Pulse therapy in pemphigus: report of 11 cases*

Pulsoterapia em pênfigos: relato de 11 casos

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Abstract: In this study, five cases of pemphigus vulgaris and two cases of pemphigus foliaceus were treated with cyclophosphamide pulse therapy associated with prednisone, resulting in the need for a smaller maintenance dose of prednisone. In three cases of pemphigus vulgaris and one case of pemphigus foliaceus, dexamethasone and cyclophosphamide pulse therapy associated with prednisone helped the lesions to heal more rapidly. Neither treatment however prevented the recurrence of the disease. Amenorrhea, myelotoxicity and Stevens-Johnson syndrome were among the cyclophosphamide side effects. All the patients treated with prednisone experienced known side effects.
Keywords: Cyclophosphamide; Dexamethasone; Pulse therapy; Pemphigus

Resumo: Neste estudo, cinco casos de pênfigo vulgar e dois casos de pênfigo foliáceo foram submetidos à pulsoterapia com ciclofosfamida associada à prednisona resultando em ação poupadora na dose de manutenção de prednisona. Em três casos de pênfigo vulgar e um caso de pênfigo foliáceo tratados com pulsoterapia dexametasona/ciclofosfamida associada à prednisona houve resolução mais rápida das lesões. Nenhum destes tratamentos impediu a recurrência da doença. Amenorreia, mielotoxicidade e síndrome de Stevens Johnson foram observados com a ciclofosfamida. Em todos os pacientes ocorreram efeitos colaterais conhecidos da prednisona.
Palavras-chave: Ciclofosfamida; Dexametasona; Pulsoterapia; Pênfigo

Drug therapy for pemphigus is generally based on high-dose systemic corticotherapy. The results of our previous studies showed that daily oral prednisone at 1-2mg/kg (maximum dose = 120mg/day) produced good initial control of pemphigus vulgaris (PV) and pemphigus foliaceus (PF), without increasing the morbidity linked to these diseases.[1,2]

Indian authors have proposed treating pemphigus using dexamethasone and cyclophosphamide pulse therapy with oral cyclophosphamide between pulses.[3,4] In two of our early publications on this subject, referring to a series of different cases, we reported the use of prednisone between pulses as part of the scheme we developed, unlike the treatment proposed by the Indian authors.[5,6]

In the present observational, retrospective and cross-sectional study, we used a new series of PV and PF patients hospitalized in the dermatology ward of the Clementino Fraga Filho University Hospital/UFRJ in Rio de Janeiro between 2005 and 2011. The study aimed to evaluate the therapeutic results and effects of cyclophosphamide and dexamethasone-cyclophosphamide pulse therapies associated with oral prednisone between pulses.

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Inclusion criteria for cyclophosphamide pulse therapy:

- Adults of both genders with histopathological confirmation of PV and PF diagnoses through skin biopsy and/or oral mucosa
- No response to daily oral prednisone at 1-2mg/kg/day for 30 days.
- ≥ 40mg/day maintenance dose of prednisone.
- Ineffectiveness of azathioprine.
- Drug reduction leading to disease recurrence.
- Severe hypertension; uncontrolled diabetes.
- Aseptic necrosis of the femoral head; psychosis.

Pre-pulse laboratory tests: blood count, biochemistry and urine sediments.

Cyclophosphamide regime:

- Dose: 600mg/m^2 of body surface in 200ml of 5% glucose given intravenously in one hour.

Ondansetron:

- Dose: 8mg in 20ml of 0.9% saline solution given intravenously during five minutes before cyclophosphamide.
- Rigorous oral rehydration from 24 hours before to 36 hours after drug application.
- Pulse therapy every three weeks.
- Criteria for suspension: leukopenia (leukocytes< 3000/μl); thrombocytopenia (platelets <100000/μl); erythrocytes in urine sediments (>10/μl).

Treatment phases:

1st: complete remission of skin lesions and partial remission of oral mucosal lesions (three active lesions);
2nd: reduction of oral prednisone to 20mg/day (10mg every ten days);
3rd: discontinuation of pulse therapy;
4th: regimen of oral prednisone withdrawal every six months (20mg to 15mg to 10mg to 5mg to 2.5mg).

Five PV and two PF patients underwent cyclophosphamide pulse therapy associated with prednisone. The treatment was suspended because of myelotoxocity (case 4) and Stevens-Johnson syndrome (case 5). At follow-up of 2-3 years, a 20mg/day maintenance dose of prednisone was applied in three cases. The number of pulses ranged from three to nine. There was recurrence in all cases: in the oral mucosa in PV patients (5 lesions) and on the face in PF patients (10 lesions) (Table 1).

