Difficult-to-Treat Nephrotic Syndrome: Management and Outcome

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A retrospective study was performed in 68 patients diagnosed as having idiopathic nephrotic syndrome with steroid-dependent, steroid-resistant or frequent relapse subtypes at the Department of Pediatrics, Siriraj Hospital during Jan 1996-Dec 2004. Male to female ratio was 3.3:1 and mean age (±SD) was 8.4 ± 3.5 years. Mean follow up time (± SD) was 47.4 ± 30.5 months. Renal biopsy was done in 60 patients, showing IgM nephropathy in 73.3%.

Fifty-four patients (79.4%) received cyclophosphamide at a dose (± SD) of 2.2 ± 0.5 mg/kg/d for 11.6 ± 3.4 weeks. Negative proteinuria at 1 year was found in 70% and prednisolone was discontinued in 52%. Leucopenia was found in 9.2%. At last follow up, 34% of the patients were still in remission. Enalapril was prescribed in 50 patients for 12.4 ± 10.0 months. Thirty-six patients also received cyclophosphamide. Remission at 1 year was achieved in 66% and prednisolone discontinued in 28%. Twelve patients (24%) were still in remission at last follow up. The results of 3 regimens: cyclophosphamide, enalapril, and cyclophosphamide plus enalapril were compared using chi-square test. Remission was significantly better in cyclophosphamide group (p = 0.014). Dipyridamole was prescribed in 14 patients due to thrombocytosis. Only 2 of 14 patients achieved remission although 11 patients received cyclophosphamide plus enalapril, and another 2 patients received only cyclophosphamide.

Complications included hypertension (44%), cataract (40%), glaucoma (15%), short stature (17.6%), and obesity (5.9%). Recurrent infection was found in 69%, including dental caries (16.2%), urinary tract infection (14.7%), intestinal parasitic infestration (10.3%), respiratory tract infection (8.8%), and skin infection (7.4%). Chronic renal failure was found in 3 patients and portal vein thrombosis was found in 1 patient.

We suggest that cyclophosphamide should be used as first line drug in difficult-to-treat nephrotic syndrome patients. Enalapril may be beneficial in some patients. Thrombocytosis may be associated with poor response to both medications. Difficult-to-treat patients also need long term follow up and surveillance for complications due to disease and/or treatment.

Keywords*: Nephrotic syndrome, Cyclophosphamide, Enalapril*

J Med Assoc Thai 2005; 88(Suppl 8): S142-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

Idiopathic nephrotic syndrome is one of the most common chronic kidney diseases in children all over the world. True incidence of the disease in Thai children is not known but annual incidence report from USA was 2-2.7/100,000 children under 16 years[1]. Although most patients responded to prednisolone, steroid-resistant, steroid-dependent, frequent relapse and severe complications are not rare[2,3]. A retrospective study in 133 pediatric patients from Siriraj Hospital showed a high steroid sensitive rate of 91% with more than half had at least one episode of relapse including 16.5% frequent relapser (unpublished data).

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The appropriate management for those patients with steroid resistant, steroid dependent and frequent relapser is still debatable[2-7].

This study is aimed to compare the outcome of various treatment regimens available in difficult-to-treat nephrotic syndrome in Thai children.

Material and Method

We retrospectively studied 200 medical records of patients less than 18 years old who were diagnosed as having idiopathic nephrotic syndrome at the Department of Pediatrics, Siriraj Hospital during January 1996 to December 2004. Only patients diagnosed as having steroid-resistant, steroid-dependent and frequent relapser type of idiopathic nephrotic syndrome and were available for follow up for at least 1 year were included. Demographic data of the patients, treatment received, and outcome of treatment and complications were recorded. Statistical analysis was performed using SPSS 11.5 (Chicago, ILL). Descriptive analysis using mean ± SD was performed for baseline parameters. Chi-square test was used to compare outcome of treatment. $P < 0.05$ was considered significant.

Treatment regimens (other than oral prednisolone) included cyclophosphamide 2-3 mg/kg/d for 8-12 weeks, enalapril 0.1-0.5 mg/kg/d, dipyridamole, levamisole and pulse methylprednisolone as in Yorgin's protocol[4]. The attending physicians selected treatment protocols according to the patient's clinical findings and his/her own experience of the regimens.

Results of treatment were evaluated using urine dipstick test for protein and urine protein/creatinine ratio. The disease was considered remission if the patient remained urine protein-free for at least 6 months.

