Study Of Effectiveness Of Pulse Therapy In Various Autoimmune Dermatoses

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Abstract: Background: Autoimmune dermatoses are the disorders of immune systems in which auto antibodies are being generated against own cells. Many therapeutic measures are available but none is highly efficacious as well as free of side effects. Objective: To evaluate the effectiveness of different regimens and modifications of pulse therapy in various autoimmune dermatoses. Methods: We have selected the patients consecutively, according to inclusion criteria, after informed written consent, and divided into fourgroups (1) pemphigus vulgaris (PV) (2) systemic sclerosis (SS) (3) systemic lupus erythematosus (SLE) (4) mixed connective tissue disease (MCTD).Various modified pulse regimens were given according to the disease entity. Monitoring of pulse therapy was done by investigating before and after the pulse.Other immunomodulator drugs and supportive treatments were given. Overall evaluation was done every three monthly. Results:Total21 patients were enrolled for this study of two years duration, which included 09 patients ofpemphigusvulgaris, 03 patients of pemphigus foliaceous,05 patients of systemic sclerosis,02 patients of systemic lupus erythematosus and 02 patients of mixed connective Tissue disease. Different scales were used for evaluation of different entities. According to patient satisfaction score, we found excellent response in cases of systemic sclerosis and mixed connective tissue disease, while good in cases of pemphigus and SLE. Conclusion: Modifications of original pulse therapy in pemphigus vulgarisand use of regimens other than DCPin connective tissue disease are highlyeffective. [Maitri S NJIRM 2017; 8(3):81-88]

Key Words: Pulse Therapy, Pemphigus, Systemic Sclerosis, Systemic Lupus Erythematosus, Mixed Connective Tissue Disease.

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Introduction: Pulse therapy is a novel modality which includes administration of suprapharmacological dose of drugs in an intermittent manner to increase the therapeutic effect and reduce the side effects[1].Corticosteroid pulse was first successfully administered by Kountz and Cohn to prevent renal graft rejection[2].Thereafter different regimens of pulse therapy were used in several dermatoses.

The complex nature and versatility of the autoimmune diseases, non-remitting course and tendency for recurrence makes the choice of therapy difficult. Different therapeutic modalities are available but none is fully efficacious as well as compliant to patient due to the side effects.

In past few years intravenous pulse therapy with steroids and/or immunomodulator drugs has shown very promising results. Although it is a lifesaving treatment, lack of significant data and fear of using high dosages of steroids, this therapy is less explored.We have conducted this study of 4 autoimmune diseases with the aim to evaluateimprovement after pulse therapy in each disease. According to guidelines given by Pasricha et al, four phases of pulse therapy had been described. Wehad modified the pulse therapy by excluding phase two.

Methods: A retrospective and prospective study was conducted in inpatient clinic of department of dermatology, venereology, leprosy, government medical college and Sir. T. hospital, Bhavnagar, from August 2013 to July 2015, after approval from human ethicsand the institutional reviewboard, Bhavnagar.

Adult patients of both genders with confirmed diagnosis based on typical clinical manifestations or proven histology/ direct immunofluorescence test were selected. Total 21 patients according to inclusion and exclusion criteria were selected[1].

Inclusion criteria were as following:

- Recalcitrant disease not responding to routine line of treatment,
- Recurrent exacerbation of the disease,
- If the given treatment was not tolerated or contraindicated,
- Who can follow up after every 28 days till the pulse therapy ends,
- The patients with normal CBC, RFT, LFT, and blood sugar, BP, chest x-ray.

We excluded the patients with extensive lesions along with sepsis,females with pregnancy, lactation, general condition too poor to tolerate immune suppressive treatment, osteoporosis and other bone disorders, severe dementia or psychiatric disease, uncontrolled diabetes, HT, TB or any other systemic disease and who refused for the treatment.