Our results (Table 1) showed that cyclophosphamide exerted a sparing action on the corticosteroid (prednisone), with patients needing lower maintenance doses of prednisone. However this did not prevent relapses.The side effects related to cyclophosphamide were amenorrhea, myelotoxicity and Stevens-Johnson syndrome; the last two ones prevented the continuation of cyclophosphamide pulse therapy.

TABLE 1: Pulse therapy with cyclophosphamide

Case	Age	Gender	Diagnosis	Dose of prednisone (pre-pulse)	Number of pulses	Follow-up			
						Period of time	Dose of prednisone	Recurrence	Location
1	45	F	PV (skin + mucosa)	80mg/day	3	3 years	20mg	yes	oral mucosa
2	50	F	PV (skin + mucosa)	60mg/day	5	2 years	20mg	yes	oral mucosa
3	60	F	PV (skin + mucosa)	110mg/day	6	2 years	20mg	yes	oral mucosa
4	59	F	PV (skin + mucosa)	120mg/day	3	myelotoxicity			
5	31	F	PV (skin + mucosa)	60mg/day	1	Stevens-Johnson syndrome			
6	59	F	PF	110mg/day	2	2 years	∅	yes	face
7	18	M	PF	60mg/day	9	1 year	40mg	yes	face

PV = pemphigus vulgaris **PF =** pemphigus foliaceus **F =** female **M =** male **∅ =** no prednisone

The most common side effects related to prednisone were: hyperglycemia, leukocytosis, weight gain, cushingoid features, hypertension and subcapsular cataract.

Comparisons with other data were not possible given the differing methodological approaches such as: inclusion and exclusion criteria, initial doses of prednisone and outcome parameters.[7-10]

Inclusion criteria for dexamethasone and cyclophosphamide pulse therapy:

- Adults of both genders with histopathological confirmation of PV and PF diagnoses through skin biopsy and/or oral mucosa.
- Severe PV (skin + mucosa): large number of lesions; secondary infection; lesions in areas of venous punctures; poor clinical condition.
- Progressive cutaneous disease (PV and PF).
- Rebound caused by the withdrawal of oral corticosteroid dosage.
- Non-control even with a dose increase of prednisone.

Pre-pulse laboratory tests: blood count, electrolytes, urea, creatinine, glucose, amylase, urine sediments, fecal parasitological, electrocardiogram, chest radiography and ophthalmological examination.

- Dose: 100mg in 500ml of 5% glucose given intravenously in two hours.
- Total: three pulses (one pulse/day).
- Blood pressure and pulse rate every 15 minutes during infusion.
- Interval: every two or three weeks.
- Cyclophosphamide on the first or second day of dexamethasone.
- Criteria for suspension: hypertensive crisis, dyspnea, palpitations, chest pain, chills, sweating, increased amylase.

Treatment phases:

1st: complete remission of skin lesions and partial remission of oral mucosal lesions (three active lesions);
2nd: discontinuation of dexamethasone, maintenance of cyclophosphamide;
3rd: reduction of oral prednisone to 20mg/day (10mg every ten days);
4th: discontinuation of pulse therapy with cyclophosphamide;
5th: regimen of oral prednisone withdrawal every six months (20mg to 15mg to 10mg to 5mg to 2.5mg).

Three PV and one PF patients underwent dexamethasone cyclophosphamide pulse therapy associated with prednisone.

Our results demonstrated that dexamethasone and cyclophosphamide pulse therapy interrupted the emergence of bullae and promoted faster involution of the lesions, but without preventing the recurrence of the disease. The number of cyclophosphamide pulses varied between 8 and 14 (Table 2). Elevation of amylase in one case was due to dexamethasone, thereby ruling out the continuation of dexamethasone pulse therapy.[9] Comparisons with the literature data was more difficult on account of the different methodologies employed.[7-10]

In all PV and PF schemes, variables such as the natural course of the disease and its severity and refractoriness cannot be discarded. Both treatments had a similar profile with regard to relapses. ❑

TABLE 2: Pulse therapy with dexamethasone + cyclophosphamide

Case	Age	Gender	Diagnosis	Dose of prednisone (pre-pulse)	Number of pulses		Follow-up			
					Dexamethasone + Cyclophosphamide	Cyclophosphamide	Period of time	Dose of prednisone	Recurrence	Location
8	34	M	PV (skin + mucosa)	110mg/day	8	6	1year	50mg	no	-
9	52	F	PV (skin + mucosa)	120mg/day	2	8	2 years	2.5mg	yes	oral mucosa
10	49	M	PV (skin + mucosa)	90mg/day	8	1	2 years	20mg	yes	nasal dorsum
11	25	M	PF	120mg/day	3	5	3 years	15mg	yes	trunk and upper limbs

PV = pemphigus vulgaris **PF =** pemphigus foliaceus **F =** female **M =** male

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