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Original Research Article

Study of dexamethasone cyclophosphamide pulse therapy in systemic lupus erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is always a challenge to the treating dermatologists. Pulse therapy is the use of supra pharmacological doses of drugs to achieve a desired therapeutic effect. The success of dexamethasone cyclophosphamide pulse therapy (DCP) in autoimmune bullous diseases has prompted dermatologists to use DCP in SLE but very few studies are available which objectively measure the outcome of DCP therapy in SLE. The aim of our study is to study the efficacy of dexamethasone cyclophosphamide pulse in patients with SLE and to use objective scoring systems to assess efficacy.
Methods: 20 SLE patients who satisfied the inclusion criteria were administered intravenous dexamethasone 100 mg over three days with cyclophosphamide 500 mg on day1, followed by oral cyclophosphamide 50 mg daily. In patients whom cyclophosphamide cannot be used oral azathioprine was given. Response to treatment was assessed using CLASI (cutaneous lupus area severity index), clinical evaluation of dermatological and systemic symptoms and laboratory parameters such as ANA, Anti dsDNA, ESR etc.
Results: All the patients showed clinical improvement with statistically significant fall in CLASI scores and anti dsDNA values. The mean duration of pulses required to achieve remission was 9 pulses. No major adverse effects were observed in any of the patients.
Conclusions: Dexamethasone cyclophosphamide pulse therapy is an effective and safe option in the management of patients with SLE.

Keywords: Systemic lupus erythematosus, Dexamethasone cyclophosphamide pulse therapy, CLASI, Anti dsDNA

INTRODUCTION

Systemic lupus erythematosus (SLE) is always a challenge to the treating dermatologists. Though complete cure remains an enigma, therapeutic advances have aimed at inducing quick remission and improving the quality of life of the patients.

Pulse therapy is administration of single or multiple daily infusions of suprapharmacological doses of drugs to achieve a desired therapeutic effect.[1] It is otherwise called as the "big shot".[2] The monumental success of dexamethasone cyclophosphamide pulse therapy (DCP) in autoimmune bullous diseases (e.g. Pemphigus) reported by Pasrischa et al., has prompted dermatologists to use DCP in SLE.[3]

Since the use of the first pulse therapy in 1976 for lupus nephritis, it has come a long way in improving the quality of life of patients with SLE.[4] The long duration of steroid therapy required and the consequent effect on hypothalamo-pituitary axis (HPA) suppression with daily

steroids makes pulse therapy, which is relatively free of such effects a welcome option in the therapeutic armamentarium of SLE.[5]

This study aims at assessing the effectiveness of DCP therapy in SLE. Also the novel aspect of this study is that the clinical improvement of dermatological manifestations will be based on well validated skin scoring system called CLASI (cutaneous lupus area & severity index).[6]

METHODS

This is a type of open labelled non randomised prospective therapeutic study. Here the patients act as their own control. A sample size of 20 patients was selected. This study was conducted at the department of dermatology, in a tertiary medical centre in South India, in association with other departments for evaluation of systemic involvement for a period of about 4 years. Institutional ethical committee clearance was obtained. The patients were selected based on the following inclusion and exclusion criteria.

Inclusion criteria

Systemic lupus erythematosus patients diagnosed as per ARA criteria.[7] Patients of age 13 to 60 years, severe skin lesions not responding to high dose daily steroids and presence of systemic involvement were included in the study.

Exclusion criteria

Patients of pregnancy, lactating mothers, children <12 years, ischemic heart disease, uncontrolled hypertension and active infections except minor upper respiratory tract infections, acute gastroenteritis and skin infections were excluded from the study.

Procedure

A detailed history and physical examination was done. The diagnostic tests such as skin biopsy, ANA, Anti dsDNA and tests to find out systemic involvement such as blood urea, serum creatinine, urine routine & 24 hour urinary protein (for renal involvement), ECG, Echocardiogram (for cardiac involvement), X ray chest, pulmonary function tests (for lung involvement), EEG, CT scan brain (for CNS involvement), creatine phosphokinase (CPK) for musculoskeletal involvement and complete hemogram, platelet count, peripheral smear (for haematological involvement) were done. Tests to assess fitness for pulse therapy such as Mantoux, blood sugar, pregnancy tests in females were also done. Informed consent was obtained from all patients. Clinical photographs were taken at serial intervals.

Administration of pulse therapy

The patients selected were hospitalised a day before the pulse therapy. Pre pulse investigations such as blood sugar, urea, serum creatinine, electrolytes, liver function tests, complete hemogram and urine routine were taken during each cycle. If all parameters were normal the pulse therapy was administered. Injection dexamethasone 100 mg in 500 ml of 5% dextrose by slow intravenous infusion over 2-3 hours was given for 3 consecutive days. On day 1, injection cyclophosphamide 500 mg was also added. On rest of the days only tablet cyclophosphamide 50 mg per day was given. In young unmarried patients and those who have not completed their family injection dexamethasone alone was given. On the rest of the days, oral azathioprine 50 mg per day was given. In patients with diabetes mellitus 8 U of regular insulin was added into the 5% dextrose solution.

