of Doses

Dosage is also one of the main factor. Basic on dosage adverse affects again 3 types.
Minimal risk – 40mg/day
Moderate risk - 40 – 80mg/day
High risk - above 80mg/day.
Most of patients will develop symptoms on first week of consumption. 90% of patients develop symptoms by between 1 -2 months (4).

Adverse / Harmful effects of Corticosteroids

Chronic use of corticosteroids in long term causes prevention of normal adrenal response of physiological stress and adrenal suppression, dyspepsia, insomnia, peptic ulcer, oral and vaginal candidiasis, glucose intolerance and anxiety. From chronic use causes cushingoid appearance, weight gain, cataracts, proxima myopathy, osteoporosis, thinning of skin, impaired wound healing and pain at injecting site. It also leads to neuro psychiatric changes including agitation, delirium and depression and thinning of bones. Most common side effects on elderly adults is hoarseness and thrush. When glucocorticoids given over a short course leads systemic fungal infection, hyper sensitive, pyogenic infection acute psychosis, renal insufficiency, diabetes mellitus, epicondylitis (1, 15).

Vasoconstrictive effect, asthma, toxic pulmonary edema, rheumatoid arthritis, cerebral edema, chronic, inflammatory disease, preterm delivery, linear pattern dose causes echymosis, leg edema, parchment like skin and sleep disorder. Threshold dose causes glycemia, depression and hypertension (17, 20).

Orofacial clefts

Reviewed medical reports and genetic counselling centres and hospitals find cases infants or fetal deaths identified with orofacial clefts, neural tube defects and limb anomalies (Shew et al, wasserman et al). On detail diagnosis cases again contains CLP (Cleft lip with or without cleft palate), CL (Cleft lip with palate)

recognised by surgical or autopsy report. By basing on X – ray ,Scan, Ultra sound study, Autopsy, Surgery reports there are many complications that is Spina bifida, Cystica, Craniora Chischisis, Anencephaly and iniencephaly. From clark (1990) classification scheme all infants and fetuses affected by anomalies aortico pulmonary separation, d – transcription of great arteries, including tetralogy of fallot, double outlet right vertical, sub aortic ventricular septal defect type – I, Pulmonary valve atresia with ventricular septal defect.

By radiology confirmed the defect of upper or lower limbs. By gathering data from 662 mothers reported Orofacial clefts, 265 report neural tube defects (NTD), 207 report conotrunal. Oroclefts again classified into Phenotopic – Isolated lip with or Without cleft palate, Isolated Cleft Palate, Multiple Cleft lip With Or Without Cleft Palate, Multiple Cleft Palate. All these effects are caused due to consumption of Corticosteroids during peri conceptional period. Both systemic and Non Systemic use of corticosteroids on first generation were associated with Cleft lip risk increases, but not use during 2nd and 3rd months said by Czeizel and Rockenbauer (2, 3).

Psychiatric Defects

Corticosteroids associated with Physiological Psychiatric effects. That is mood lability, Cognitive impairment and anxiety, behavioural disturbances. This level of mood change and Psychiatric disorder not diagnosable. Most frequently observed symptoms is agitation, distractibility, anxiety, fear, hypomania, insomnia, irritability, lethargy, pressured speech, tearfulness, restlessness and akathesia (4).

Major Symptoms

These defects are diagnosable affective syndrome delirium, Psychotic or Psychiatric condition including mania, depression or mixed state. With short term therapy effects are hypomania or euphoria and with long term therapy tends to engender depression symptom, Frank Psychosis, Delusion, Typified by Hallucination and disorganized thought in several cases Psychosis frequently include suicidal ideation, aggression (4, 15).

Cognitive Deficit

On short term therapy effects are hippocampal dysfunction and reversible atrophy of hippocampal neurons. After 4 to 5 days of dexamethasone shows memory deficiencies. On analysis/research of Lewis and Smith found that Psychiatric reactions ranging from 13% to 62% with average 27.6%. These reactions at 3 – point scales that is mild, moderate, severe.

Previously there is no Psychiatric symptoms up to 8 days after receiving high dose of methyl predinisolone to 50 patients. In which 26% developed mania 10% developed depression within 3 days of initiation therapy. On excessive endogenous cortisol (One of the Glucocorticoid) production causes Cushingoid disease (4).