Results

During January 1996 to December 2004, 68 patients were considered to have difficult-to-treat nephrotic syndrome. Male to female ratio was 3.3:1 and mean age was 8.4 ± 3.5 years (range 2-15 years). Most (72%) patients received oral prednisolone treatment from other hospital before being referred to Siriraj Hospital and the mean age at first diagnosis of idiopathic nephrotic syndrome was 5.5 ± 3.2 year. More than half (55.9%) of the patients were steroid-dependent; 39.7% were steroid-resistant, with 1.5% as frequent relapser. Two patients had severe hypertension possibly from steroids. Mean duration of follow up was 47.4 ± 30.5 month. (Table 1)

Renal Pathology

Renal biopsy was performed in 60 patients (88.2%). The followings were pathologic diagnoses: IgM nephropathy 44 patients (73.3%), IgM nephropathy with additional features 12 patients (20%), focal segmental glomerulosclerosis (FSGS) 3 patients (5%), and membranous nephropathy, 1 patient (1.7%). Increased serum creatinine (more than 1.5 mg/dl) was found in the followings; 1 patient with IgM nephropathy, 2 patients with IgM nephropathy and additional features and 1 patient with FSGS. Hypertension was found in the followings; 15 patients with IgM nephropathy, 7 patients with IgM nephropathy with additional features, 2 patients with FSGS and the patient with membranous nephropathy. Hypertension was also found in 5 of 8 patients without renal histology.

Treatment Regimens

1. Cyclophosphamide

Most (79.4%) patients received oral cyclophosphamide with a mean dosage of 2.2 ± 0.5 mg/kg/

Table 1. Demographic data of the 68 difficult-to-treat patients

Male : Female ratio	3.3 : 1
Mean age (yr)	8.4 ± 3.5
Type of nephrotic syndrome:	
steroid-resistant	27 patients (39.7%)
steroid-dependent	38 pateints (55.9%)
frequent relapsed	1 patient (1.5%)
Renal histology (n=60):	
IgM nephropathy	44 patients (73.3%)
IgM nephropathy with additional features	12 patients (20%)
Focal segmental glomerulosclerosis	3 patients (5%)
Membranous nephropathy	1 patient (1.7%)

Table 2. Management and outcome according to subtype of difficult-to-treat patients

Medication	Remission at 1 year	Remission at last follow up	Chi-square test
1. Cyclophosphamide (n=54):	38	20	- at 1 year
steroid-dependent (n=29)	23	16	p = 0.04
steroid-resistant (n=24)	14	4	- at last follow
frequent relapsed (n=1)	1	0	up p = 0.01
2. Enalapril (n=50):	33	12	- at 1 year
steroid-dependent (n=27)	20	8	p = 0.25
steroid-resistant (n=20)	10	3	- at last follow
frequent relapsed (n=1)	1	0	up p = 0.49
severe hypertension (n=2)	2	1	

Table 3. Remission at last follow up according to treatment regimens

Regimen	Remission	Chi-square test
- Cyclophosphamide (n=18)	11	P = 0.017
- Enalapril (n=14)	3	
- Cyclophosphamide and Enalapril (n=36)	9	

d. Mean accumulating dose was 233.9 ± 106.6 mg/kg with a mean duration of 11.6 ± 3.4 weeks. Negative proteinuria at 1 year was achieved in 70% and oral prednisolone was discontinued in 52%. Twenty patients (34%) still had negative proteinuria at last follow up (47.4 ± 30.5 month). Mean urine protein-free time was 15.4 ± 20.3 months after cyclophosphamide treatment. Leucopenia (white blood cell count less than 4,000/cu.mm) was found in 9.2%. Hemorrhagic cystitis, severe alopecia or severe infection was not found. Patients with steroid-dependent benefit more from cyclophosphamide than steroid-resistant patients at one year (p = 0.042) and at last follow up (p = 0.011). (Table 2)

2. Enalapril

Enalapril was prescribed in 50 patients (73.5%) and was the only medication other than steroids in 14 patients. Half (52%) of the patients received enalapril at a dosage of 0.1 mg/kg/d and 18% received 0.5 mg/kg/d. Mean duration of enalapril was 12.4±10.0 months. Remission at 1 year was achieved in 66% and oral prednisolone discontinued in 28%. Mean protein-free time was 8.0 ± 8.9 months. Only twelve patients (24%) were in remission at last follow up. Significant hypotension or hyperkalemia was not found. Renal failure was found in 2 patients. The first one was an 11-year-old boy with IgM nephropathy and 55% segmental sclerosis. Enalapril was initially prescribed but due to increased serum creatinine at 1 month, it was discontinued and oral cyclophosphamide was given. The patient remained in anasarca condition despite treatments. After enalapril discontinuation, serum creatinine level continued to rise and he eventually developed end-stage renal disease and had to be on hemodialysis. The second patient was a 14-year-old girl with FSGS. Enalapril was prescribed initially but at 6 months, her serum creatinine rose from 0.4 mg/dl to 2 mg/dl when she developed acute diarrhea. Cyclophosphamide was given instead of enalapril without success. Despite discontinuation of enalapril, her serum creatinine level was still 2 mg/dl at last follow up. Using Pearson chi-square test to compare the results of cyclophosphamide, enalapril and cyclophosphamide plus enalapril, remission at last follow up was significantly better in cyclophosphamide group (p = 0.014) (Table 3).

