Case Report

Methylprednisolone Treatment in Children with Nephrotic Primary Focal Segmental Glomerulosclerosis

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Objective: *To examine the effectiveness of pulse methylprednisolone in children with nephrotic primary focal segmental glomerulosclerosis.*

Material and Method: *Medical records of children, who were treated with a pulse methylprednisolone regimen for nephrotic syndrome resulting from primary focal segmental glomerulosclerosis between 1987 and 2005, were retrospectively reviewed. The age,gender, urine protein, serum creatinine, and glomerular filtration rate at the onset of nephrotic syndrome were recorded. Urine protein, serum creatinine, glomerular filtration rate, and percentile of height before and after methylprednisolone treatment were compared.*

Results: *There were six patients (4 male, 2 female) in the present report. The mean age at onset was 9.5 $\pm$ 2.2 years. Hypertension was noted in four patients and mild renal insufficiency in three. All patients had nephrotic-ranged proteinuria at onset and they were initially treated with prednisolone. Two were steroid-dependent and four were steroid-resistant. All of the steroid resistant cases were also resistant to oral cyclophosphamide. After methylprednisolone treatment, remission of proteinuria was noted in five patients (83%) (2 complete, 3 partial). Mean duration to remission was 20.8 weeks. There were no significant changes in serum creatinine (p = 0.43), GFR (p = 0.78) and percentile of height before and after treatment. No hypertension or cardiac arrhythmia was detected during methylprednisolone administration. The follow-up period after completion of the methylprednisolone regimen was 19.5 $\pm$ 15.2 months (range 4-36 months). The clinical course of five patients with remission was characterized by sustained remission in three patients. Two patients relapsed at 2 and 8 months after treatment.*

Conclusion: *Methylprednisolone was effective and safe in treating nephrotic children with primary focal segmental glomerulosclerosis. There was a high incidence of relapse shortly after the cessation of treatment. However, a larger number of patients and longer period of follow-up are needed to confirm this conclusion.*

Keywords: *Nephrotic syndrome, Focal segmental glomerulosclerosis, Steroid resistance, Pulse methylprednisolone*

J Med Assoc Thai 2006; 89 (12): 2145-9
Full text. e-Journal: *http://www.medassocthai.org/journal*

Minimal change nephrotic syndrome (MCNS) is the most common renal pathology in children with primary nephrotic syndrome. Most MCNS cases respond to steroid therapy with excellent long-term outcome[1]. Although focal segmental glomerulosclerosis (FSGS) represents a minority group of primary childhood nephrotic syndrome cases[2], about 34% of these patients progress to end-stage renal disease (ESRD) in 11 years[3,4]. Treatment is very problematic, since less than 30% respond to standard prednisolone therapy[5] and there is still no evidence of effective treatment for this condition. Several kinds of intervention, such as cyclophosphamide, cyclosporin, methylprednisolone, and mycophenolate mofetil have been used in steroid resistant FSGS with variable success rates. Among these, aggressive protocols using a high dose of pulse methylprednisolone combined with oral prednisolone, with or without alkylating agents, were tried with varying results[6-10].

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The authors report the experience of intravenous pulse methylprednisolone (IVMP) therapy in Thai patients.

Material and Method

Medical records of FSGS patients with steroid resistant nephrotic syndrome treated with IVMP, were retrospectively reviewed. Renal biopsy was performed if proteinuria persisted after 4-8 weeks of oral prednisolone treatment at 60 mg/m^2/day. Thirty pulses were given in 82 weeks as shown in Table 1[9]. The age, gender, urine protein, serum creatinine and glomerular filtration rate at the onset of nephrotic syndrome were recorded. Urine protein, serum creatinine, glomerular filtration rate, and percentile of height before and after methylprednisolone treatment were compared.

All data are expressed as mean $\pm$ standard deviation. Comparisons between groups were performed with the Student t-test for continuous data. A $p < 0.05$ was considered statistically significant.

Results

Six patients (4 male, 2 female) with nephrotic syndrome and FSGS were treated with IVMP. The average urine protein was 143 $\pm$ 65 mg/kg per day (range 74-245 mg/kg per day). The characteristics of all patients are shown in Table 2. Patient No. 1 and No. 2 had steroid dependent NS for 1 year and 8 months, respectively before becoming steroid resistant. The other four patients were initially resistant to steroid and cyclophosphamide. Three patients (50%) had a glomerular filtration rate (GFR) of less than 100 ml/1.73m^2/min at the onset of disease. Four patients (67%) had hypertension. Among those with hypertension, two had a GFR of less than 100 ml/1.73m^2/min. The mean duration of prior oral prednisolone and cyclophosphamide treatment was 38 $\pm$ 48 months (range 8 - 132 months).