Effect of corticosteroids on Memory

Hippocampal is essential for declarative memory (41) not essential for non – declarative memory. For consciousness and recollection of past information declarative memory is necessary. Whereas there is no need of consciousness to recollect the past memory for non – declarative. When we use corticosteroids it affects the hippocampal that leads to human cognition (103, 136) Cortisol interacts with hippocamphal neurons to cause cognition deficit. Dexamethasone is used to the Younger's recall task. On fourth day of treatment declarative memory performance, there is no immediate and delayed effects. When the dose is increased on treatment then there is an observation of immediate and delayed effects. In contrast to Youngers there is no any effect is observed in elders. This observations observed on New Comer's Laboratory (5).

Effect of Corticosteroids on Asthma Patients

For severe asthma corticosteroids includes most prevalent Chronity that is dyspeptic disorder (65%), Psychiatric disorder (38%), Obesity (42%), Hyper tension (34%), Hyper Cholesterolaemia (15%), Osteophorosis (16%), Type – II Diabetes (10%), Chronic Kidney disease (14%), Osteopenia, Cardiovascular disease (10%). In which hyper Cholesterolaemia and Glaucoma at high risk. 1.5 – 2 times higher risk diseases are Sleep disorders, Cataract and Chronic Kidney disorders. 5 times risk of Osteoporosis, 4 times risk by dyspeptic disorder (6, 13).

Effect of Corticosteroids on Metabolism

Generally Corticosteroids used to suppress the allergic response and inflammation, inappropriate immune response. In common Hydro cortisol used instead of cortisol when it is deficient. But these agents effects the carbohydrate, protein , lipid metabolism leads to Glucogenisis, Fatty acid mobilization and protein catabolism and some other side effects also. Short term use of Corticosteroids causes Hyper Glyscemia, edema, abnormal blood pressure, Gastro intestinal bleeding and serious diseases are Psychiatric problems, increasing in infection, poor wound healing and hyper kalemia.Use of ICS (Inhaled Cortico Steroids) Suppress the growth velocity of Child and adolescents approximately half inch (7).

Dermatological effects by Corticosteroids

Thin, Fragile, Bruising, mild hirsutism, Facial erthyma, Acne, Increasing sweating, Striae (permanent).

Haematological effects: Polymorpho nuclear, Leucocytes increased, decrease in Lymphocytes, Eosinophils, Monocytes.

Cushingoid Habitus – Buffalo Hump, moon facies. Using of corticosteroids reduces testosterone and oestrogen, which are responsible for regulation of bone metabolism and it leads to hypogonadism in female and males (8).

Induces Osteophorosis by Corticosteroids

Osteophorosis and fracture noticed within few years after introduction of steroids. In first six months greatest rate of bone loss is observed. Compression of blood vessel with ischemia due to fat increased at marrow cavity. In 1994 a 27 yrs old women having chicken pox when steroid dose is consumed within 24 hours she get ventilated due to disseminated intra vascular cognition, renal failure, Pneumonia, hepatitis and bilateral acute retinal necrosis. This case conclude that how serious and vericella in patients. CS users had increased levels of Physical inactivity, Frailty, immorbility and double in risk of hip fracture (8, 21). Rheumatoid arthritis, inflammatory bowel disease, poly myalgia, Rheumania, Chronic pulmonary disease and transplantation, fracture risk in regions of vertebral bodies, ribs, decrease bone formation ratio by inhibiting Osteoblastic activity in bone marrow, life span decreasing of Osteoblast, suppression of Osteoblast function (18).

Cause Hyper Glycemia by Corticosteroids

Increase in insulin resistance with pre existing and new onset sugar is due to use of corticosteroids associated with hyper glycemia and with high dose, overweight, old age, non white ethnicity, reduce glucose uptake by muscles (11, 18).

Cataracts and Glucoma diseases by Corticosteroids

On GC therapy glaucoma is a serious Ocular complaint and also it increases intraocular pressure leads to visual field loss, Optic nerve atropy, and Optic dis cupping painlessly (11).

Gastro intestinal disease

Peptic ulcer, candidiasis and pancriasis are involved in gastrointestinal side effects. From the report of PUD (Peptic Ulcer Disease) in CS treatment patients observe "stress ulcer". Experimental using of GCS increases Gastric acid secretion, haemorrhage, dyspepsia, esophageal ulceration and abdominal distension. A case study on Swedish population clears or conclude that an increased risk of acute pancreatitis on GC therapy (8).