Pulse rate, blood pressure and ECG were monitored before start of the infusion. Intermittent monitoring of pulse and blood pressure were done every half an hour during the infusions. The electrolytes and blood sugar were measured after the end of pulse therapy. If all parameters were normal the patient was discharged the next day. The next pulse was repeated after 28 days. In addition oral chloroquine 250 mg per day was given. All patients were instructed to maintain a daily fluid intake of 2 L to prevent the development of haemorrhagic cystitis. Calcium supplements (1500 mg/day) were given to all patients to prevent the development of osteoporosis. During the 3 days of pulse therapy, potassium chloride syrup was given to minimise the risk of development of hypokalaemia. Ophthalmic examination was done before the start of therapy and every 6 months to rule out glaucoma and posterior sub capsular cataract.

Evaluation of response

Disease activity was evaluated by measuring the CLASI score as represented in Table 1, clinical assessment of improvement in malar rash, photo-sensitivity, discoid rash, alopecia, oral erosions, fever, joint pain and symptoms pertaining to other system involvement, laboratory monitoring of renal function tests including blood urea, serum creatinine and 24 hour urinary protein, total and differential counts, erythrocyte sedimentation rate (ESR), ANA titre, Anti dsDNA titre.

RESULTS

Of the twenty patients the youngest was 17 years old and the oldest was 34 years old. The mean age of the patients was 23.2 years. The study group included 19 females and 1 male, with a female: male ratio of 19:1.The average duration of illness of the patients included in the study before pulse therapy was initiated was 16.5 months. The shortest duration was 2 months and the longest duration

was 42 months. Only those patients who had skin manifestations were included in this study. The prevalence of the common skin manifestations is represented in Figure 1. Other cutaneous manifestations seen were livedo reticularis in 1 patient (patient no.6) who also had neurological manifestations; bullous lesions seen in one patient (patient no. 5) urticarial vasculitis in 1 patient (patient no. 2) and vasculitic ulcers were seen in 3 patients.

Table 1: Cutaneous lupus area & severity index (CLASI).

Anatomical location	Erythema; 0-absent, 1-pink, faint, 2-red, 3-dark red/purple/crusted haemorrhagic	Scale/ hypertrophy; 0-absent,1- scale, 2-veruccous/hypertrophic	Dyspigmentation ;0-absent, 1-dyspigmentation.	Scarring/atrophy/panniculitis; 0-absent, 1-scarring, 3-severely atrophic scarring or panniculitis
Scalp				
Ears				
Nose (including malar area)				
Rest of face				
V area of neck				
Past. Neck & shoulder				
Chest				
Abdomen				
Back, buttocks				
Arms				
Hands				
Legs				
Feet				
Mucous membrane			**Dyspigmentation**	
0-Absent			1- Lasts less than 12 m	
1-Present			2- Lasts more than 12 m	
Alopecia				
Recent hair loss (within the last 30 days/as reported by patient)			**Scarring**	
0-No 1-Yes			NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both	
Alopecia (clinically not obviously scarred)			Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant			0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	
Total activity Score:			**Total disability Score:**	

