Pediatr Nephrol (1994) 8: 1–3

Pediatric Nephrology

Original article

Intravenous pulse cyclophosphamide – a new regime for steroid-resistant minimal change nephrotic syndrome

Ravi Elhence, Sanjeev Gulati, Vijay Kher, Amit Gupta, and R. K. Sharma

Department of Nephrology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow – 226001, (U. P.) India

Received August 21, 1992; received in revised form July 2, 1993; accepted July 9, 1993

Abstract. The treatment of steroid-resistant minimal change nephrotic syndrome (MCNS) continues to pose a therapeutic challenge. We conducted a randomised prospective controlled trial to evaluate the efficacy of IV cyclophosphamide compared with oral cyclophosphamide in 13 children with biopsy-proven steroid-resistant MCNS. All 7 patients receiving IV cyclophosphamide achieved remission; this was sustained in 4 patients, while 3 relapsed. However, even these 3 patients subsequently became steroid sensitive. Of the 6 patients who received oral cyclophosphamide, 2 dropped out, 1 responded and 3 children continued to remain steroid resistant. The children who received IV cyclophosphamide had more sustained remissions, longer periods without proteinuria and fewer significant side effects; this was achieved at a lower cumulative dose.

Key words: Steroid-resistant – Minimal change disease – Intravenous pulse cyclophosphamide

Introduction

Corticosteroids represent the therapy of choice for minimal change nephrotic syndrome (MCNS). However, 7% of children with MCNS are steroid resistant, i.e. continuing non-responders and subsequent non-responders [1]. These patients continue to pose a therapeutic challenge to the nephrologists. A number of treatments, including oral cyclophosphamide (OCP), have been tried, without any sustained benefit in this subgroup of patients [2–6]. Intravenous pulse cyclophosphamide (IVCP) has been shown to have sustained efficacy in lupus nephritis and other vasculitic disorders [7, 8]. We conducted a prospective randomised controlled trial to compare the efficacy of bolus IVCP and OCP in steroid-resistant MCNS patients.

Correspondence to: V. Kher

Patients and methods

Between 1990 and 1991, 150 children were diagnosed with nephrotic syndrome and treated with standard prednisolone therapy [5]. Twenty-six were steroid resistant, 20 classified as continuing non-responders, while 6 were subsequent non-responders [1]. No patients were positive for hepatitis B surface antigen. Of the 20 non-responders, 14 had MCNS on renal biopsy; 13 of these were enrolled in the study after informed consent. Clinical features of these children are described in Table 1. The children were randomized to receive IVCP (group 1) or OCP (group 2). There were 7 children in group 1; 2 were continuing non-responders, while 5 were subsequent non-responders. There were 6 children in group 2; 3 were continuing non-responders and 3 subsequent non-responders. Two patients in group 2 were lost to follow-up as they moved to another city.

The patients in group 1 were given pulse IVCP 500 mg/m^2 per month for 6 months; group 2 patients received 2.5 mg/kg per day OCP for 8 weeks. Both groups were given identical doses of oral prednisolone concurrently according to the following schedule – 60 mg/m^2 per day for 4 weeks, 40 mg/m^2 per alternate day for 4 weeks, which was tapered over next 4 weeks. The response was evaluated in terms of complete remission (proteinuria <4 mg/m^2 per hour and serum albumin >35 g/l) and non-remission (proteinuria >40 mg/m^2 per hour) according to the criteria of the International Study of Kidney Disease in Children [5]. The duration of remission, total proteinuria-free days and side effects were also studied.

Results

The results are shown in Table 2. All the 7 patients in group 1 achieved complete remission; in 4 the remission was sustained and there was no relapse. The other 3 patients relapsed after a mean remission of 8.7 months; however, even these patients subsequently became steroid responsive. Figure 1 depicts the observed pattern of proteinuria in response to IVCP. In group 2 only 1 of the 4 patients had a sustained remission, while the other 3 did not respond and remained non-responsive (Fig. 2). Two

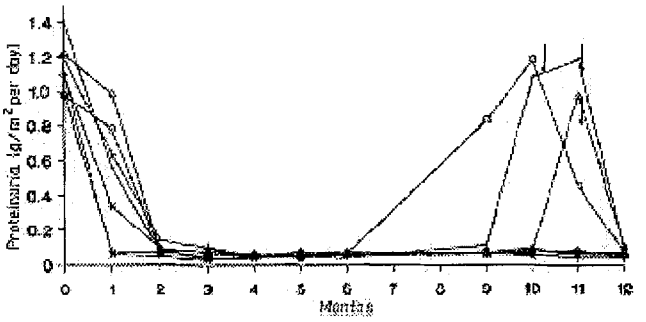

Fig. 1. Profile of proteinuria in patients in response to IV pulse cyclophosphamide therapy. –●–, Patient 1; –|–, patient 2; –✳–, patient 3; –□–, patient 4; –×–, patient 5; –◇–, patient 6; –△–, patient 7; ↓, steroid therapy

