Original Article

Pulse versus Oral Methylprednisolone Therapy in Pemphigus Vulgaris

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Background: **Although corticosteroids have dramatically altered the prognosis of patients with pemphigus vulgaris, morbidity and mortality from systemic corticosteroid side-effects remains high. High-dose intravenous methylprednisolone has been used successfully in blistering diseases to avoid the complications of long-term orally-administered glucocorticoids. The objective of this study was to compare the effectiveness and side-effects of oral and pulse steroid therapy in the treatment of pemphigus vulgaris.**

Methods: **One hundred and twenty-three patients with pemphigus vulgaris were categorized into two groups of study and control according to the disease severity and patient's preferred method of treatment. The study group included 36 males and 36 females. The control group included 26 males and 25 females. The mean ± SD age of the two groups was 42.6 ± 11.9 and 46.9 ± 12.8 years, respectively. The mean ± SD duration of the disease was 6.8 ± 1.1 months in new cases (n = 45) and 25.9 ± 26.0 months overally in the study group; it was 7.2 ± 1.8 months in new cases (n = 30) and 28.4 ± 24.6 months overally in the control group. During the induction phase, we performed pulse therapy with methylprednisolone in three consecutive monthly courses. Each course included 1000 mg intravenous methylprednisolone for 4 days plus 500 mg intravenous cyclophosphamide for 1 day. In this phase, the control group received 1 – 2 mg/kg/day oral prednisolone for 28 days plus 1.5 mg/kg/day azathioprine. All patients were followed for at least 12 months during which period, clinical response, relapse rate, and side-effects were evaluated.**

Results: **Pulse intravenous methylprednisolone with cyclophosphamide was generally safe and well-tolerated. Therapeutic responses of skin and mucosal lesions, rates of complete remission and relapse, and major organ-specific complications were similar in both groups. Significant statistical differences existed in total orally-administered prednisolone in one year, admission duration, and annual weight increments between the two groups ($P < 0.05$).**

Conclusion: **Considering the side-effects of long-term oral steroids, hazards of obesity, and complications of long-term hospitalization, pulse methylprednisolone could be considered in patients who have problems with long-term admissions or with high-dose oral steroid usage, and also in obese patients.**

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Introduction

Pemphigus vulgaris is a chronic fatal blistering disorder with production of antibodies against desmosomal proteins, 130 KD desmoglein 3.[1] The histologic changes include acantholysis and intraepidermal bullae formation.

With newer therapeutic modalities, the most important of which include systemic steroids[2] with or without immunomodulation, the mortality rate of the disease has been significantly decreased.[2 – 4]

Although systemic steroids are the cornerstone of therapy, there is no consensus on the treatment of this disease.[5 – 8] Long-term use of intermediate to high doses of oral steroids is the most common method of systemic administration of steroid

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therapy.[2]

Because of relapse, long-term hospitalization, and complications of both the disease itself and the therapeutic methods,[9 – 15] more appropriate and effective treatments are needed.

Recently, a few dermatologic and non-dermatologic disorders have been successfully controlled by high doses of intravenous steroids.[16 – 21] A number of recent reports showed that intravenous high-dose steroid pulse therapy such as methylprednisolone or dexamethasone is an effective method for the control of pemphigus vulgaris.[22 – 28] The objective of such treatments is to get a quicker and stronger efficacy and to decrease the need for long-term administration of glucocorticoids in order to face fewer long-term steroid-related adverse effects.[17]

This clinical trial was conducted to compare the intravenous steroid pulse therapy with the conventional oral steroid therapy of pemphigus vulgaris.

Patients and Methods

The study was conducted on 123 patients with pemphigus vulgaris at the Departments of Dermatology of Bu-Ali and Loghman Hakim Hospitals from February 1997 through January 2003.

Patients were categorized into two groups of study and controlled according to the disease severity and patient's preferred method of treatment. The study group included 36 males and 36 females. The control group included 26 males and 25 females.

The clinical suspicion of the skin and/or mucosal involvements was confirmed by histology and immunofluorescence findings.