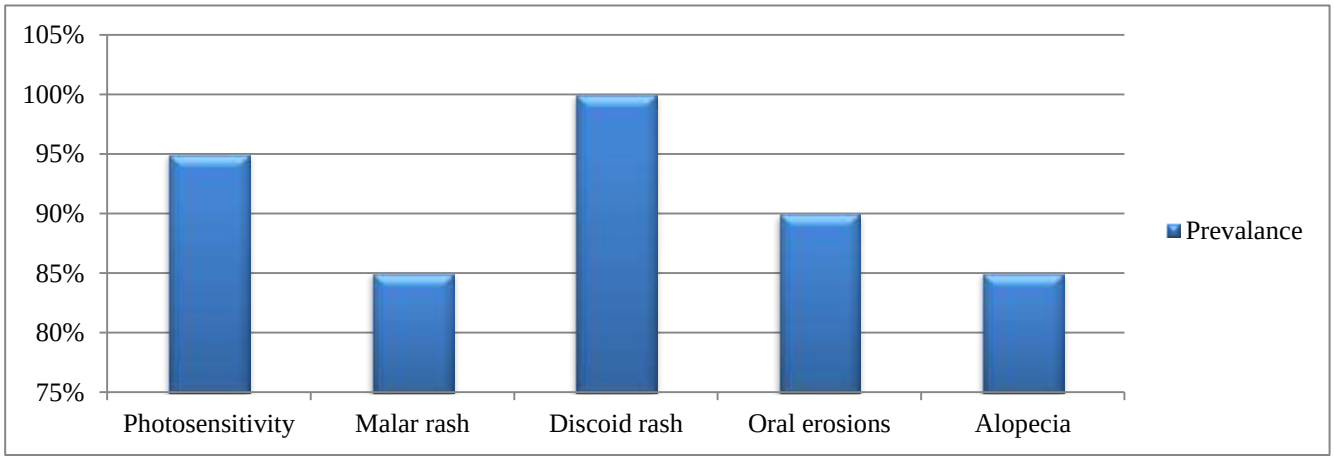
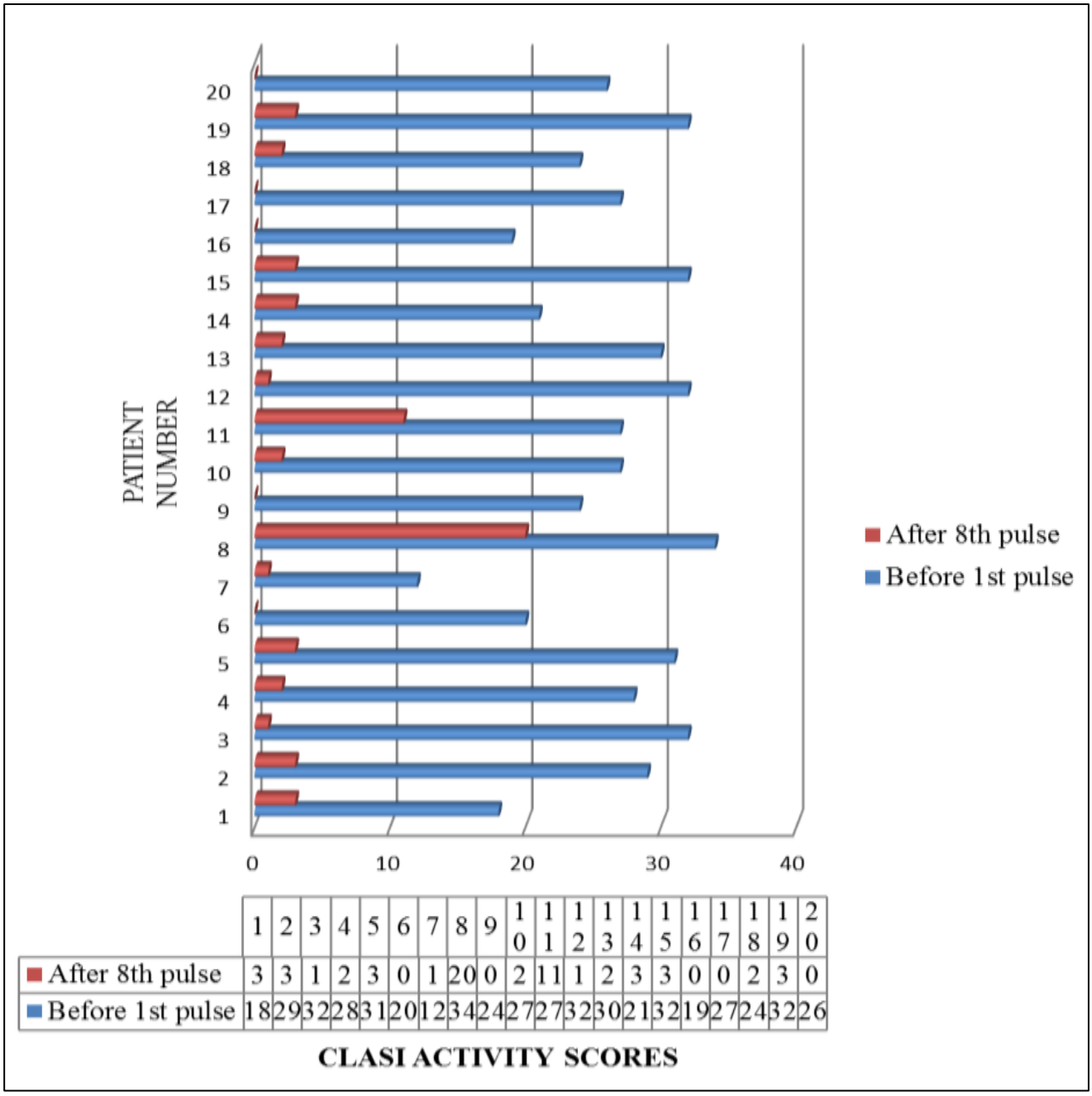


Figure 1: Prevalence of cutaneous manifestations of SLE among the study population.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
After 8th pulse	3	3	1	2	3	0	1	20	0	2	11	1	2	3	3	0	0	2	3	0
Before 1st pulse	18	29	32	28	31	20	12	34	24	27	27	32	30	21	32	19	27	24	32	26

Figure 2: CLASI Activity scoring in response to pulse therapy.

Cutaneous lupus area and severity index (CLASI)

The activity score of CLASI was between 12 and 34, out of a total score of 70 at the initiation of treatment. There was a fall in the CLASI activity scores in all the 20 patients at the end of 8 cycles of pulse therapy. The final CLASI activity score was 0 in 5 patients (25%). In 13 other patients (65%) the CLASI activity score recorded a marked fall to a score of less than 5. In 2 patients (10%) alone there was an activity score of more than 10.

The difference in the CLASI activity scores before the initiation of pulse therapy and after the completion of 8 pulses were analysed using the paired 't' test. The standard deviation (S.D) was 5.785. The standard error of difference (S.E) was 1.294. The final t value was 17.85.The probability of error (p value) for the given t values with a degree of freedom of 19 was less than 0.005. Since the probability of error was very low ($p < 0.05$), the difference in the CLASI activity before and after the pulse therapy was statistically significant.