Effect of Corticosteroids on Fetus

Low birth weight, neonatal blood pressure, air leak syndrome, need of oxygen supplement, chronic lung disease, brancho pulmonary, dyplasia, respiratory distress syndrome, intra ventricular haemorrhages. Death, infection, retinopathy of prematurity (10, 14).

Effect of Corticosteroids on women

Fever (Intraparatum, postnatal), glucose intolerance, hyper tension, puerperal sepsis, choriamnionitis, death (14).

Effect on Children

On receiving Oral glucocorticoids 50% of children effected with nephritic syndrome or asthma, depression, anxiety and also increase in tearfulness, insomnia, irritability, fatigue, argumentativeness, aggression and inactiveness, delay of puberty in young children. On observation of 150 cases by Braunig et al Corticosteroid induced Psychosis on 26 Patients with Suicidality, 15 with Suicidal ideation, 3 completed Suicide and 8 who are attempted Suicide. In paediatric population 73% receiving CS therapy develops irritability, adrenal suppression/insufficiency is associated with higher mortality. This adrenal suppression leads to shock, hyper tension, decreased consciousness, lethargy, seizures or even death at hypo glycemia (87-91), hyper activity, insomnia, memory and attention deficiency, especially in 10yrs age. In adults the effect is unrecognised until a physiological stress like illness, injury (4, 9, 11).

Abnormal lung function, glucose intolerance, neuro disability, visual and hearing impairment, intellectual impairment, cerebral palsy, developmental delay, sometimes death also (14). After congenital heart surgery post operative inflammation is developed to reduce it suggest corticosteroids to children. There is no any significant prediction of ventilation duration or ICU. In perioperative corticosteroids impact hyper glycemia, infection (16).

Cardiovascular Effect by CS

Fluid retention happen by mineralocorticoid along with it several effects are edema, hypertension, weight gain, arrhythmias, by renal excretion of salts, polyuria, weight loss, polydipsia. Coronary artery disease, ⩾ 7.5mg/day predinesine dose causes myocardio infection, coronary vascularisation, angina, hospitalisation by heart stroke, transient ischemic attack (18).

Effect on Corona Patients

During pandemic period of Covid -19 there is no effective anti viral treatment. So, Patients treated with symptomatic therapy. In clinics for this severe Pneumonia Corticosteroids (Gluco, Predinisolone, Predinosine, dexamethasone or Cortisol or Hydro Cortisol or Methyl Prednisolone) are widely used. According to Russell Colleagues or et al suggested that to, should not use CS in Covid -19 because, induces lung injury. But China front line physicians recommended courses of CS at low to moderate dose. We know that CS is for anti inflammatory and immune response suppression. Gluco corticoids suppress the production of IL – 2, interferon – γ in T lymphocytes and shift T- cell responses from Th1 to Th2; immature T and B cell precursors induce programmed cell death, prolonged removal of Viral RNA form air ways feces of patients, blood.

All the above effects leads to develop bacterial infection due to immune suppression, longer stay in hospitals and risk mortality also (19).

Prevention of adverse effects

All the above said effects of Corticosteroids are unavoidable. But, some of the effects we can prevented by;

- Using less dose of Corticosteroids for shortest period to achieve the treatment goals.
- Management of pre - existing comorbid conditions.
- Monitoring of patients under treatment.
- Appropriate immunization before the initiation of treatment.
- If any other medications is there then merit attention before initiating therapy.
- By modifying the chemical structure of the Corticosteroids (17, 18, 23).

Conclusion

It is clear that consumption of Corticosteroids causes minor to major harmful effects. This risk factors is based on the doses that is, low to high and short term to long term use. Corticosteroid use, affects the fetus, children and youngers, womens also. Fetal problems, Orofacial clefts on new born babies, Psychiatric disorders, chronic disorders, Asthma, Cataracts, Suicidal activity, Cardiovascular disease, Lung diseases, infections, Gastro intestinal diseases, dermatological diseases, Osterophorosis, Arthritis and sometimes death also. To avoid these effect, therapy of Corticosteroids is avoided or to use short term course than long term course or to use low doses than high doses.

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