Patient selection had no limitation for gender, race, age, and previous therapeutic modalities for pemphigus vulgaris. Patients who had received previous steroid pulse therapy for any reasons or had major organ dysfunction were excluded from the study. Patients were divided into two groups of intravenous steroid pulse therapy (study group) and conventional oral steroid therapy (control group). During the induction phase of treatment, the study group patients received three courses of pulse therapy with one month intervals. Each course included 500 mg cyclophosphamide (diluted in 200 mL DW5%) which was infused in one hour on the first day and 1000 mg methylprednisolone (diluted in 500 mL DW5%), which was infused within 3 – 4 hours, in all four days of each courses of pulse therapy. The vital signs of patients were checked every 15 minutes during the treatment; each hour for the first six hours; and then every six hours for 12 hours after the completion of each infusion of pulse therapy. After the first course of pulse therapy, patients received pulses of 50 mg/day cyclophosphamide plus 30 mg/day oral prednisolone. The study group patients were discharged from the hospital one day after the completion of each course of pulse therapy, if no problem was encountered. The steroid dose administered was tapered down in this group according to the following protocol: 30 mg/day, 25 mg/day, and 20 mg/day, each for one month; 17.5, 15, and 12.5 mg/day, each for two months; 10 mg/day for 3 months; and 7.5 and 5 mg/day, each for six months. Discontinuation of the treatment depended on patients' clinical status and direct immunofluorescence (DIF). If not possible, we continued steroids at a dose of 5 mg/day for longer periods.

The control group patients received 100 – 150 mg/day azathioprine plus 1 – 2 mg/kg/day prednisolone during the induction phase. The dose of azathioprine was decreased to 40 mg/day after four weeks. Then, if there was no other medical indications for hospitalization, the patient was discharged from the hospital. Oral prednisolone dosage was tapered down 5 mg/day until it reached 20 mg/day. Then, it was tapered similar to the pulse group.

Before the onset of treatment, for both groups EKG, chest X-ray, complete blood count, and a cardiology consultation to exclude those with heart disease, were requested.

For the study group, laboratory examinations were repeated six hours after the completion of each pulse, one week thereafter, and monthly following the pulse therapy.

For the control group, laboratory examinations were performed weekly during their hospitalization and monthly, thereafter.

Patients were classified on the bass of theseverity of skin lesions into: intact; mild <10% skin involvement; moderate with 10 – 35% involvement; and severe >35% skin involvement of total body surface area. We classified the mucosal lesions as intact, defined as no mucosal involvement; mild with only oral involvement; moderate with involvement of two mucosal

surfaces; and severe with involvement of more than two mucosal surfaces. Also, patients were categorized according to their response to treatment during the induction phase and follow-up time, into three groups: responders who had good healing with no new lesions; nonresponders who had no new lesions but had poor healing; and resistants who had poor healing and developed new mucosal and/or cutaneous lesions.

All patients were visited every month for at least 12 months. The mean ± SD follow-up period was 17 ± 3.2 months. At each visit, subjective complaints, complete physical examinations including vital signs and weight, urinalysis, complete blood counts, and renal and liver function tests were recorded. Appropriate medical the consultations were done according to patients' complaints, physical or laboratory findings during the induction phase, and the follow-up time. As an example, a patient with a systolic blood pressure above 140 mmHg systoic or diastolic pressure of 85 mmHg, was referred to a cardiologist for further evaluation. So gastrointestinal problems were rechecked by a gastroenterologist, ophthalmologic complaints by an ophthalmologist, and mood disorders by a psychiatrist.

A relapse was defined as the appearance of more than five new skin and/or mucosal lesions within a period of three days; Tzanck smears, biopsy specimens, and DIF were always performed after a relapse. Indirect immunofluorescence was not performed due to lack of facilities. These patients were treated by doubling the steroid dose administered at the time.

Statistical analysis

Data analyses were done using χ^2 or Fisher exact test, when appropriate, and Student's *t*-test, with SPSS version 11.5. A *P* value less than 0.05 was considered significant.

Results

One hundred and twenty-three patients were divided into two groups; 72 in the study and 51 in the control groups. In the study group, 36 patients were male and 36 were female. The mean ± SD age of the patients was 42.6 ± 11.9 (range: 24 – 70) years. The mean ± SD duration of disease was 6.8 ± 1.1 months in the new patients (n = 45) and 25.9 ± 26.0 months, overally. Because of pemphigus vulgaris, 27 patients (known cases) had been treated previously at least once with oral prednisolone with or without adjuvants including azathioprine (n = 21), cyclophosphamide (n = 4), cyclosporine (n = 1), intravenous immunoglobulin (n = 4), plasmapheresis (n = 1), and gold (n = 1). The mean ± SD prednisolone dosage before the beginning of the study was 8.1 ± 12.8 mg/day.