Whereas the activity score showed significant improvement in all but two patients, the damage score showed a different picture. The damage score which measures the residual dyspigmentation and scarring showed an initial increase in some patients as the disease activity subsided and the malar and discoid rashes left

behind dyspigmentation and so did the mucosal erosions. The dyspigmentation took a long time to improve and seemed unrelated to the number of pulses. The overall cutaneous response in each patient as quantified by the CLASI was as shown in the Figure 2.

Photosensitivity

A history of photosensitivity was noted in all but one patient which is 95% of the study population. At the end of 8 cycles of pulse therapy, photosensitivity disappeared in all but 3 patients (15%).

Malar rash

The characteristic malar rash was present in 17 out of the 20 patients (85%). At the end of 8 pulses, there was complete disappearance of malar rash in 14 patients with percentage improvement of 82% as shown in Figure 3a and 3b.

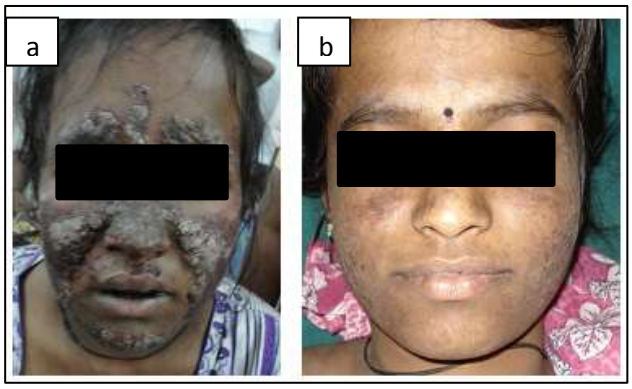


Figure 3: Malar rash- before the 1st pulse (3a) and after the 8th pulse (3b).

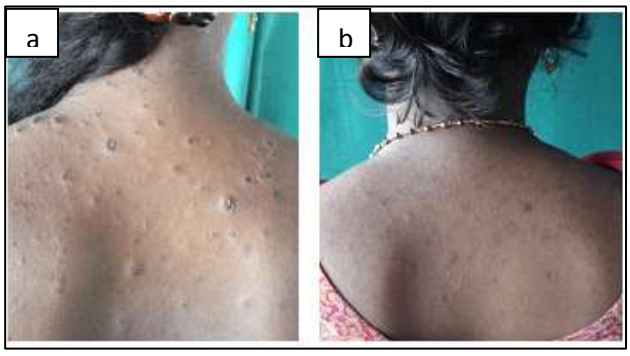


Figure 4: Discoid rash over back- before the 1st pulse (4a) and after the 8th pulse (4b).

Discoid rash

Discoid rash was the most common manifestation presenting in 100% of the patients at the start of pulse therapy. At the end of 8 pulses, 7 patients (35%) had complete disappearance of the discoid rash. In the rest, there was moderate improvement with lesions showing minimal scaling in 11 patients (55%). There was a persistence of discoid rash in only 2 patients (10%). Figure 4a & 4b and 5a &5b.

Figure 5: Discoid rash over the ear (Schuster's sign) - before the 1st pulse (5a) and after the 8th pulse (5b).

Oral erosions

At the initiation of the study, oral erosions were present in 18 out of the 20 patients (90%). At the end of 8 cycles of pulse therapy there were persistent erosions in only 2 patients with percentage improvement of 88% as shown in Figure 6a & 6b.

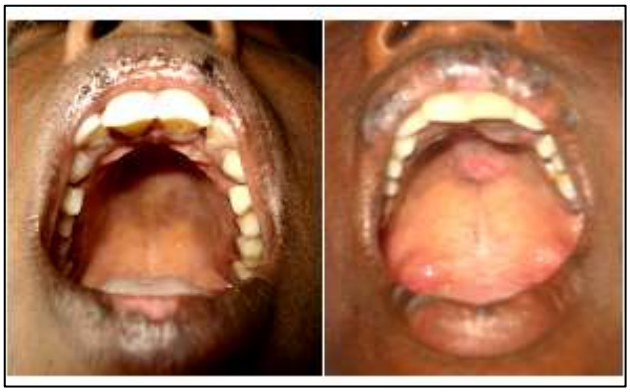


Figure 6: Oral erosions- before the 1st pulse (6a) and after the 8th pulse (6b).

Figure 7: Lupus hair- before the 1st pulse (7a) and after the 8th pulse (7b).

Alopecia

Alopecia was seen in 17 out of the 20 patients (85%). There was diffuse alopecia in all 17 patients, whereas lupus hair was seen in 6 patients. At the end of 8 cycles of pulse therapy, clinically appreciated alopecia was seen in 3 patients. Alopecia improved in 14 patients with a percentage improvement of 82 % as seen in Figure 7a & 7b.