Detailed history and thorough dermatological and systemic examination was done for each and every patient.Photographs were captured at the beginning of treatment and then every six monthly. Biopsy was taken wherever required to confirm the diagnosis. Few specific investigations were done as following:
for pemphigus(PV)-Tzanck smear and Desmogleinlevels[3],for systemic sclerosis (ss) - lung volume and capacity,anti-SCL-70,for systemic lupus erythematosus (SLE) -anti-dsDNA, proteinuriaand other investigations according to SLICC (systemic lupus international collaborating clinics) criteria,for mixed connective tissue disease(MCTD) -muscle enzymes, SGOT, LDH & CPK- MB. Standard monitoring guidelines[1] for corticosteroids and immunomodulator drugs were followed in each case. Routine hematological investigations including CBC, RFT, LFT, electrolytes, blood sugar, urine routine analysis, ECG were done prior as well as after each pulse completion,chest x-ray, x-ray pelvis- to rule out avascular necrosis of femur (AVN), PAP smear in females, stool test, ophthalmic examination to rule out cataract, glaucomawere carried out baseline, six monthly and/or whenever required.For immunomodulator drug monitoring, the routine and respective investigations according to drugs were done initially weekly for one month, then fortnightly for three months and then monthly till the end of pulse.

Desmoglein levels were done in five patients of pemphigus.Due to unavailabilityof facilitiesat institute and non-affordability of patients, indirectimmunofluorescence of serum forantibody levels could not be donein each patient.
We have given dexamethasone cyclophosphamide pulse (DCP) in PV and in SS,dexamethasone azathioprine pulse (DAP)in patients not responding to DCP anddexamethasone pulse(DP) in young patients of PV and SS group.Methyl prednisolone pulse(MPR) was given in MCTD and SLE group.
Before every pulse cycle we took the written informed consent in patient's own language for pulse as well as for photographs. We had referred the patients to rheumatologist whenever possible, in affording patients.

Dexamethasone cyclophosphamide pulse (DCP): In phase 1, dexamethasone 100 mg in 5% dextrose was given as a slow IV infusion over two hours for three consecutive days along with cyclophosphamide 500 mg infusion on second day. Cyclophosphamide 50 mg was givenorallyevery day between the pulses.Phase 1 was considered till no new lesions appeared and no further need of oral corticosteroids in between pulses. Between each pulse, gap of 28 days was maintained.We modified pulse phases by directly shifting the patients to phase 3 after phase 1 was over due to side effects, reduced compliance of patients and increase in dropout rate[4]. In phase 3, only oral cyclophosphamide 50 mg/day was given for 1 year, while in phase 4, all the drugs were withdrawn and the patient was followed-up for as long as possible.

Dexamethasone azathioprine pulse (DAP): Patient received oralazathioprine (1-2 mg/kg/day) daily instead of oral cyclophosphamide and no I/V infusion of azathioprine[5].

Dexamethasone pulse (DP): The patient does not receive cyclophosphamide orally or in the pint.It was given to the patient in whom cyclophosphamide/ azathioprine is contraindicated.

Methyl prednisolone pulse (MPR): In MPR pulse, 1000 mg ofmethyl prednisolone in 1 pint of 500 ml of normal saline per day over 3 consecutive days[6].No oral MPR or any other immunomodulator drug. Phase two and three were eliminated and patients were directly shifted to phase four.

As a part of the protocol, the following supportive drugs were given to all the patients:Oral calcium 500 mg + vitamin D3 (250 IU) daily[5].Tablet ibandronate (150 mg) orally once a monthaccording to the standard guidelines to prevent steroid induced osteoporosis.In female patients contraception was advised.Results were evaluated every 3 months, based on various scales and parametersspecific for the disease. We have followed the cases for 2 years to see the effects and to monitor the side effects.

Results: Total21 patientswere enrolled in this study and divided into following four groups: (1) pemphigus

(12 cases) - 09 patients of pemphigus vulgaris (PV), 03 patients of pemphigus foliaceous (PF), (2) systemic sclerosis (SS) (05 cases), (3) systemic lupus erythematosus (SLE) (02 cases), (4) mixed connective tissue disease(MCTD)(02 cases). Improvement in cases with different dermatoses are showed in figure 1 to figure 10.

In pemphigusgroup:eight female and fourmale patientsparticipated. Majority of the patients (11) belonged to mean age group of 25-45years. One lady with oral manifestations was aged 60 years. Eight patients had more than 50%, three patients had 25-50% and one patient less than 25% body surface area involved.