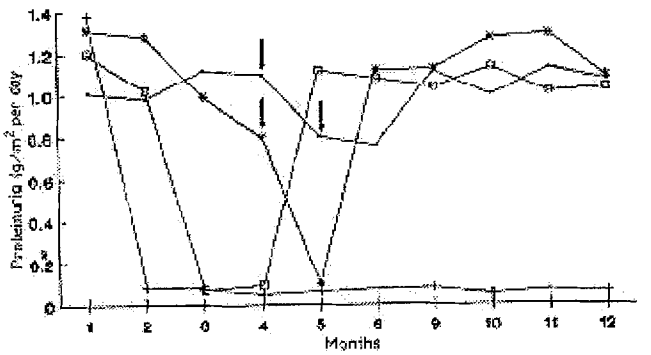

Fig. 2. Profile of proteinuria in patients in response to oral cyclophosphamide therapy. –●–, Patient 1; –|–, patient 2; –✳–, patient 3; –□–, patient 4; ↓, steroid therapy

children had received 36 and 45 days of OCP therapy, without response at the time they were lost to follow-up. The mean duration of proteinuria-free days in group 1 was higher than in group 2. Furthermore, patients in group 1 received 60% lower cumulative doses of cyclophosphamide than those in group 2. Other than transient nausea and vomiting, there were less side effects in group 1. One of the children in group 2 developed pneumonia, while no infectious complications were observed in group 1.

Discussion

This study suggests that IVCP is more effective than OCP in steroid-resistant children with MCNS. Patients receiving IVCP had a higher frequency of overall remission, longer duration of proteinuria-free days, a lower cumulative dose and fewer side effects.

The management of children with steroid-resistant MCNS remains a problem [6]. Although a number of therapeutic protocols have been advocated for frequently relapsing nephrotic syndrome, there are few data in steroid-resistant children with MCNS. Zietse et al. [3] found that cyclosporine A (CsA) reduced proteinuria in patients with nephrotic syndrome refractory to steroid therapy. However, the proteinuria recurred on discontinuation of CsA. Pulse methylprednisolone therapy has also been tried, but no controlled trials are available and the treatment can be associated with several side effects, including death [2, 6].

OCP therapy has proved to be valuable in overcoming the limitations of steroid therapy in frequent relapsers and steroid-dependent children with MCNS [9]. Its effect is additive to that of steroids [10]. Moreover the effect is sustained even after discontinuation of therapy. However,

Table 1. Clinical features of patients in the study group

		Age at onset* (years)	Duration of nephrotic syndrome* (years)	Sex	Pre-therapy investigations			
					Serum protein* (g/dl)	Serum albumin* (g/dl)	Serum creatinine* (mg/dl)	24-h urine protein* (g/m² per day)
Group 1								
IV								
Patient no.	1	4	11	F	3.3	1.4	1.1	1.41
	2	2	8	M	4.1	1.7	1.1	1.20
	3	12	1	M	4.0	2.0	1.0	1.11
	4	2.5	0.5	M	5.5	2.0	0.5	0.98
	5	4.0	12	M	4.2	2.3	1.0	1.10
	6	0.5	8.5	M	4.6	2.1	0.7	0.99
	7	3.0	9.0	M	3.2	1.0	0.6	1.22
Mean ± SD		4.0±3.73	7.14±4.51		4.12±0.78	1.78±0.45	0.85±0.25	1.14±0.14
Group 2								
Oral	1	14.0	0.5	M	5.2	2.0	1.0	1.01
	2	6.5	6.5	M	4.1	1.6	0.5	1.41
	3	11.5	3	M	5.0	2.2	0.5	1.31
	4	1.0	8	M	3.3	1.7	1.0	1.20
Dropped out	5	2.0	7	M	3.0	1.5	0.7	0.97
Dropped out	6	1.5	10	F	3.2	1.3	0.4	1.03
Mean ± SD		6.08±5.5	5.83±3.47		3.9±0.95	1.71±0.33	1.03±0.56	1.15±0.17

* $p > 0.05$

Table 2. Comparison of response to the treatment regimens[a]

	Group 1 IV cyclosphamide (n = 7)	Group 2 Oral cyclophosphamide (n = 4)
Remission	7 (100%)	1 (25%)
Mean proteinuria-free days	274.3 ± 44.6	165 ± 165
Follow-up (months)	12 ± 1.4	13 ± 3.9
Cumulative dose	90 mg/kg	150 mg/kg
Side effects		
Vomiting	4/7	0
Infection	0	1/4
Alopecia	0	2/4

[a] Values are mean ± SEM

similar results have not been obtained in steroid-resistant patients [6]. Most authors agree that the duration of remission induced by alkylating agents is roughly proportional to the length of the course of treatment. However, the potential side effects of these drugs has led to limitation of their use. The response rate with OCP has varied from 27.2% to 50% [11, 12]. The observed response rate of 25% with the oral therapy in the present study is consistent with these reports.