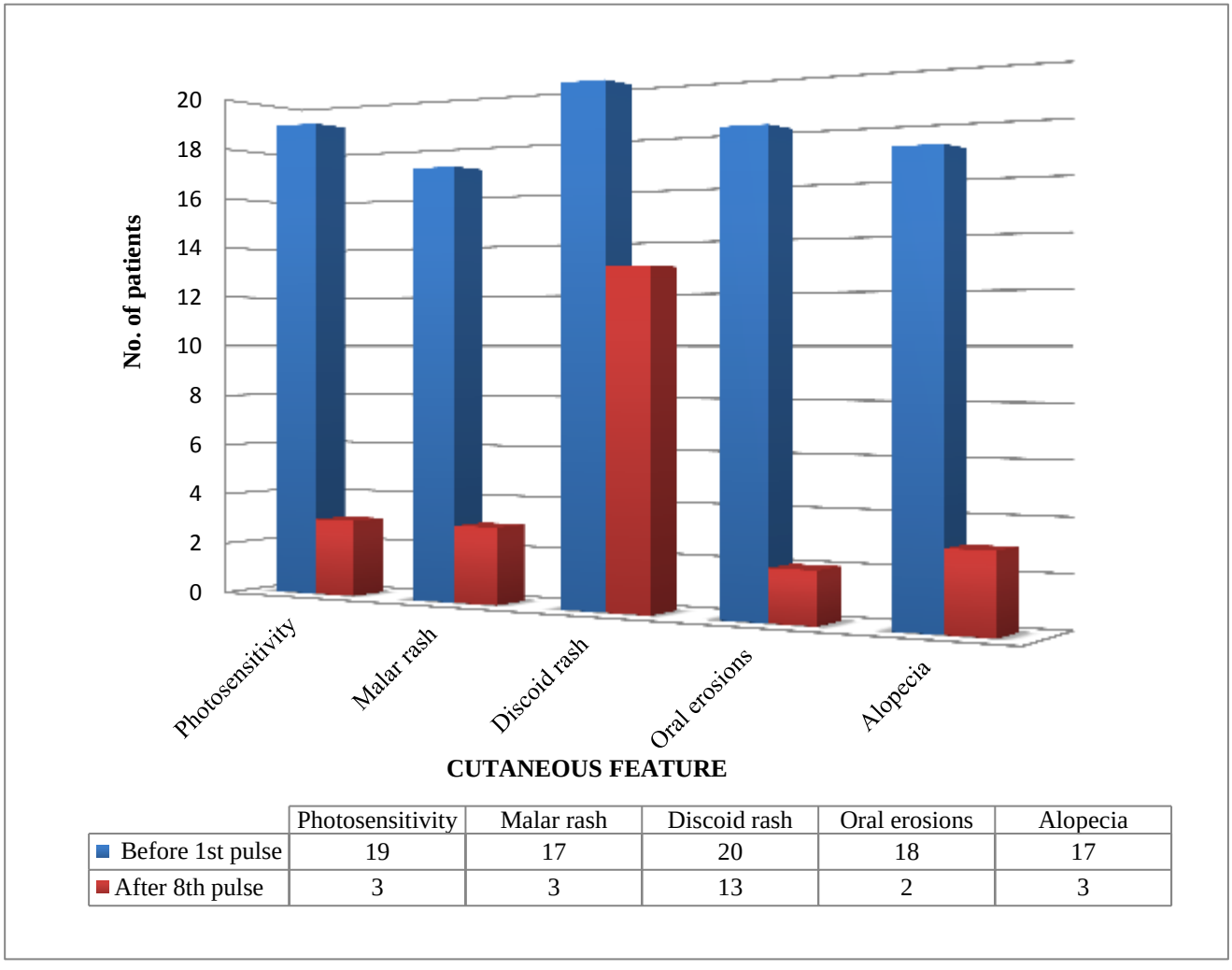
The overall improvement of individual cutaneous features with pulse therapy was represented graphically in Figure 8.

Fever

At the initiation of pulse therapy, fever in the absence of any focus of sepsis was recorded in all but 4 patients who comprise 80% of our study population. Fever in most cases was of low grade and intermittent in nature. With the completion of 8 pulses, fever was noted in 2 patients (10%). Both the patients initially became afebrile soon after the first pulse, but it reappeared after the 6th pulse in one patient and after the 7th pulse in another.

