METHYLPREDNISOLONE PULSE THERAPY IN MANAGEMENT OF NON RESPONDER NEPHROTIC SYNDROME

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Abstract - Some patients with the diagnosis of childhood nephrotic syndrome are unresponsive to conventional treatment regimens. Recent studies of more aggressive therapies have provided strong evidence of the benefit of high dose methylprednisolone (MP) protocol with alternate - day prednisone alone or with alternate - day prednisone plus an alkylating agent (1) in these patients.

From May 1996 to May 1997 we have treated 14 patients with non-responder nephrotic syndrome with methyprednisolone protocol. Eight patients had histologic diagnosis of focal segmental glomerulosclerosis, 3 diffuse mesangial proliferation and 3 has minimal change disease. Cylosporin was added in two patients to methylprednisolone at the beginning of the second course of therapy. The patients were observed for an average of 8 months (range 4-12 months). In the last follow up there were no patients in remission and all remained nephrotic. Seven patients had persistent massive proteinuria with normal creatinine clearance (CrCl). Two had decreased CrCl. Five progressed to end-stage renal disease. These observations suggest that "Pulse" methylprednisolone is not effective in patients with non responder nephrotic syndrome.

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INTRODUCTION

Of children with nephrotic syndrome, 10-15% will be resistant to therapy with steroids, and most of these patients will have focal segmental glomerulosclerosis (FSGS) on biopsy. In contrast to minimal change disease (MCD), 75-80% of patients with FSGS will remain proteinuric after treatment with conrticosteroids or a cytotoxic agent and most of these unresponsive patients will slowly progress to end-stage renal disease (ESRD) (2). A variety of agents have been used to treat these patients, but the results have been generally unsatisfactory (3).

At very high doses, corticosteroids can harden the membrane lipids, diminish the protein interaction and block the enzymatic activities (4). Mendoza and coworkers have reported a response rate of 65% in patients with steroid resistant nephrotic syndrome (SrNS) when treated with a regimen of IV methylprednisolone (M-P) in combination with an oral alkylating agent (5). Based upon the experience of Mendoza (3) Tune (2) and their coworkers we treated 14 patients with non-responder nephrotic syndrome (Non RNS) with a similar protocol and report our experience over the past 4-12 (average 8) months in these patients.

PATIENTS AND METHODS

Patients: All patients who met the following criteria were included in this study: (a) presentation with nephrotic - range proteinuria (> 40 mg/m^2/h), (b) failure of nephrotic proteinuria to resolve after treatment with oral prednisolone at 60 mg/m^2/day for 8 weeks and a course of cyclophosphamide or cyclosporin with conventional doses for 8 weeks, (c) absence of renal insufficiency, (d) biopsy diagnosis of FSGS, MCD or diffuse mesangial proliferation (DMP) by the criteria of the International Study of Kidney Disease (ISKDC)(6), (e) in children diagnosis of primary nephrotic syndrome.

They were then begun on the M-P protocol as in table 1. The maximum dose of M-P was 1g. Patients who had shown no response at the end of the alternate - week treatment were classified as non-responder to M-P and treatment was discontinued. The protein and creatinine excretion were calculated by 24 hour urine collection. Also the protein/creatinine ratios were calculated as the quotients of the concentration of protein (mg/dl) and creatinine (mg/dl) in 24 hours urine sample. The glomerular filtration rate (GFR) was estimated from the serum creatinine concentration and height using the formula of Schwartz and associates(7). Progress was monitored by urine protein quantitation in the hospital, or, after discharge form the hospital. Two patients received cyclosporin A in conjunction with methylprednisolone. Supportive treatment e.g. diuretics were given when required.

Renal pathology : The criteria of ISKDC were used for the diagnosis of MCD, DMP and FSGS(6).

Statistics : Group outcomes were compared by Tukey - HSD procedure. P value < 0.05 was considered significant.

RESULTS

Fourteen patients (7male, 7 female) aged 1.5 to 16 (average 10 years) years, were treated with the M-P/every-other-day prednisone regimen. Two children (14%) received one course of cyclosporin. Prednisone resistance was primary in 12 and acquired in 2. Except for one case who was followed for only 4 months, all patients were followed for at least 12 months. As shown in table 2 all patients had massive proteinuria(> 40 mg/m^2/h) at the end of the third course of M-P pulse therapy and no patients achieved remission.

Fourteen patients were followed for renal function and the results are shown in table 3. Five of 14 patients progressed to ESRD. Two of these children developed renal insufficiency with estimated GFR of 52 and 46 ml/min per 1.73 m^2.