According to the severity of skin lesions which were explained earlier, two (2.7%) patients had intact skins, 29 (40.2%) mild, 35 (48.6%) moderate, and six (8.3%) had severe skin lesions. Ten (13.8%) patients had intact mucosa, 29 (40.2%) mild, 23 (31.9%) moderate, and ten (13.8%) had severe mucosal involvements.

In the control group, 26 patients were males and 25 were females. The mean ± SD age of the patients was 46.9 ± 12.8 (range: 23 – 71) years. The mean ± SD duration of disease in this group was 7.2 ± 1.8 months in new patients (n = 30) and 28.4 ± 24.6 months, overally. Because of pemphigus vulgaris, 21 patients (known cases) had been treated previously at least once with prednisolone alone or with adjuvants including azathioprine (n = 13), cyclophosphamide (n = 5), cyclosporine (n = 3), and intravenous immunoglobulin (n = 1). The mean ± SD prednisolone dosage before the beginning of the study was 9.7 ± 13.8 mg/day. There were four (7.8%) patients with intact skins, 18 (35.2%) with mild, 23 (45%) moderate, and 6 (11.7%) with severe skin involvements. There were four (7.8%) patients with intact mucosa, 26 (50.9%) with mild, 13 (25.4%) moderate, and eight (15.6%) patients with severe mucosal involvements.

There were no significant differences between the two groups. Therapeutic responses of skin and mucosal lesions in the study and control groups are summarized in Table 1.

Relapse occurred in nine (12.5%) patients of the study (six known and three new cases) and in seven (13.7%) of the control (five known and two new cases) groups ($P > 0.05$). The mean ± SD time interval of relapse was 8.8 ± 1.8 months after the onset of therapy in the study group and 8.2 ± 2.1 months in the control group ($P > 0.05$).

No mortality was seen in the study group but one patient in the control group died of septicemia within the first month of study.

The mean ± SD total dose of oral prednisolone received during one year (including induction phase and follow-up) in the study and control groups was 5916.3 ± 452.1 mg and 11087 ± 1533.1

Table 1. Therapeutic response of the study and control groups.

Groups	Therapeutic site	Response	Responder *n* (%)	Nonresponder *n* (%)	Resistant *n* (%)	Total *n*
Pulse	Skin	Total	65 (92.8%)	4 (5.7%)	1 (1.4%)	
		New case	41	3	0	70
		Old case	24	1	1	
	Mucosa	Total	51 (82.2%)	8 (12.9%)	3 (4.8%)	
		New case	33	5	2	62
		Old case	18	3	1	
Control	Skin	Total	38 (80.8%)	8 (17.0%)	1 (2.1%)	
		New case	25	5	0	47
		Old case	13	3	1	
	Mucosa	Total	34 (72.3%)	10 (21.2%)	3 (6.3%)	
		New case	20	6	1	47
		Old case	14	4	1	

mg, respectively ($P < 0.01$).

The mean ± SD weight increment during one year in the study and control groups was 2.2 ± 0.9 and 5.4 ± 1.2 kg, respectively ($P < 0.01$). The mean ± SD admission duration in one year in the study and control groups was 14.3 ± 1.9 and 38.0 ± 8.0 days ($p < 0.01$), respectively.

Complication rates during the induction phase and follow-up are shown in Table 2. No significant statistical differences were found between the two groups in terms of rate of complications during the induction phase and follow-up. However, the total incidence of muscle weakness in the control group was significantly higher than the study group ($P < 0.01$).

Discussion

In spite of the effectiveness of oral corticosteroids in the treatment of pemphigus vulgaris, development of severe side-effects like obesity, osteoporosis, ocular problems, and impaired ACTH reserve limits their use.[15, 16] In order to decrease the side-effects and perhaps to obtain therapeutic effects that are different from those of conventional doses of oral prednisolone,[19 – 21, 29] pulsed administration of high doses of corticosteroids has been used successfully in the treatment of pemphigus vulgaris and has been found to be of lower risk in terms of significant adverse events, if contraindications are carefully taken into account.[15, 19]

Unfortunately, there are several aspects that are actually not still clear enough. First, we need a more objective method to quantify the severity of the disease before and during the course of the treatment. Recent studies have suggested protocols to assess the oral and systemic lesions in pemphigus vulgaris by monitoring the specificity and titer of autoantibodies along with the clinical

Table 2. Complication rates during the induction phase and follow- up in the study and control groups.