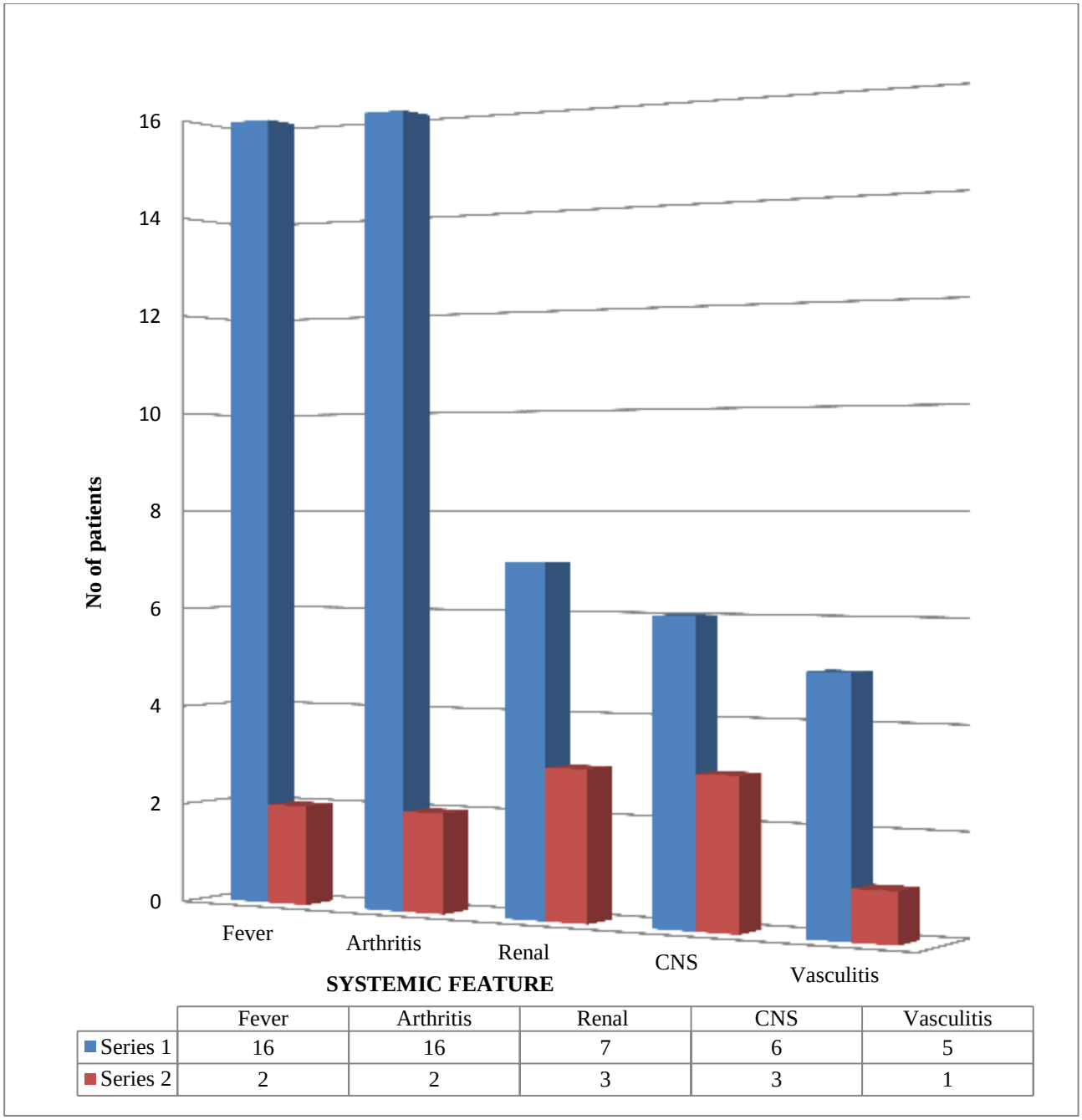
Systemic manifestations

All but 3 patients had systemic manifestations before the initiation which amounted to 85% of the study population. The most common systemic manifestation was joint involvement with non-erosive arthritis being reported in 80% (16 patients), followed by renal involvement in 35% (7 patients). 6 patients (30%) had neurological involvement, of which 5 of them had seizures whereas one patient had altered behaviour followed by seizures. There was vasculitis in 5 of the patients (25%) of which 2 patients (10%) had retinal vasculitis and presented with diminished vision. The rest 3 patients had vasculitic ulcers. There was serositis in one patient (5%). Similarly, pulmonary involvement with interstitial pneumonitis was reported in one patient (5%) before the start of pulse therapy. At the end of 8 cycles of pulse therapy, 5 patients (25%) continued to have systemic manifestations. Fever and arthralgia were present in 2(10%), renal and CNS involvement in 3 patients and vasculitis in 1 patient. One patient newly developed interstitial lung disease after 7 pulses. Improvement in systemic manifestations with pulse therapy is represented in Figure 9.



	Photosensitivity	Malar rash	Discoid rash	Oral erosions	Alopecia
Before 1st pulse	19	17	20	18	17
After 8th pulse	3	3	13	2	3

Figure 8: Improvement in cutaneous manifestations with pulse therapy.



	Fever	Arthritis	Renal	CNS	Vasculitis
Series 1	16	16	7	6	5
Series 2	2	2	3	3	1

Figure 9: Improvement in systemic symptoms with pulse therapy.

Anti dsDNA levels

All the patients except one (95%) showed positivity for anti dsDNA as measured by the immunofluorescence technique. The anti dsDNA values were quantified in serial dilutions. It was of low titres up to 1 in 40 in six patients (30%). In four patients (20%) there was a very high titre positivity of 1 in 1280. The other nine patients (45%) had moderate titres ranging from 1 in 160 to 1 in 640. After 8 cycles of pulse therapy there was a fall in titres in all patients excluding two (10%) whose titres remained at very high levels of 1 in 1280 dilutions. Anti dsDNA antibody became negative in 6 patients (30%). The fall in titres was by 2 to 4 folds in most other patients. Of these, 10 patients (50%) had low titres of up to 1 in 40 dilutions. 3 patients (15%) continued to have moderate values. Overall, 2 patients (10%) had a static titre of anti dsDNA antibodies. The rest (90%) showed a fall in titre. No patient showed increase in anti dsDNA antibody titres. The anti dsDNA levels before and after 8 pulses was statistically analysed using the paired‘t’ test. The mean of variance was 319; the standard error of the difference was 92.516. The final t value was 3.45. The p value for the given t values and degree of freedom was less than 0.005, hence the difference between the 2 groups was statistically significant. Hence there was a statistically significant fall in the anti dsDNA levels after 8 pulses.