3. Other medications

Levamisole 5.5 ± 5.5 mg/kg/dose three times a week for 7.6 ± 8.2 months was prescribed in 11 patients. All of which received cyclophosphamide with 9 also received enalapril. Remission was achieved in only 2 patients at 6 months. No complication was found, however, no patient was in remission at last follow up. Methylprednisolone according to Yorgin's protocol[4] was given to 7 patients for a mean duration 3.1 ± 1.7 months. No patient achieved remission and no serious complication was found. Fourteen patients with high platelet count received dipyridamole with a

mean dosage of 3.4 ± 1.6 mg/kg/d for 18.0 ± 13.5 months. Mean platelet counts were 679,462 ± 204,539/cu.mm. and 424,154 ± 60,908/cu.mm. before and after treatment, respectively. Remission was achieved in 2 patients in this group. Side effects included nausea in 14.3% and severe headache in 7.1%.

Complications

Complications found in 68 difficult-to-treat patients during follow up period included hypertension 44%, cataract 40%, glaucoma 15%, short stature 17.6%, obesity 5.9%, hyperlipidemia 6%, renal tubular acidosis 1.5% and inguinal hernia 1.5%. Infection was also commonly found (69%) including dental caries 16.2%, urinary tract infection 14.7%, gastrointestinal parasitic infestation 10.3%, minor skin infection 7.4%, cellulitis 4.4%, perianal abscess 2.9%, repeated respiratory tract infection 8.8%, pneumonia 1.5% and tuberculosis 2.9%. Cataract was the only complication found to be less common in those with remission at last follow up than those without (21.7% vs. 48.9%, p = 0.03).

A 17-year-old patient developed portal vein thrombosis as diagnosed by Doppler ultrasound. Platelet count was 414,000/cu.mm. PT and PTT were normal. Protein C was 25.9% (normal 45-93%), protein S was 92% (normal 41-114%), antithrombin III was 70.07% (normal 90-131%), D-dimer 3,400 mg/L (normal 0-300 mg/L), and fibrinogen was 629.98 g/L (normal 1.57-4 g/L). Low-molecular-weight heparin and coumadin were prescribed. Repeated ultrasound at 8 months revealed improved flow in portal vein but he was thereafter lost to follow up.

Chronic renal failure was found in 3 of 68 patients (4.4%). Two of which received cyclophosphamide plus enalapril without success as described above. The third patient was a 10-year-old boy with steroid-resistant nephrotic syndrome. He developed hypertensive encephalopathy and was then referred to us. Renal histology showed IgM nephropathy with 73% global sclerosis and 6% segmental sclerosis. Enalapril was given without success. His estimated GFR remained stable at about 40 ml/min/1.73 M^2 at last follow up.

Discussion

Idiopathic nephrotic syndrome is commonly found among Thai children. Although most of the patients respond to prednisolone, significant numbers were are steroid-resistant, steroid-dependent, or frequent relapsers. Complications such as infection, hypovolemia and thrombosis were common .These patients also often developed long-term complications due to prolonged medications. The response to steroid therapy carries a greater prognostic value than the renal histology features.

An International Study of Kidney Disease in Children trial found a 48% relapse rate in children treated with a combination of cyclophosphamide and prednisolone compared to a 88% relapse rate in patients on prednisolone alone[8]. Meta-analysis study found that the success of cyclophosphamide varied widely. Leucopenia occurred in about one-third of the patients. Remission rates after 2 years were 72% and 40% for frequent relapser and steroid-dependent patients, respectively[5]. Another retrospective study in 106 steroid-sensitive nephrotic patients revealed several factors correlated with the rate of sustained remission, i.e., age older than 5.5 years, frequently relapser (vs. steroid-dependent status), leucopenia, and a cumulative dosage more than 5,040 mg/m^2 body surface area[9]. Our study revealed a similar 70% and 34% remission rates at 1 year and at last follow up, respectively. The lower incidence of leucopenia (9.2%) in our study may be due to rather low dose of cyclophosphamide (2.2 ± 0.5 mg/kg/d, accumulating dose of 233.9 ± 106.6 mg/kg) comparing with other study[5]. Although the outcome of cyclophosphamide is better than other regimens in this study, the long-term toxicity such as malignancy, pulmonary fibrosis, ovarian fibrosis, and sterility must be kept in mind.