Organ-specific complications		Induction phase	Follow-up	Induction phase	Follow-up
Urinary tract	Pyuria	6	15	2	13
	Hematuria	2	4	1	2
Psychology	Anxiety	6	5	8	6
	Depression	2	2	5	1
Cardiovascular	Hypertension	8	15	3	6
	Ischemic heart dis.	5	4	4	3
	Arrhythmia	3	3	3	2
Gastrointestinal	Epigastric pain	8	5	10	5
	Dyspepsia	3	5	7	4
	Bleeding	2	1	1	3
	Peptic ulcer	2	1	2	2
Musculoskeletal	Pain	2	1	3	2
	Weakness	6	3	9	7
Ocular	Glaucoma	1	2	1	3
	Conjunctivitis	7	4	5	6
Diabetes mellitus		5	6	3	7
Flushing		4	1	1	1

features.[30, 31] Second, pulse corticosteroid usually seems to result only in short-term relief from the disease and most likely needs continued administration of oral corticosteroids.[19] Third, to evaluate the pulse vs. conventional oral therapy of pemphigus vulgaris, conduction of double-blinded randomized clinical trials are needed. At last, whether this approach results in an overall reduction in side-effects, relapses or mortality, or increasing the incidence of remissions are unknown. In pemphigus, the largest experience has been made by using intravenous mega-doses of dexamethasone or methylprednisolone and cyclophosphamide. Furthermore, the addition of an oral immunosuppressive agent, such as cyclophosphamide or azathioprine has been used to reduce the overall steroid dose.[28] Nevertheless, these drugs have their own side-effects including myelosuppression, hemorrhagic cystitis, infertility, and cancer of bladder that have been observed with azathioprine[32 – 34] and cyclophosphamide.[35, 29]

Considering these findings, our study included two groups of patients who had no significant differences in gender, duration of their diseases, previous therapies, severity of skin and mucosal lesions, laboratory findings, and underlying problems.

During the study, we found no difference in the rates of complete remission, relapse, or the time interval of the relapse. Major organ-specific complications and therapeutic responses of skin and mucosal lesions within each severity were not significant too.

We did not find any study that compares these two therapeutic methods in the treatment of pemphigus vulgaris. Only a few case series had been reported on pulse therapy. The largest one[34] included 255 Indian patients with the disease treated with dexamethasone plus cyclophosphamide pulse (DCP) at 4-weekly intervals. Low-dose oral cyclophosphamide (50 mg daily) was administered between pulses. Pulsing continued until clinical remission and was followed by a consolidation phase of a further six DCP courses. Oral cyclophosphamide was then continued alone and if there were no relapses after one year, all medications were discontinued. In this study, the overall rate of complete remission was 72%, resistance to DCP was 3.4%, and mortality was 4%. These values were 92.8%, 1.4%, and zero, respectively in our trial. In addition, 62% of Indian patients experienced amenorrhea/azoospermia; hemorrhagic cystitis occurred in 0.6% (2 patients). These seem to be due to longer duration and higher doses of intravenous cyclophosphamide. In comparison to these side-effects, we found no definite cases of amenorrhea/azoospermia or hemorrhagic cystitis. Only transient hematuria and temporary disruption of menstruation were seen.

Another study[25] reported success rate of 88% for DCP in 50 Indians with pemphigus vulgaris.

One European study[28] reported complete remission in 12 patients with severe oral pemphigus vulgaris treated with three courses of 3 – 5 days of methylprednisolone pulse therapy plus oral azathioprine.

Werth has compared these two therapeutic protocols.[27] It was only a retrospective study that included two heterogeneous groups of patients with completely different therapeutic regimens for each patient. It included nine patients who had received pulse therapy and six patients who had received conventional treatment. Some received only one course of pulse therapy, while others received two courses. This study showed the superiority of pulse therapy over conventional treatment.

We observed significant differences in the total amount of orally-administered prednisolone, weight gain, and admission duration between the two groups.

Since it has been inferred that the most side-effects of steroids are due to the long-term usage of intermediate to high doses of oral steroids,[17] using the pulse therapy method can probably reduce the incidence of oral steroids side-effects in long-term.

Regarding the positive relationship between obesity and other major diseases,[36] and considering the lower chance of developing overweight in the pulse therapy method, pulse therapy could be applied as an alternative treatment, specially in patients who are at risk of these diseases.

Reducing the duration of long-term hospitalizations is beneficial for both the patient and society as it decreases economic costs and the complications of long-term hospitalizations.

Therefore, pulse therapy could be considered, at least, for pemphigus vulgaris patients with limitations of admission duration who cannot tolerate high-dose oral steroid. Nonetheless, more studies are needed to confirm this.

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