Antinuclear antibodies (ANA)

The antinuclear antibody showed very high levels 1:1280 in 2 patients, high levels (>1:160) in 7, moderate levels (1:80) in 2 patients and low levels (1:40 & 1:10) in 10 patients. So at the start of pulse therapy 50% of patients had low levels, 10% of patients had moderate levels, high levels in 35% and very high levels in 10%. After 8 pulses ANA was negative in 4 patients (20%), low levels in 14 patients (60%), and moderate levels in 2 patients (10%). The most common pattern observed was rim or peripheral pattern in 9 patients (45%) followed by homogenous pattern in 8 patients (40%) and speckled pattern in 3 patients (15%). There was no absolute correlation between the disease activity and antinuclear antibody levels. Also the pattern of ANA did not influence the response to pulse therapy.

Erythrocyte sedimentation rate

At the initiation of pulse therapy ESR was elevated in 15 patients (75%). At the end of 8 pulses it remained elevated in 5 patients. The percentage improvement was 66%. The ESR values had good correlation with systemic disease activity than cutaneous disease activity.

Total leucocyte count

There was no significant decrease in total leukocyte count in any of the patients at the initiation of pulse therapy. There was no correlation with disease activity and total leukocyte count.

Duration taken for clinical remission

All the cutaneous features showed improvement with pulse therapy, showing improvement beginning from the first pulse itself. Photosensitivity started showing improvement after a minimum of 3 pulses. The average duration taken was around 5 months in 85% of the patients. Malar rash required between 2 and 5 pulses to disappear. In 15% it still persisted at the end of 8 pulses. The average time duration taken for improvement of malar rash was 3.5 months. Among the cutaneous lesions, oral lesions were the first to show improvement. It took a minimum of 1 and a maximum of 3 pulses for improvement. The average duration required was 2.3 pulses in 90% of the patients. Discoid rash showed improvement only by 8th pulse with persistence of minimal scaling of discoid rash over the concha in almost all patients. Alopecia started to improve after a minimum of 3 pulses. The time duration noted here is the duration taken for the beginning of regrowth of hair. The average number of pulses required was 5 in 70% of the patients.

Among the systemic manifestations, fever improved in all the patients after the first pulse. But in 2 patients it reappeared after the 6th and 7th pulses respectively. The arthralgia required a minimum of 2 to a maximum of 6 pulses to disappear in 87% of the patients who had non erosive arthritis at the beginning of treatment. The duration taken for clinical remission of the cutaneous and systemic manifestations in each patient is represented in Table 2.

Table 2: Duration taken for clinical remission.

Patient No	Photosensitivity	Malar rash	Discoid rash	Oral erosions	Alopecia	Fever	Joint pain
1	4	4	8+	3	4	1	3
2	5	3	8+	2	-	1	4
3	5	4	8+	3	5	1	2
4	6	4	8+	2	6	1	1
5	6	3	8+	2	7	1	6
6	4	4	6	-	6	1	-
7	5	4	8+	2	6	-	-
8	8+	8+	8+	4++	8+	6++	8+
9	3	2	6	1	4	1	6
10	6	4	8+	2	3	1	5
11	8+	8+	8+	6++	8+	7++	7++
12	4	4	8+	3	7	1	4
13	6	5	8+	2	3	1	5
14	8+	8+	8+	-	6	1	6
15	6	3	8+	1	6	1	-
16	-	-	6	2	6	1	-
17	7	4	7	1	4	1	4
18	5	5	8+	2	-	-	7
19	6	4	8+	3	6	1	4
20	6	4	6	2	3	1	3

+: Persistence of activity; ++: Relapse of activity.

Adverse effects

The overall incidence of adverse effects was low. The commonest side effect noted was menstrual irregularities in 4 patients. There was oral candidiasis in 5 patients. Pyogenic skin infections were noted in 2 patients. Urinary tract infections were observed in 3 patients. One patient developed acneiform eruptions after the 3rd pulse. There was a fall in platelet count in 2 patients, following which pulse therapy was withheld for 2 weeks and continued after the values normalised. None of the patients required platelet transfusion. There was darkening of complexion reported in 1 patient.

Duration of pulse therapy required

Among the 20 patients, 7 patients who had a CLASI score of 0-2 with no systemic manifestations at the end of 8 cycles were taken to have clinical remission. 6 patients who had a CLASI score of 3-10 and also had slightly elevated anti dsDNA titres were given a total of 10 pulses to achieve clinical remission. Patient no. 1 who had pulmonary disease and patient no.6 who still had neurological involvement and a high titre of anti dsDNA of 1 in 160 required an additional of 6 more pulses to achieve remission. Patient no.11 received total of 18 pulses. At the time of completion of the study, among the eighteen patients who had achieved clinical remission, the mean number of pulses required to achieve remission was 9. Patient no.18 was continuing treatment at 11 pulses. Patient no. 8 defaulted after the 9th pulse. Once the patients attained remission, they were considered to have completed phase I. A further number of 6 pulses were given in phase II. None of the patients in phase II showed relapse of disease activity at the time of completion of study.