Pulse methylprednisolone at 30 mg/kg, with a maximum dose of 1 gm, was administered as shown in Table 1. After completion of treatment, five patients (83%) achieved remission. Two had complete remission and three had partial remission. The average time to remit was 20.8 $\pm$ 9.6 wk (range 8-32 wk) and there were no statistical differences in serum creatinine ($p = 0.43$) and GFR ($p = 0.78$) before or after treatment. The mean duration of follow-up after cessation of pulse methylprednisolone was 19.5 $\pm$ 15.2 months (range 4-36 months). At the end of the follow-up period, two completely remitted patients were still in remission, with one being administered oral prednisolone at 10 mg and the other 15 mg every other day. In three patients with partial remission, two relapsed in two months and 8 months after completion of IVMP. One patient, who had been followed-up for 5 months, was still in remission while receiving 5 mg of prednisolone every other day (Table 3).

Discussion

Although FSGS is well known as the leading cause of ESRD, there has been no effective treatment proven up to now. Because of the increasing incidence of FSGS among adult and child patients with nephrotic syndrome[11,12], a reliable therapeutic guideline on evidence-based data is urgently needed. Until now, there has been variability in the treatment of FSGS. A survey of North American pediatric nephrologists reported that cyclosporin was the most widely used drug, which accounted for 73.9%, while 44.3% of them often or sometimes used methylprednisolone combined with an alkylating agent, and 52.3% used methylprednisolone without an alkylating agent[13]. The success of high dose intravenous methylprednisolone in treating acute rejection episodes in renal transplantation initiated its use in the treatment of severe glomerulonephritis. Only six pulses of 30 mg/kg of intravenous methyl-

Table 1. High-dose intravenous methylprednisolone (M-P pulse) regimen

Week	Methylprednisolone*	#	Prednisolone
1-2	30 mg/kg 3 times/week	6	None
3-10	30 mg/kg q 1 wk	8	2 mg/kg qod**
11-18	30 mg/kg q 2 wk	4	$\pm$ taper
19-50	30 mg/kg q 4 wk	8	Slow taper
51-82	30 mg/kg q 8 wk	4	Slow taper

* Maximum dose = 1,000 mg
** Maximum dose = 60 mg

Table 2. Clinical characteristics of patients

Number	Age at onset (years)	Gender	Urine protein at onset mg/kg/day	Serum creatinine at onset mg/dL	GFR at onset ml/1.73m^2/min	BP	Status	Time before IVMP therapy (months)
1	6	M	175	1.1	54	Normal	Steroid dependent ↓ Steroid resistant	132
2	10	M	246	0.5	140	High*	Steroid dependent ↓ Steroid resistant and cyclophosphamide resistant	24
3	8	M	167	0.8	78	High*	Steroid resistant cyclophosphamide resistant	41
4	11	F	94	0.5	153	Normal	Steroid resistant cyclophosphamide resistant	12
5	10	F	74	0.7	100	Normal	Steroid resistant cyclophosphamide resistant	11
6	12	M	100	1.1	76	High*	Steroid resistant cyclophosphamide resistant	8
Mean $\pm$ SD	9.5 $\pm$ 2.2		143 $\pm$ 65	0.78 $\pm$ 0.27	100.2 $\pm$ 40.0			38 $\pm$ 47.6

M, male; F, female; GFR, glomerular filtration rate; BP, blood pressure; IVMP, intravenous methylprednisolone
High BP*: blood pressure > 95th percentile for age, gender and height

Table 3. Result of IVMP therapy

Number	Outcome	Time to remission (weeks)	Urine protein at the end of IVMP	Serum Cr (mg/dL) pre	Serum Cr (mg/dL) post	Serum GFR (ml/1.73m^2/min) pre	Serum GFR (ml/1.73m^2/min) post	Follow-up time (months)	Recent status
1	PR	8	38 mg/kg/day	0.7	0.6	123	145	5	Relapse
2	CR	16	U pr/U cr 0.12	0.8	0.8	92	105	36	Remission
3	PR	32	U pr/U cr 0.7	0.6	0.9	118	93	36	Relapse
4	CR	28	3 mg/kg/day	0.5	0.6	168	132	9	Remission
5	PR	20	U pr/U cr 0.7	0.8	0.8	87	96	27	Remission
6	Resistant	-							Nephrotic syndrome treated with Mycophenolate mofetil
Mean		20.8 $\pm$ 9.6		pre 0.68 $\pm$ 0.13	post 0.74 $\pm$ 0.13 p = 0.43	pre 117.6 $\pm$ 32.3	post 114.2 $\pm$ 23.1 p = 0.78		

CR, complete remission; urine protein < 4 mg/kg/day or Upr/ Ucr < 0.2
PR, partial remission ; Urine protein 4 mg/kg/day - 40 mg/kg/day or Upr/Ucr > 0.2 - < 2
IVMP, intravenous methylprednisolone; Upr, Urine protein; Ucr, urine creatinine; Cr, creatinine; GFR, glomerular filtration rate

prednisolone was given in the present report[14]. Further studies extended this regimen to 30 pulses per course with or without alkylating agents[6]. Some reported a favorable outcome with a highly sustained remission rate[6,8,15], while other results were less satisfactory[7,16]. The discordance of these studies might be due to patient selection, race, or the difference in IVMP regimens.

