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Dexamethasone Cyclophosphamide Pulse Therapy in Dermatology.

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Abstract: *pulse therapy is the administration of supra therapeutic administration of steroid for a very short period . This form of thrapy has very excellent response with very few side effects . steroid has anti-inflammatory as well as immunosuppressive effects.*

Keywords: *dexamethasone cyclophosphamide pulse , steroid*

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I. Introduction

Pulse therapy means the administration of large(suprapharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effects and reduce the side-effects.[1] The first reported use of pulse administration of corticosteroids is attributed to

Kountz and Cohn who used it to prevent renal graft rejection in 1973.[2] It was later used for treatment of lupus nephritis in 1976 .[3] In India, Pasricha and Srivastava introduced dexamethasone-cyclophosphamide pulse (DCP) therapy for the pemphigus group of disorders in 1986 in AIIMS,New Delhi.[4] Since then pulse therapy is been commonly used to treat various other diseases like systemic sclerosis, systemic lupus erythematosus, dermatomyositis,pyoderma gangrenosum, toxic epidermal necrolysis, StevenJohnson's syndrome, lichen planus, alopecia areata, sarcoidosis,and systemic vasculitis.[5]

DEFINATION- Pulse therapy refers to the administration of a drug intermittently to accelerate the therapeutic efficacy. In other words pulse therapy refers to intravenous infusion of high dose of steroids for one or more days for quicker, better efficacy and to decrease the side effects of long‑term steroids.[6-8)

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DCP therapy –

It is a fluoridated glucocorticoid, is a long acting agent half-life of 36-72 h. It is 6.7 times more potent than prednisolone, has negligible mineralocorticoid effect with almost no sodium retaining tendency and a small equipotent volume.

Dosage-

Dexamethasone is administered at a dose of 4-5 mg/kg (300 mg) per pulse.

Administration of pulse therapy-

Initially, the duration of infusion was 10-20 min. However, rapid infusions are known to be associated with a higher risk of hemodynamic abnormalities, now-a-days the corticosteroid preparation is dissolved in 500 ml of 5% dextrose and infused IV, slowly over 2-3 h.

Advantage of pulse therapy-

1. An immediate profound anti-infl ammatory effect is achieved and the toxicities seen with conventional high dose oral therapy are low. Faster clinical recovery from symptoms than with oral therapy, the clinical improvement is seen to last about 3 weeks after one pulse.
2. No prolonged suppressive effect on the hypothalamic –pituitary axis.

Mechanism of action-

Glucocorticoids act by 2 mechanisms on cells. One is through low concentration that is through genomic effect and another through high concentration that is through non‑genomic effect.

At low concentration—Genomic effect

Glucocorticoids act by binding to the intracellular glucocorticoid receptor (GCR) which results in formation of GCR complex which activates the mitogen‑activated protein kinase (MAPK) signaling pathway. This process leads to dimer formation and subsequent binding to specific DNA regulatory sequences known as GLUCOCORTICOID RESPONSE ELEMENTS (GREs), which results in anti‑inflammatory and

immunosuppressive effect by upregulation or down regulation of specific genes that encode for proteins, such as many cytokines and adhesion molecules.[9]

At high concentration—Non‑genomic effect

Glucocorticoids exert their effects by non‑genomic mechanism such as membrane bound receptors or physiochemical interaction with cellular membranes resulting
in rapid immunosuppression via apoptosis and induction of lipomodulin. There are also post transcriptional effects of Glucocorticoids which include effects on RNA translation,
protein synthesis, and secretion. End result of all these many effects is that Glucocorticoids inhibit the access of inflammatory cells to the tissues, interfere with function of fibroblasts and endothelial cells and suppress production and effects of humoral factors.[9

CYCLOPHOSPHAMIDE-

Cyclophosphamide is an alkylating agent. It has the ability to form strong electrophiles that form covalent linkages to electron rich groups of DNA. The active metabolite is phosphoramide mustard, which undergoes cyclization to the reactive aziridium intermediate, which in turn alkalizes the DNA. The result is irreparable damage to the DNA and subsequent apoptosis of the cell. Cyclophosphamide although

highly toxic to the rapidly dividing cells is different from several other cytotoxic agents in that it is toxic to the cells in all phases of the cell cycle.[

INDICATIONS-

The dermatological disorders in which corticosteroid
pulse therapy has been advocated are:[10]
1. Pemphigus vulgaris.
2. Bullous dermatitis herpetiformis.
3. Alopecia totalis.

Infrequently used in the therapy of:
1. Severe Steven-Johnson syndrome (SJS).
2. Pyoderma gangrenosum.
3. Vitiligo with rapidly progressive disease.
4. Exfoliative dermatitis.