DISCUSSION

The mean age of our patients was much less than the average age reported in literature. Also, there was more number of female patients in this study compared to the other studies.

The most common skin manifestation in our study was discoid rash (100%) whereas in other studies it occurred in a frequency ranging from 25-50%.[5,8,9] This discrepancy may be due to the study being conducted in the department of dermatology and only those patients with skin manifestations being included in the study. The most common manifestation in other studies was photosensitivity, which was the second most common (90%) in our study, along with oral erosions.[5,8] Malar rash and hair loss were noted in 85% each whereas in other studies it ranged from 70-75%. Among the systemic manifestations, arthritis was reported in 80% of our patients compared to 57% in other Indian studies and 90% reported in western literature.[5,8,9] Renal involvement was seen in 35% in our study in concordance with other studies where it was between 21.4%-67%.[4]

The cutaneous feature to show an early response was oral erosions which resolved after a mean of 2.3 pulses in our study. A similar figure of 1-3 pulses has been reported by Dhabhai et al.[8] The percentage improvement was 88%. Malar rash took an average of 3.5 pulses for resolution, similar to that observed by Dhabhai et al (2-5 pulses).[8] Discoid rash took a longer duration, the earliest being 6 pulses for resolution. In 75 % of our patients it was still persistent with minimal scaling without any erythema at the end of 8 pulses. Previous studies also indicate that discoid rash was difficult to treat taking anywhere between a minimum of 2 pulses to a maximum of 16 pulses for complete resolution. Alopecia responded after 2-7 pulses at a mean of 5 pulses. Statistics by Dhabhai et al also report similar figures of 2-6 pulses for resolution, with the longest duration required being 17 pulses in one case.[8]

Similar to previous study published by Dhabhai et al and Sudip et al, fever was the earliest to respond.[8,9] In most cases it resolved with one pulse, which was same as the duration observed in other studies. The percentage improvement in our study with one pulse was 90% which is similar to that seen by Sudip Das et al.[9] The number of pulses taken for remission of arthritis showed a wide variation, responding after the very first pulse in one patient whereas in some it took up to 6 pulses. The mean duration in most cases was 4.2 pulses. In the Dhabhai et al study, the mean duration was also a similar 4 pulses.[8] The range was from 2-11 pulses. Of the 7 patients who showed renal involvement in our study, there was an initial favourable response in all of them with renal parameters and 24 hour urine protein normalising after 1-3 pulses. Out of these at least 3 patients showed exacerbation of renal disease. In the previous study, nephritis was reported only in fewer patients (4) with persistence of nephritis in 75% even after 12 pulses. The seizures showed a remission after 5 pulses in this study whereas remission was reported after 8 pulses by Dhabhai et al.[8]

The anti dsDNA antibodies became negative in 35% of patients after the 8 pulses which was similar to the figures reported by Dhabhai et al where 33% showed negative anti dsDNA after 8 pulses. The exact number of pulses required for the anti dsDNA levels to become negative in each patient could not be calculated in this study, since the measurements were taken at long intervals- i.e. at the initiation of pulse therapy, after 8 pulses and after 12th pulse in those who continued to have disease activity. In the previous studies the minimum duration to achieve a negative anti dsDNA level was 4 pulses. In a nutshell, though subjective improvement was reported beginning with the first pulse itself, objective improvement of most of the cutaneous manifestations were seen commonly around the fourth pulse. The serological parameters improved after 8 pulses in the majority of the patients.

The overall adverse effect profile observed in this study was low. Common side effects of pyogenic skin

infections and candidiasis were similar to that noted in previous studies. Generalised pigmentation of skin was reported in one patient which was also observed by Pasricha et al and Dhabhai et al.[3,8] Acneiform eruptions were seen in one patient in our study which was not reported in the previous studies. Pasrisha et al have reported generalised pruritus which was not seen in our study.[3] Menstrual irregularities were seen in 35% of our patients. Previous studies have not mentioned any reports of menstrual irregularities.[9] Dhabhai et al have reported cardiac arrest proving fatal in one patient.[8] No such adverse effects were noted in any of our patients.

CONCLUSION

The conclusions derived from this study are that dexamethasone cyclophosphamide pulse therapy is an effective therapeutic option for treatment of SLE. Rapid induction with prolonged remission of SLE is achieved with pulse therapy. Pulse therapy is safer than oral steroids with respect to decreased hypothalamo pituitary axis suppression and decreased osteopenia. Though the duration of pulse therapy is arbitrary, depending upon the degree of remission achieved in individual patients, the mean duration required would be 9 pulses in SLE as per this study. An extension of pulse therapy by another 6 cycles even after clinical remission may be required with an aim to sustain the duration of clinical remission.

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