A recent meta-analysis showed that angiotensin-converting enzyme inhibitors (ACEI) significantly reduced urine protein excretion in various renal diseases and was associated with slower progression to end-stage renal disease[10]. A number of studies had confirmed the antiproteinuric effect of ACEI in children with nephrotic syndrome, especially in steroid-resistant subtype[6,11-13]. High-dose (0.6 mg/kg/d) enalapril was associated with a significantly greater reduction of urine protein/creatinine ratio (52% vs. 33%) than with low-dose (0.2 mg/kg/d). ACEI alone or in combination with cyclophosphamide was beneficial in two-thirds of the patients in our study. But after its discontinuation, proteinuria reappeared. From our study and others, we suggest that enalapril should begin at 0.2 mg/kg/d and gradually increased to 0.5 mg/kg/d, aiming to achieve a 50% reduction in proteinuria. Blood levels should be monitored for creatinine and electrolytes. Prolonged duration of treatment may also be needed[6].

Levamisole has been reported to reduce the risk of relapse in steroid-dependent nephrotic syndrome and frequent relapsers in several studies[6,14-17]. In a

retrospective study, the efficacy of 6 months levamisole was similar to cyclophosphamide 8-12 weeks[17]. In our study, only 18.2% of the patients achieved remission. This may be due to a large proportion of steroid-resistant patients in our study.

Initial enthusiasm for usage of pulse methylprednisolone in patients with steroid-resistant nephrotic syndrome has been decreased by subsequent studies that have failed to produce similar results[3, 18]. None of the 7 patients in our study achieved remission.

The incidence of thromboembolic complications in nephrotic children have been reported to be approximately 3% but with pulmonary embolism reported to be as high as 28% in patients with steroid-dependent subtype[2]. Several factors contributed to increased risks of thrombosis in nephrotic patients including hypercoagulability state, hypovolemia, immobilization, and infection. One patient (1.5%) in our study developed portal vein thrombosis. Dipyridamole was prescribed in 14 patients; thirteen patients in this group received cyclophosphamide; 11 patients also received enalapril and another one received only enalapril. Only 2 from 14 patients in this group achieved remission. We suggest that thrombocytosis may be associated with poor response to cyclophosphamide and/or enalapril.

End-stage renal disease was reported in at least 50% of patients with steroid-resistant nephrotic syndrome compared to less than 3% in those with steroid-sensitive subtype[3]. In the Southwest Pediatric Nephrology Study Group, patients with FSGS were at a high risk with 21% progressed to end-stage renal disease and 23% with decrease GFR[19]. The incidence of chronic renal failure in our study was 4.4% including 1 patient (1.5%) who reached end-stage renal disease .This finding is different from others, considering that 39.7% of the patients in our study was steroid-resistant.

In conclusion, the management of steroid-dependent, steroid-resistant, and frequently-relapsing nephrotic syndrome is still a challenge to physician. Morbidity rate from prolonged medications and the disease itself are still high. We suggest that cyclophosphamide should be considered a first line therapy. Enalapril may be beneficial in some patients. Thrombocytosis may be associated with poor response to cyclophosphamide and/or enalapril. Controlled studies on newer drugs are needed in these groups of patients, especially after cyclophosphamide failed to induce remission.

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โรคไตเนโฟรติกที่รักษายากในเด็ก: การรักษาและผลการรักษา

อัจฉรา สัมบุณณานนท์, นวรัตน์ จงเจษฎ์, วิบูล สุนทรพจน์, อนิรุธ ภัทรากาญจน์, สุโรจน์ ศุภเวคิน

โรคไตเนโฟรติกส่วนใหญ่จะตอบสนองดีต่อเพรดนิโซโลน แต่มีผู้ป่วยจำนวนหนึ่งซึ่งมีปัญหาในการรักษาเนื่องจากเกิดภาวะดื้อต่อเพรดนิโซโลน ไม่สามารถหยุดยาได้ หรือเกิดอาการกำเริบใหม่บ่อยๆ หลังหยุดยา การศึกษานี้ทำในผู้ป่วยเด็กโรคไตเนโฟรติกที่รักษายาก 68 ราย ซึ่งมารับการรักษาในภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างปี พ.ศ. 2539-2547 โดยมีอัตราส่วน เพศชาย: เพศหญิง = 3.3:1 อายุเฉลี่ย 8.4 ± 3.5 ปี ร้อยละ 39.7 เป็นผู้ป่วยที่ดื้อต่อเพรดนิโซโลน ร้อยละ 55.9 ไม่สามารถหยุดยาได้ และร้อยละ 1.5 มีโรคกำเริบบ่อยหลังหยุดยา ระยะเวลาติดตามการรักษาเฉลี่ย 47.4 ± 30.5 เดือน