Others:[11]
1. Autoimmune blistering disorder.
2. Systemic sclerosis.
3. Systemic lupus erythematosus.
4. Dermatomyositis.
5. Toxic epidermal necrolysis (TEN).
6. Lichen planus.
7. Alopecia areata.
8. Sarcoidosis.
9. Systemic vasculitis

Laboratory Monitoring

Before Starting the Therapy

As a routine, it is mandatory to admit every patient enrolled for pulse therapy. Hemogram, serum electrolytes, renal and liver function tests, blood sugar (including
hemoglobin A1c), urine microscopic examination, chest X-ray, electrocardiogram and pregnancy test are some of the preliminary laboratory tests to be done at the fi rst
visit. Blood sugar, serum electrolytes, urine microscopic examination, body weight and blood pressure should be monitored at baseline and at each visit of the patient.[11]

During and Following Therapy

Careful record of heart rate, respiratory rate and blood pressure every 15-30 min should be maintained. If an arrhythmia is suspected, the infusion is discontinued; an
electro cardiogram and blood levels of sodium, potassium, calcium and magnesium are obtained and abnormalities are rectified. Careful screening for occurrence or
exacerbation of infections should be done. Estimate blood levels of sugar and electrolytes every other day.[10]

Contraindication in Pulse Therapy

1. Systemic infections, fungal sepsis, uncontrolled hypertension and hypersensitivity to the steroid preparation.[10]

2. Absolutely contraindicated in pregnant, lactating and unmarried patients.

Adverse Effects-
Due to corticosteroids
• Viral, bacteria, and fungal infections
• Hyperacidity
• Diabetes mellitus
• Hypertension
• Demineralization of bone/Avascular necrosis
• Spontaneous rupture of the Achilles tendon.[12]
Due to cyclophosphamide
• Leucopenia
• Thrombocytopenia
• Diffuse loss of hair
• Diffuse hyper‑pigmentation of skin and hyperpigmented bands in nails
• Hemorrhagic cystitis
• Gonadal damage
• Carcinogenesis.[13]
Due to pulse therapy
• Hiccups
• Facial flushing
• Weakness
• Metallic taste
• Muscle and bone pain
• Generalized swelling
• Diarrhea
• GI bleeding
• Headache
• Loss of taste
• Menstrual irregularities
• Hair loss
• Sleep disturbances
• Palpitations
• Hypotension
• Arrhythmias
• Congestive cardiac failure
• Pulmonary oedema
• Ischemic heart disease
• Sudden death
• Acute psychosis
• Seizure
• Anaphylaxis.
The most common side effects are
• Flushing
• Palpitations
• Weakness
• Menstrual irregularities
• Bad taste/Diarrhea
• Headache
• Sleep disturbances
• Polyuria
• Acute cardiovascular complication
• Infections.

DCP Therapy is Divided into four Phases
1st phase
Dexamethasone 100 mg in 5% dextrose as a slow IV infusion over 2 h for three consecutive days along with cyclophosphamide 500 mg infusion on one of the days is instituted.[14] DCPs are repeated every 28 days until no new lesions appear between pulses. Cyclophosphamide 50 mg/day is given orally on the remaining days.

During this phase, the patient may develop recurrences in between the DCPs and conventional doses of oral corticosteroids can be given to achieve quicker clinical
recovery.15] After the skin and mucous membrane lesions have subsided completely and the additional medications are withdrawn, the patient is considered to have entered phase II.[16]

2nd phase

Phase of remission while on therapy. DCP schedule is given for duration of 9 months.

3rd phase

Monthly pulses are terminated and oral cyclophosphamide is continued for duration of 9 month.

4th phase

Treatment is stopped and patients are followed-up for next 10 years.

Modifi cations of DCP Therapy

There are following modifi cations of DCP therapy

Dexamethasone Azathioprine Pulse Therapy

Cyclophosphamide is known to cause oligo/azoospermia and amenorrhea. For unmarried patients who have not completed their family, cyclophosphamide was replaced by 50 mg of azathioprine daily during the fi rst three phases.[16]

Dexamethasone Methotrexate Pulse Therapy

Cyclophosphamide was replaced by 7.5 mg of methotrexate weekly given orally, during the fi rst three
phases of pulse therapy.[16]

DCP Therapy in Children

DCP therapy can be given to patients of all ages but thedoses have to be reduced to half for children below the age of 12 years.[17]

DCP Therapy in Systemic Diseases

Diabetic patients need to be given 10 units of soluble insulin for every 500 ml bottle of 5% dextrose dissolved in the same drip. In addition, patient's regular treatment for diabetes mellitus is continued. Similarly patientshaving concomitant diseases such as hypertension and tuberculosis must receive the respective medication.[17] If there is serious infection the pulse may be delayed for a week or two until the infection is under control.[18]

Conclusion

Steroid as an intermittent pulse therapy is much safer than daily administration. HPA axis suppression is one of the serious side-effects of long-term steroid therapy. It can be easily avoid by steroid pulse therapy. Now-a days this mode of therapy is some sever and chronic disease of dermatology such
As pemphigus, erythroderma, TEN/SJS etc

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