Kumar's scoring system: Skin Score:0 – Quiescent, 1 - <10 % BSA, 2 - 11-30 % BSA, 3 - >30 % BSA

Mucosal Score :0 - No mucosal involvement, 1 - Minimal disease (buccal mucosa , labiogingival , lingual , palatal , pharyngeal), 2 - Moderate disease(buccal and labiogingival, lingual, palatal or pharyngeal), 3 - Severe disease (extensive oral erosions, i.e., >3 mucosal sitesAffected) The results were analyzed using Kumar's scoring system[7]which includes mucosal as well as cutaneous findings (Table-1). We included 5 patients of systemic sclerosis in this study. All showed excellent response (Table no- 2). Total 2 patients of SLE were included in this study; results are mentioned in table-3. Changes in parameters as depicted in table-4 were observed in 2 cases of MCTD. Current status of all the patients, who received pulse therapy, is shown in table-5. Immediate and delayed adverse effects have been described in table no 6 and 7.

Patient Satisfaction Score[7]

Result	Score
None	0
Mild	2
Good	4
Very Good	6
Excellent	8

Table-1: Evaluation based on Kumar[7] Scoring system for pemphigus

No. of patients	Skin score		Mucosal score	
	Before pulse	After pulse	Before pulse	After pulse
1	0	0	3	0
2	3	0	0	0
3	3	0	2	0
4	3	0	0	0
5	3	0	2	0
6	3	1	0	0
7	3	2	2	1
8	3	1	2	1
9	3	2	1	1
10	3	1	3	1
11	3	1	3	0
12	3	3	2	2

Table- 2: Systemic sclerosis

Para Meters	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Before	after	before	after	before	after	before	After	before	after
Modified Rodnan's skin score[8-9]	20	10	26	14	21	11	33	19	30	21
Raynaud's Pheno-menon[10] (minutes)	3	7	<1	5	3	>6	1	>5	1	>3
Mouth Opening (fingers)	2	>3	2	>3	1&1/2	3	2	3	1	3
Lung volume and capacity	Moderate restrictive pattern	mild	Moderate restrictive pattern	mild	Early interstitial lung changes	Mild Pattern	normal	normal	normal	normal
Patient Satisfaction score	0	6	0	8	0	6	0	6	0	4

Table- 3: SLE

Clinical parameters	Patient 1		Patient 2	
	Before pulse	After pulse (9 pulse cycles)	Before pulse	After pulse (3 pulse cycles)
Malar rash, discoid rash	severe	Mild	moderate	mild
Photosensitivity	moderate	mild	moderate	mild
Joint pain	moderate	Absent	moderate	mild
Oral ulcer	moderate	Absent	Severe	moderate
Alopecia, lupus hair	severe	Absent	moderate	moderate
Amenorrhea	moderate	moderate	Absent	Absent
Fever	moderate	Absent	Moderate	mild
Depression, psychosis	Absent	Absent	Absent	severe
Patient satisfaction score	--	6	--	2

Table-4: Mixed Connective Tissue Disease

Parameters	Patient 1(09 pulse cycles)		Patient 2(04 pulse cycles)	
	BeforePulse	After pulse	BeforePulse	After pulse
Myositis/synovitis	Severe	Absent	Severe	Mild
Raynaud's phenomenon(minutes)	1	>5	2	>5
Acrosclerosis	Severe	Absent	Severe	Mild
Muscle enzymes	Raised	Within normal limits	Normal	Normal
Patient satisfaction score	2	8	2	4

Table- 5: Current Status (After 2 years of study)

Current Status	No. of patients in each disease			
	Pemphigus(12)	Scleroderma(05)	SLE (02)	MCTD (02)
Remission	5 (41.67%)	5 (100%)	1 (50%)	1 (50%)
Relapse	1 (8.34%)	-	-	-
Defaulter	4 (33.34%)	-	1 (50%)	-
Stopped due to side effects	2 (16.67%)	-	-	1 (50%)

Table- 6: Immediate side effects

Immediate side effects	No. of patients (%)
Weakness, dizziness	15 (71%)
Anorexia	5 (24%)
Epigastric pain, nausea	8 (38%)
Headache, flushing	5 (24%)
Fever, malaise, myalgia	3 (14%)
Palpitation, rise in BP	3 (14%)

Table- 7: Delayed side effects

Delayed side effects	No. of patients (%)
Cushingoid facies, weight gain, gynecomastia	6 (29%)
Diabetes	4 (19%)
Cataract	4 (19%)
Hypertension	3 (14%)
Diffuse hair loss,	3 (14%)
Warts	2 (10%)
Amenorrhea	2 (10%)
Avascular necrosis of femur	2 (10%)
Cardiomegaly	1(5%)
Active tuberculosis	1(5%)