In our study IVCP was found to be beneficial in all 7 children to whom it was administered. In 5 of these the remission was sustained after completion of six monthly pulses of IVCP. The mean duration of proteinuria-free days in this group was 274.3 days, with a mean duration of follow-up of 12 months. Although nausea and vomiting were more frequent in these patients, they were essentially self limiting and did not recur when bolus therapy was administered over a longer period of 4 h. There were no potentially serious side effects such as leucopenia, infections, alopecia and haemorrhagic cystitis. Long-term evaluation of the gonadal function of these children is being planned. Although our results are preliminary, they do suggest a possible successful treatment for steroid-resistant children with MCNS.

References

1. Brodehl J (1986) Nephrotic syndrome in children: diagnosis and treatment. World Paediatr Child Care 1: 9–18
2. Ponticelli C, Fogazzi GB (1989) Methylprednisolone pulse therapy for primary glomerulonephritis. Am J Nephrol 9: 41–46
3. Zietse R, Wenting GJ, Kramer P, Mulder P, Schlekamp MA, Weimer A (1989) Contrasting response to cyclosporine in refractory nephrotic syndrome. Clin Nephrol 31: 22–25
4. Waldo EB, Benfield MR, Kohaut EC (1992) Methylprednisolone treatment of patients with steroid resistant nephrotic syndrome. Pediatr Nephrol 6: 503–505
5. Ponticelli C, Tarastino A, Banfic G, Fogazzi GB (1992) Glomerulonephritis. In Gonic HC (ed) Current nephrology vol 15. Mosby Year Book, St Louis, pp 1–33
6. Niaudet P, Habib R, Gagnadoux MF, Tete MJ, Broyer M (1988) Treatment of severe childhood nephrosis. In: Grunfeld JP, Bach JF, Grosnier J, Funck Brentano JL, Maxwell MH (eds) Adv Nephrol 17: 151–172
7. Austin HA, Klippel JH, Balow JE, LeRiche NG, Steinberg AD, Plotz PH, Decken JL (1986) Therapy of lupus nephritis – controlled trial of prednisolone and cytotoxic drugs. N Engl J Med 314: 614–619
8. Haga HJ, D'Cruz D, Asherson R, Hughes GRV (1992) Short term effects of intravenous pulses of cyclophosphamide in the treatment of connective tissue disease crisis. Ann Rheum Dis 51: 885–888
9. Chiu J, Drummond KN (1974) Long term follow up of cyclophosphamide therapy in frequently relapsing minimal lesion nephrotic syndrome. J Pediatr 84: 825–830
10. Brodehl J (1991) Steroids and cytotoxic drugs in the treatment of minimal change disease nephrotic syndrome. In: Hatono M (ed) Proceedings of the XIth International Congress of Nephrology, July 15–20, 1990. Springer, Tokyo, pp 1458–1467
11. Srivastava RN, Agarwal RK, Moudgil A, Bhuyan UN (1985) Late resistance to corticosteroids in nephrotic syndrome. J Pediatr 107: 66–70
12. Siegel NJ, Gur A, Krassner (1975) Minimal lesion nephrotic syndrome with early resistance to steroid therapy. J Pediatr 87: 377–380

Literature abstract

Clin Nephrol (1993) 40: 26–30

Tubular proteinuria in steroid sensitive multi-relapsing nephrotic syndrome

A. I. Piqueras, V. Shah, S. A. Hulton, T. M. Barratt, and M. J. Dillon

The urinary excretion of N-acetyl-β-D-glucosaminidase (UNAG) and retinol binding protein (URBP) was studied in 65 with steroid sensitive multirelapsing nephrotic syndrome (MRNS): 28 on cyclosporin A (CyA) therapy, 22 on prednisolone (P), 15 off-treatment and in 32 normal children to assess renal tubular damage or dysfunction. The urinary protein excretion was expressed in relation to that of creatinine (UNAG/UC in μmol pnp/h/mmol; URBP/UC in μg/mmol). There was a weak but significantly negative correlation between age and both, UNAG/UC ($r = -0.38$, $p < 0.01$) and URBP/UC ($r = -0.50$), $p < 0.05$) in normal children, but not in nephrotics. In normals and in patients off steroids an association between these two proteins was found ($r = 0.38$, $p < 0.05$; $r = 0.56$, $p < 0.05$ respectively). Geometric mean UNAG/UC was significantly higher in nephrotics on CyA therapy (26.5 ± 4.0), and on P (37.0 ± 7.9) as well as in those off-treatment (16.3 ± 3.1) compared to normal children (9.3 ± 3.4). There was a further increase in those with raised urinary albumin: creatinine ratio (UA/UC) (>0.1 mg/mg). URBP/UC was not increased in any of the groups of children with MRNS. Raised NAG in urine may therefore indicate active nephrotic syndrome rather than being due to the drug therapy.