Scleroderma or Systemic Sclerosis - Treatment by Dexamethasone-Cyclophosphamide Combination Pulse Therapy

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ABSTRACT

Introduction: Systemic sclerosis is a multisystem, autoimmune disease of connective tissues involving skin, gut, lungs, kidneys and vessels. Present treatment is largely based on targeting specific components of pathogenesis like immune activation, fibrosis of skin and obliterative vasculopathy. In present study immunosupressive, anti-inflammatory effect of corticosteroids and cyto toxic effects of cyclophosphamide on lymphocytes has been used to this effect. Study aimed to determine the efficacy and weigh the risk and benefit ratio of Dexamethasone-Cyclophosphamide combination pulse therapy in patients of systemic sclerosis.

Material and methods: 15 patients of Systemic sclerosis fulfilling the inclusion criteria were given DC pulse therapy every 28 days. The assessment of these patients was done under the following headings for 6 months:- Skin biopsy, modified Rodnan score, pulmonary function test, Raynaud's phenomenon, ESR-value, subjective improvement, quality of life index scoring and any side effects of pulse therapy.

Result: There was a good reduction in Rodnan score, 8 patients showed excellent improvement in pulmonary function test. Subjective improvement was noticed in all patients with quality of life index improved in all patients. No major side effects were noticed during the study and follow up.

Conclusion: DC pulse therapy is an excellent option for patients of Systemic sclerosis in the early stages of the disease, before complete fibrosis of lungs occur.

Keywords: Scleroderma, Systemic Sclerosis, Dexamethasone-Cyclophosphamide

INTRODUCTION

Systemic sclerosis is a multisystem, autoimmune disease of connective tissues. It usually involves skin, endothelial lining of gastrointestinal tract, respiratory system, small
vessels and renal system.

Etiopathogenesis of systemic sclerosis includes:-

1. Immune activation
2. Fibrosis of skin
3. Obliterative vasculopathy

There is a complex interaction between

Genetics

Host ◁ Environment

An etiological agent effecting genetically predisposed patient to trigger molecular and cellular changes in fibroblasts, endothelial cells, B cells and T cells, leading to fibrosis, obliteration of small arteris and arterioles, production of auto antibodies and dis regulation of cytokine and growth factors respectively.[1]

Treatment options include use of antifibrotics, immunosuppressants and vasodilators. New therapy targeting specific components of pathogenesis are being tried increasingly.

Present study is based on immunosuppressive and anti-inflammatory effects of glucocorticoids on cells[2,3] and cytokoxic effects on lymphocytes causing immunosuppression by cyclophosphamide.[4]

Dexamethasone and cyclophosphamide has been administered as pulse therapy which means large doses of drugs are administered by an intermittent way to increase their efficacy and minimize side effects.

Pasricha and Srivastava brought the concept of using dexamethasone – cyclophosphamide pulse therapy for pemphigus in 1981, in India.[5] Study was conducted to determine the efficacy of Dexamethasone cyclophosphamide pulse therapy in patients of systemic sclerosis and to weigh the risk and benefit ratio of such therapy.

MATERIAL AND METHODS

Study was conducted in the department of dermatology of Rohilkhand Medical College and Hospital, Bareilly**.** After taking ethical clearance from the committee, study was conducted for six months and patients were followed up for another six months. An informed consent, describing all possible treatment options of scleroderma and possible side effects and usage of dexamethasone and cyclophosphamide was taken from every patient.

15 patients (who met the criteria of diagnosing scleroderma by 2013 ACR/EULAR) 12 females and 3 males, were given DC combination pulse therapy every 28 days for six months. Their age varied between 16 years to 45 years.

80mg of dexamethasone was given with 200mg of cyclophosphamide in 500ml of 5% dextrose over 2hrs on day one, followed by administration of 80mg of dexamethasone iv for next two days. Pregnant ladies and lactating mothers were not included in the treatment trial, other females were advised strict precautions for contraception during the therapy.

The assessment of these patients was done under the following headings for 6 months

Skin biopsy, modified Rodnan score, pulmonary function test, Raynaud's phenomenon, subjective improvement, quality of life index scoring and side effects of pulse therapy,

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Calculation of modified Rodnan score

Rodnan score evaluates patient's skin thickness by clinical palpation using 0-3 scale for each of 17 surface anatomic areas of the body.

(0=normal, 1=mild thickness, 2=moderate thickness, 3=severe thickness with inability to pinch the skin into a fold).

Modified Rodnan skin score (mRSS) was used to follow progress in all patients. This score is surrogate of disease severity and is main outcome measure of studies of disease modifying drugs.