Discussion: Pulse therapy was used to prevent renal graft rejection and in lupus nephritis initially. But lateron it was started being used commonly in several other dermatoses also like pemphigus, systemic sclerosis,systemic lupus erythematosus, dermatomyositis and less commonly inpyoderma gangrenosum,extensive lichen planus, prurigonodularis, generalized morphea, DLE, scleredema, recurrent alopecia universalis, extensive vitiligo, Darier's disease,Hailey-Hailey disease and sarcoidosis.[1]

Long term daily use of corticosteroids leads to various adverse effects like diabetes, hypertension, infection, obesity, glaucoma, osteoporosis, psychosis and many other complications. Daily pill burden may also decrease patient compliance whileit does not successfully decrease the remission of the autoimmune disease.Daily use of systemic steroids poses a problem of HPA axis suppression.

So, pulse therapy of corticosteroid alone or combined with immunosuppressant drug has proved to be a boon for chronic autoimmune or connective tissue disorders. It not only reduces the side effects, pill burden and cost of the treatment but also helps to maintain long term remission[11].At very large concentrations steroids dissolve in the cell membrane achieving greater membrane stability and reduced non-genomic cell function thus decreasing the side effects[11].So, we conducted this study to find out the changes in various autoimmune dermatoses other than pemphigus, in which pulse therapy is not very well explored as well as to find out the beneficial modifications in pulse therapy and different regimen.

Pemphigus group: In pemphigus group, we waited till the lesions became non-infected; pus culture report was negative before institution of pulse therapy to prevent the chances of patient going into sepsis. With this intervention, we found the patients require less number of pulses in phase-1 similar to findings of study of Narsimha Rao et al[5].Further we modified pulse therapy phases in our study. In phase-1, on an average we gave 10-12 pulses to the patients till no flare up of disease and no requirement of oral corticosteroids and then we directly shifted to phase-3. In phase -3 oral cyclophosphamide or azathioprine had been given.After 3-4 pulses, all the patients started showing good response in skin lesions, while mucosal and scalp lesions were quite persistent in nature. We administered injection triamcinolone acetate (10mg/ml) intralesionally in scalp lesions in two patients and in oral lesions in one patient, as there was very mild improvement even after 5-6 pulses[5].

Figure-1: Oral lesions prior pulse therapy

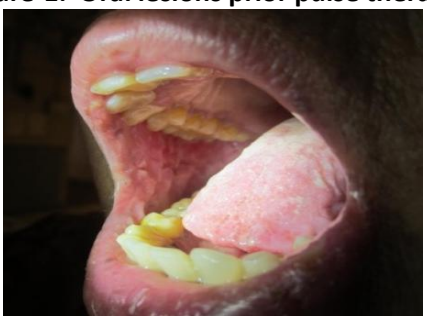


Figure-2: Oral lesions after pulse therapy

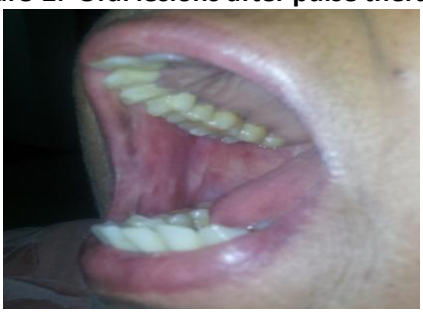


Figure-3: cutaneous lesions prior pulse therapy

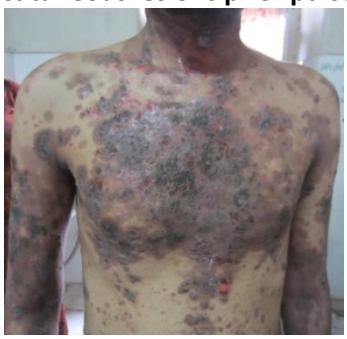
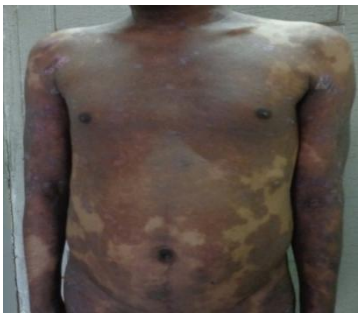


Figure-4 : cutaneous lesions after pulse therapy



Similar remission rate was observed with studies of Renu Roy et al[12] and Masood Q et al[13] studies. They had studied 37 and 30 patients with remission rate

40% and 46%, of two and three years duration respectively, while our study was of 12 patients with remission rate of 42% and duration of 2 years.