ผู้ป่วยร้อยละ 79.4 ได้ยาซัยโคลฟอสฟาไมด์ขนาด 2.2 ± 0.5 มก./กก./วัน ด้วยระยะเฉลี่ย 11.6 ± 3.4 สัปดาห์ พบว่าโรคสงบ ร้อยละ 70 และสามารถหยุดยาเพรดนิโซโลนได้ร้อยละ 52 พบภาวะเม็ดเลือดขาวต่ำร้อยละ 9.2 ผู้ป่วยร้อยละ 34 ยังอยู่ในภาวะโรคสงบเมื่อติดตามการรักษาครั้งสุดท้าย ผู้ป่วยร้อยละ 73.5 ได้ยาเอนนาลาพริลเป็นระยะเวลาเฉลี่ย 12.4 ± 10.0 เดือน (ร้อยละ 52.9 ได้ยาซัยโคลฟอสฟาไมด์ร่วมด้วย) พบว่าโรคสงบร้อยละ 66 สามารถหยุดยาเพรดนิโซโลนได้ร้อยละ 28 และผู้ป่วยร้อยละ 24 ยังอยู่ในภาวะโรคสงบเมื่อติดตามการรักษาครั้งสุดท้าย แต่มีภาวะไตวายในผู้ป่วย 2 ราย ซึ่งไม่ดีขึ้นหลังหยุดยาเอนนาลาพริล

เมื่อเทียบผลการรักษาระหว่างผู้ป่วยที่ได้ยาซัยโคลฟอสฟาไมด์ เอนนาลาพริล และซัยโคลฟอสฟาไมด์ร่วมกับเอนนาลาพริล โดยใช้ Chi-square test พบว่ากลุ่มที่ได้ซัยโคลฟอสฟาไมด์อย่างเดียวมีภาวะโรคสงบได้มากที่สุด (p = 0.014) ผู้ป่วย 14 ราย ได้รับยาต้านเกล็ดเลือดเนื่องจากมีเกล็ดเลือดสูง พบสามารถลดปริมาณเกล็ด เลือดลงได้ แต่พบมีโรคสงบเพียง 2 ใน 14 ราย โดยผู้ป่วยในกลุ่มนี้ 11 รายได้ทั้งซัยโคลฟอสฟาไมด์ และเอนนาลาพริล และผู้ป่วยอีก 2 รายได้ซัยโคลฟอสฟาไมด์อย่างเดียว

โรคแทรกซ้อนที่พบในผู้ป่วยเด็กโรคไตเนโฟรติกที่รักษายาก ได้แก่ ความดันโลหิตสูง ร้อยละ 44, ต้อกระจกร้อยละ 40, ต้อหิน ร้อยละ 15, ตัวเตี้ย ร้อยละ 17.6, อ้วน ร้อยละ 5.9 ภาวะติดเชื้อพบได้บ่อย ร้อยละ 69 ได้แก่ ฟันผุ ร้อยละ 16.2, ติดเชื้อในทางเดินปัสสาวะ ร้อยละ 14.7, พยาธิในทางเดินอาหาร ร้อยละ 10.3, ติดเชื้อในทางเดินหายใจร้อยละ 8.8 และติดเชื้อที่ผิวหนัง ร้อยละ 7.4 พบผู้ป่วยไตวายเรื้อรัง 3 ราย และ portal vein thrombosis 1 ราย ผู้ทำการศึกษาเสนอว่า ควรเลือกใช้ยาซัยโคลฟอสฟาไมด์เป็นยาตัวแรกในผู้ป่วยโรคไตเนโฟรติกที่รักษายาก เอนนาลาพริลอาจมีประโยชน์ในผู้ป่วยบางราย และภาวะเกล็ดเลือดสูงอาจบ่งถึงการตอบสนอง ไม่ดีต่อยาทั้ง 2 ชนิด ผู้ป่วยเด็กโรคไตเนโฟรติกที่รักษายาก ควรได้รับการเฝ้าระวังและรักษาภาวะแทรกซ้อนซึ่งพบได้บ่อย