The 82-week-regimen of IVMP was used in the present study. All patients had been steroid resistant, with some cyclophosphamide resistant, before starting the IVMP regimen. No alkylating agents were prescribed for these patients because of the awareness of a prior high cumulative dosage of cyclophosphamide. The mean duration of follow-up after completion of the IVMP regimen was 19.5 $\pm$ 15.2 months (range 5-36 months). Among five patients, who achieved complete and partial remission, sustained remission was noted in three (60%) with a follow-up period of 9 months, 27 months and 36 months. All of them were still receiving oral prednisolone at a dosage of 5 mg-10 mg every other day.

Relapse occurred shortly in two patients (40%) after the completion of IVMP (2 months and 8 months). Both of them had GFR at onset less than 80 ml/1.73m^2/min (Table 2, 3). According to the presented data, the IVMP regimen was effective and safe in treating children with steroid and cyclophosphamide resistant nephrotic syndrome with FSGS. However, the early relapse cases doubts its superiority to other regimens. It is also noted that the patients in the present report initially had normal to mild renal impairment, so such treatment may not be applicable to treat patients with more degree of renal impairment. With respect to this view, an alternative approach using multidrug vasodilators maybe helpful to restore renal function in these patients[17].

Conclusion

From the present report, methylprednisolone was effective and safe in treating nephrotic children with primary FSGS with mild renal impairment. However, a high incidence of relapse shortly after the cessation of treatment was noted. A multicenter randomized controlled trial is needed to confirm the efficacy of IVMP.

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รายงานผลการรักษาผู้ป่วยเด็กกลุ่มอาการเนฟโฟรติกปฐมภูมิชนิด focal segmental glomerulosclerosis ด้วย methylprednisolone จำนวน 6 ราย

เสาวลักษณ์ โอภาสถิรกุล, วัฒนา ชาติอภิศักดิ์

***วัตถุประสงค์**: เพื่อรายงานผลของการรักษาด้วย pulse methylprednisolone ในผู้ป่วยเด็กที่เป็นเนฟโฟรติกปฐมภูมิชนิด focal segmental glomerulosclerosis*

***วัสดุและวิธีการ**: เป็นการศึกษาจากเวชระเบียนของผู้ป่วยเด็กดังกล่าวย้อนหลังในช่วงปี พ.ศ. 2530 - พ.ศ.2548 โดยศึกษาข้อมูลด้านอายุ เพศ โปรตีนที่รั่วออกมาทางปัสสาวะ ระดับของครีอาตินินในเลือด การทำงานของไต รวมถึงเปอร์เซ็นต์ไทล์ของความสูงของผู้ป่วย*

***ผลการศึกษา**: ผู้ป่วยทั้งหมด 6 ราย (ชาย 4, หญิง 2) ทุกคนเคยได้รับการรักษาด้วยการกินเพรดนิโซโลนมาก่อน โดย 2 รายเป็นชนิด steroid dependent และอีก 4 ราย ไม่ตอบสนองต่อทั้งสเตียรอยด์ และ oral cyclophosphamide จากการรักษาด้วยเมททิลเพรดนิโซโลน พบว่าผู้ป่วย 5 คน (83%) มีระดับโปรตีนในปัสสาวะลดลง (2 รายมี complete remission อีก 3 รายมี partial remission) ระยะเวลาเฉลี่ยตั้งแต่เริ่มรักษาจนถึง remission เท่ากับ 20.8 สัปดาห์ ไม่พบความแตกต่างของระดับครีอาตินินในเลือด การทำงานของไต และเปอร์เซ็นต์ไทล์ของความสูงก่อนและหลังการรักษาไม่พบความดันโลหิตสูง และการเต้นของหัวใจที่ผิดปกติระหว่างการให้ยา ระยะเวลาการติดตามผลการรักษาเท่ากับ 19.5 $\pm$ 15.2 เดือน ในผู้ป่วย 5 รายที่ตอบสนองต่อการรักษาพบว่า 3 รายยังคงมี remission ผู้ป่วย 2 รายมีการกลับเป็นซ้ำหลังหยุดเมททิลเพรดนิโซโลน 2 เดือน และ 8 เดือน ตามลำดับ*

***สรุป**: จากรายงานผลการรักษานี้พบว่า เมททิลเพรดนิโซโลน เป็นยาที่ได้ผลและปลอดภัยในการรักษาผู้ป่วยเด็กเนฟโฟรติกปฐมภูมิชนิด focal segmental glomerulosclerosis แต่พบอุบัติการณ์ของการกลับเป็นซ้ำได้บ่อยหลังจากหยุดการรักษาได้ไม่นาน*