Systemic Sclerosis: In one patient of systemic sclerosis, along with other characteristic features of SS, all the signs and symptoms of esophagus involvement were present. She was under the treatment of a general surgeon for it and had typical changes of parrot beak appearance and lower esophageal sphincter dysfunction in barium meal and oesophagoscopy report. Administration of DCP arrested progression of disease and we noticed reversal of signs and symptoms. At the end of the therapy patient was free from Raynaud's phenomenon, dyspnoea, binding down of the skin and was able to open mouth almost fully, improvement in skinlesionsand oesophagoscopy was normal.

Figure-5: stellate ulcers after pulse therapy

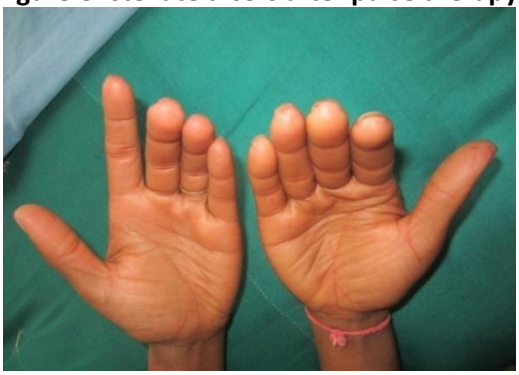
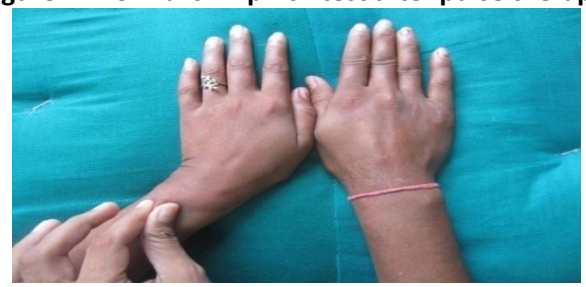


Figure-6: Normal mouth opening after pulse therapy

The most widely accepted method for monitoring skin changes in systemic sclerosis is by simple clinical palpation. The modified rodnan skin score (MRSS) employs a qualitative rating scale (0, normal skin; 1, mild; 2, moderate; 3, severe thickening) of the findings on clinical palpation of 17 body areas.According to MRSS, we found a sustained and major decrease in each patient. Mean pre pulse MRSS was 26, mean post pulse MRSS15.2 and mean difference being 10.8, which is showing a huge decrease in MRSS.

Figure-7: Normal skin pinch test after pulse therapy



Systemic Lupus Erythematosus: We gave MPR pulse in cases of SLE due to its intermediate acting, potent, anti-inflammatory action with a low tendency to induce sodium and water retention[11].Out of two patients of SLE, one patient developed severe psychosis after three pulses and left the treatment. The remaining patient of SLE showed a very good response in overall clinical features starting from 4th pulse.

Figure-8: Lupus hairprior pulse therapy

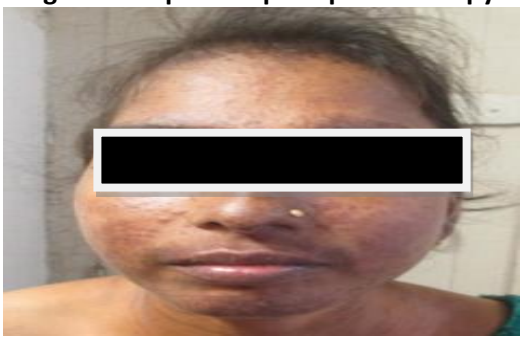
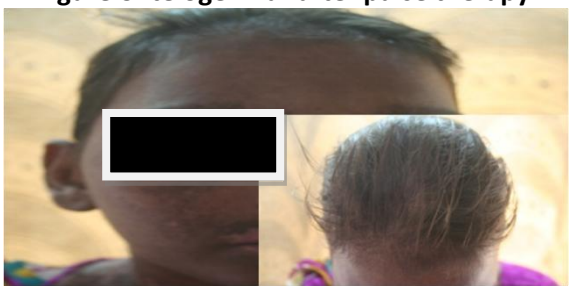