The other 7 patients had massive proteinuria with normal GFR (CrCl > 80 ml/min per 1.73 m^2). No significant difference was observed in the initial estimated GFR or Pru/Cr ratios in patients before and after the end of the third course M-P protocol (P>0.05 Tukey-HSD procedure). We found a transient complication with this protocol. One patient developed mild hypertension which was easily treated. All patients showed weight gain during the first courses of therapy. No arrhythmia or acute rise in blood pressure was noted during the M-P infusion. No patient developed striae or asepetic necrosis. One patient developed cataract at the end of the alternate week course, which was mild and non progressive. No serious bacterial infection, acute gastrointestinal bleeding or diabetes occurred during treatment with M-P (8). Eight of 14 (57%) had microscopic hematuria and there was no significant difference in hematuria before onset and at the end of alternate week M-P pulse P>0.05 (chi-square test). One patient received an allograft kidney. Most of patients had moderate to severe osteoporosis upon bone densitometry but none had clinical signs of bone disease.

Table 1. High - dose, intravenous M-P regimen

Week	Methylprednisolone*	No	Prednisone**
1-2	30 mg/kg 3 week	6	none
3-10	30 mg/kg week	8	2 mg/kg every other day**
11-18	30 mg/kg 2 weeks	4	+/- taper
19-50	30 mg/kg 4 weeks	8	slow taper
51-82	30 mg/kg 8 weeks	4	slow taper

* Maximum dose = 1000 mg.

** Maximum dose = 60 mg.

Table 2. M-P Protocol results :

	Pru/Cru*	No.	%
Remission,	< 0.2	none	-
Mild proteinuria	> 0.2-0.5	none	-
Moderate proteinuria	< 0.05-1.9	none	-
Nephrotic proteinuria	> 2.0	14/14	100%

* Urine protein / Creatinine ratios (mg/mg)

Table 3. Results of M-P protocol on renal function a,b

	n	%
Disappearance of proteinuria	none	-
Proteinuria with normal CrCl	7/14	50%
Proteinuria with decreased CrCl	2/14	14.28%
ESRD	5/14	35.71%

a CrCl = Calculated Creatinine Clearance [G Schwartz 1987]

b Normal CrCl > 80 ml/min per 1.73 m^2

DISCUSSION

A common histopathologic lesion in children with nephrotic syndrome is FSGS. The etiology of this condition is unknown(5). There are two hypotheses for the induction FSGS, a) prolonged proteinuria [Glasser and coworkers 1977] and b) focal coagulation in the glomeruli [Duffy and coworkers. 1970] (9). Renal biopsies from children with idiopathic nephrotic syndrome (INS) will show MCL in 85-90% of random cases and approximatelly 65% of cases referred for problems in management [Whit and coworkers 1970]. The outcome of the steroid - resistant early focal sclerosis is thought to be uniformly poor, whereas the outcome of steroid-responsive late focal sclerosis is thought to be better(10). FSGS is found in 5-6% of unselected and 10-20% of referred cases [with and coworkers 1970, Churge and coworkers 1970].

It is currently unclear if any form of therapy can improve the natural history of patients with nephrotic syndrome resistant to oral steroids. Waldo and associates [1992], reported disappointing results with intravenous methylprednisolone therapy of 10 nephrotic children with FSGS resistant to oral steroids. In the initial response to M-P therapy, there were 1 complete and 2 partial (proteinuria below the nephrotic range) responses; in 2 children, proteinuria initially decreased by an average of 60%, but they remained nephrotic. By the end of the study, (range 4-64, average 47, months) all patients were abnormal: six had ESRD, 2 were proteinuric and uremic, and 2 were proteinuric without uremia. Waldo and coworkers [1992] explained that the poor results of this experience were related to ethnic difference or more conservative treatments(3). In our study all patients were white caucasians treated with aggressive M-P pulse. In contrast to the encouraging results of Tune and coworkers, our experience with a similar protocol was not successful. We did not find any remission in the 14 patients treated with M-P while, 18 of the 23 patients in Tune's study had a favorable response (2). Five of 14 patients develped ESRD, two children (14%) had decreased CrCl and 7 (50%) had nephrotic range proteinuria after 4-12 (average 8) months of follow up. Inghllie (1991) reported that black and Hispanic patients with FSGS were more likely to progress to ESRD than whites had (78% vs 33%, $P<0.001$)(3). Adhikari and Coovakia showed that African children with idiopathic nephrotic syndrome are unresponsive to oral steroid as well as other races(11). Waldo and coworkers reported that M-P pulse can not induce remission is black children with idiopathic (SrNS) or FSGS. It appears that black patients are generally resistant to steroid, oral or high dose M-P pulse. The maximum effectivenes of methylprednisolone appears to depend on its early administration(12). In our experience the prolonged period 1.5-7 years (average 3.5 years) between the appearance of resistance to classic treatment and using M-P pulse may be an important factor regarding our results. Conclusion: M-P protocol can not induce remission in children with INS who are non responder to oral steroid, cyclophosphamide or cyclosporine.

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