Calculation of lung functional score was computed according to FEV1as follows:

FEV1 80% or more of predicted value was given score 1, FEV1 70-79% of predicted value was given score 2, 60-69% FEV1 of predicted: score 3, 50-59% FEV1 of predicted: score 4, 40-49% FEV1 of predicted: score 5, 40% FEV1 or less: score 6

Calculation of GUT functional score for upper GI was based on early satiety, anorexia, and nausea or vomiting

Score 1 for occasional symptoms, mild, little reduction in oral intake

Score 2 for moderate, intermittent symptoms, with some reduction in oral intake

Score 3 for more, severe persistent symptoms throughout day with marked reduction in oral intake on most days

For esophageal symptoms of dysphagia or odynophagia scoring was as follows

Score 1 for occasionally difficult or painful swallowing of solid foods or pills

Score 2 indicates intermittent dysphagia or odynophagia with solid foods, pills, but not for liquids or soft foods

Score 3 indicates dysphagia or odynophagia for almost all oral intakes on most days

For lower GI symptoms

Score 1 for occasional loose or liquid stools on some days

Score 2 for intermittent loose or liquid stools throughout day without requiring intervention to prevent or correct volume depletion

Score 3 indicates voluminous diarrhea requiring intervention to prevent or correct volume depletion.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the statistical analysis. Descriptive statistics like mean and percentages were used to interpret the data.

RESULT

Clinical history of the patients revealed that duration of illness was variable with a range between one year to four years. All patients had tightening of skin, one third of them having ulcers on fingers. Symptoms of difficulty in breathing were reported by twelve of them. History of Raynaud's phenomenon was reported in all most all of them. Difficulty in opening mouth and dysphagia was seen in four patients.

Skin became supple in all the patients with good reduction in Rodnan score. Skin ulcers healed quickly with topical medications. Eight patients showed excellent improvement in dyspnoea and pulmonary function tests.

There was an initial improvement in Raynaud's phenomenon in all patients. Mouth opening and dysphagia improved in all four patients. Quality of life index and subjective feeling improved in all patients. None of our patients suffered from scleroderma renal crisis. No major side effects of long term steroid therapy were noted as study was for shorter duration.

DISCUSSION

Though the pathogenesis of systemic sclerosis is multifactorial, complex and not yet fully known to medical fraternity, it's certainly clear that altering immunological response of body by steroids and other drugs like cyclophosphamide, mycophenolate mofetil, methotrexate and rituximab have beneficial effects and disease modifying capacity in systemic sclerosis.[4] Experience of earlier investigators like Pasricha JS[6] and Vishalakshi Viswanath, Amey D Sonavane, Aditi C Doshi, and Mrunal G Parab[7] on use of dexamethasone-cyclophosphamide pulse therapy encouraged us to do the study.

Basis of using Intravenous high dose steroids

Dexamethasone is economical and infusion of high doses of steroids for one or more days is efficacious with quick results and decreased side effects as compared to long term usage of steroids.[8] At higher concentrations glucocorticoids act on cell membrane receptors leading to immunosuppression via cell death and inhibition of prostaglandins and leukotrienes (induction of lipomodulin). They also inhibit nuclear factor kappaB via direct interaction with transcription factors.[9]

Basis of using cyclophosphamide

Cyclophosphamide produces immunosuppression by cytotoxic effect on lymphocytes. It has shown its efficacy in scleroderma lung study 1 (SLS 1) in the treatment of SSc interstitial lung disease (ILD).[10] FAST study has also shown the beneficial effects of cyclophosphamide on lung function in SSc patients.[11] It is also used in patient with rapidly progressive fibrotic activity in skin or lungs.[4]

Use of Dexamethosone as a single agent for pulse therapy in SSc has been reported by Pasricha et al[12], Gupta and Ahmad et al.[13,14] With improvement in skin and respiratory symptoms. Improvement in skin lesions of scleroderma occurred in short duration of six months treatment of dexamethosone pulse therapy by Sharada et al.[15] Beneficial use of intravenous cyclophosphamide as a single agent in alveolitis has been reported by Airo et al.[16]

We used combination of steroids and cyclophosphamide as pulse therapy for shoter duration of six months. It has shown good effects on skin and pulmonary function of SSc patients. Patients with Raynauds phenomenon though showed early benefit but it's difficult to comment in such a short duration of six months as these benefits can be seen only in winter in our area. Quality of life index improved in all patients.

Complications

Possible Side effects of DC combination pulse therapy based on experience of previous investigators are increased susceptibility to infections like candidiasis, amenorrhea in women, azoospermia in men, hair loss, flushing, generalized weakness, decreased sleep, pancytopenia, septicemia, pituitary adrenal suppression.[17-20] Scleroderma renal crisis during cyclophosphamide pulse therapy for interstitial lung disease and its treatment by angiotensin converting enzyme inhibitor with plasma exchange has been reported by Norihiro Nagamura

and Seikon Kin.[21] Yamanishi Y, Yamana S, Ishioka S, Yamakido M reported development of ischemic colitis and scleroderma renal crisis following methyprednisolone pulse therapy for progressive systemic sclerosis from Japan.[22]

None of our patients developed renal crisis or any other major complications. Pasricha J S also claim in a letter to editor of Indian J Dermatol Venereol Leprol that renal crisis has never been observed among their patients on DCP therapy.[5]

CONCLUSION

Given in adequate dosage dexamethasone and cyclophosphamide combination pulse therapy has definitive role and advantage in treatment of systemic sclerosis. Though this study was for shorter duration and involved small sample size but results are promising.

DC pulse therapy is not a cure for systemic sclerosis as it is for vesicobullous disorders. But it reduces the progress and fibrosis, makes prognosis better and life easier for patients. So it becomes the duty of dermatologists to diagnose this collagen-vascular disorder at its earliest stage for maximum benefit to patients.

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