Figure-9: telogen hairafter pulse therapy



Resolution of fever and oral ulcers were earliest in most of the cases after one – two pulses which is very similar to the findings seen in study of Dhabhai R et al[14]. While in contrast to that study, malar rash showed mild improvement after 6-7 pulses.The common side effects seen in our study was darkening of complexion in contrast to thebacterial and candidial

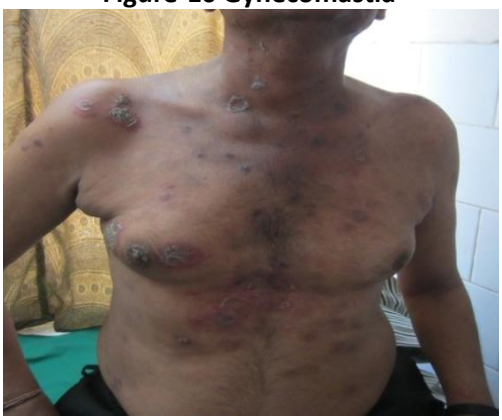
infections of the skin and oral mucosa, which were the common side effects of the previous study.Another difference between these two studies was, we gave MPR pulse while DCP was given in previous study.[14]

Mixed Connective Tissue disease: In the Group of MCTD, two patients were included. According to Alarcon-Segovia criteria[15], we evaluated the patients. Both the patients showed a very good clinical as well as laboratory parameter improvement. But we had to stop pulse therapy in one patient due to development of avascular necrosis of femur after 4th pulse of phase-1.The reason of avascular necrosis (AVN) of femur seems to be the long term intake of oral corticosteroids taken even before the pulse therapy[17].Muscle weakness was the first to resolve after three pulses, followed by Raynaud's phenomenon and acroscleosis.

Possible adverse effects and intervention for prevention and treatment: There are certain adverse effects we noted possibly developing after pulse therapy. Immediate side effects were very mild and transient which we treated in a conservative manner[16]. But few ADRs were developing after four-five pulses and measures for prevention as well as treatment we had to take.

In our study, 4 patients (19%) developed raised blood sugar levels after pulse. We had given few units of soluble insulin in the pint according patient's blood sugar levels along with pulse regimen.We used normal saline pint rather than pint of DNS in these patients. We had to continue injectable human Insulin or oral antihypoglycemic drugs according to physician's advice even after pulse therapy. We managed characteristic features like Cushingoid facies, weight gain, and gynecomastia by exercise, diet management.

Figure-10 Gynecomastia



Four patients had to undergone cataract operation in phase 3 and 4. Three patients were prescribed anti-hypertensive medicines. Two patients suffered from amenorrhea were given hormonal therapy for withdrawal bleeding as advised by gynecologist. Pulmonary Tuberculosis infection was observed in one patient and the pulse therapy was stopped. Verruca vulgaris were observed in two patients. One patient was treated with cryotherapy as only few lesions and improved while another patient had severe, resistant, numerous warts. The patient was treated with autoimplantation as well as mycobacterium welchi vaccine.

Limitations of study: There were few drops out cases in this study. The reasons for drop out were long standing non- remitting course of disease itself, financial loss of daily wedges of other family member due to 4-5 days monthly admission at hospital, long duration of treatment, possible side effects of treatment as well as lack of awareness and education of their disease.Therefore evaluation of treatment was done at different stages of pulse therapy. A study with large sample size of various autoimmune dermatoses is required further.

Conclusion: We achieved100 % remission in systemic sclerosis, 50 % in systemic lupus erythematosus and mixed connective tissue disease and approximately 42 % in pemphigus. The results are conclusive of pulse therapy is a useful modality in resistant cases of autoimmune disorders especially in non-affording cases. We found modifications of original Pulse therapy and use of regimens other than DCP, are highly effective in various autoimmune dermatoses.

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Conflict of interest: None

Funding: None

Cite this Article as: Maitri S, Hita M. Study Of Effectiveness Of Pulse Therapy In Various Autoimmune Dermatoses. Natl J Integr Res Med 2017; 8(3):81-88