Effect of enalapril in children with steroid resistant primary nephrotic syndrome

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Abstract

Background A significant proportion of children with nephrotic syndrome become steroid dependent or steroid resistant who need further medication with cytostatic or other immunosuppressive drugs such as cyclophosphamide or chlorambucil. Unfortunately studies show that the drugs give no good results and cause adverse effects.

Objective To establish the effect of enalapril in decreasing proteinuria in children with steroid resistant nephrotic syndrome.

Methods We conducted a clinical trial in Nephrology Division, Pediatrics Department, Dr. Sardjito General Hospital from January 2004 to October 2005. Subjects were randomized to either receive prednisone and enalapril (Enalapril Group) or prednisone and cyclophosphamide (CPA Group). The main parameter was proteinuria level, which was examined at the beginning of the study and then every two weeks for eight weeks.

Results Remission rate in enalapril group was 96% whereas in CPA group was 82% (P=0.09). Proteinuria level reduction in Enalapril Group from the beginning until the end was 606.92 mg/dl (99%) whereas in CPA Group the reduction was 712.97 mg/dl (91%). Statistically, there was no significant difference in the average decrease of proteinuria level between both groups (P=0.30). Odds ratio for overall adverse events in combined prednisone and enalapril therapy group compared to combined prednisone and cyclophosphamide therapy group was 0.29 (CI 95% 0.17;0.41).

Conclusion Combined prednisone and enalapril has similar effect to combined prednisone and cyclophosphamide in children with steroid resistant nephrotic syndrome. Overall adverse events in combined prednisone and enalapril group was lower than that in combined prednisone and cyclophosphamide group. [Paediatr Indones 2007;47:55-59].

Keywords: enalapril, proteinuria, steroid resistant, nephrotic syndrome

Nephrotic syndrome is a clinical disorder with symptoms of severe proteinuria, hypoproteinemia, edema, and can be accompanied by hyperlipidemia. Hematuria, hypertension and decrease in kidney function may occur. Nephrotic syndrome can occur any time in primary or secondary glomerular diseases, indicating that nephrotic syndrome is not an isolated disease.

The treatment of first choice in nephrotic syndrome is steroid; however a significant proportion of children with nephrotic syndrome develops steroid resistant. Damanik reported that 83.7% patients was steroid sensitive and 16.3% was steroid resistant, whereas Roth et al reported that 30% of nephrotic syndrome patients will develop frequent relapse or steroid resistant. Several studies report that cytostatic or immuno-suppressive drugs given to patients with steroid resistant or frequent relapse nephrotic syndrome give unsatisfactory results and many adverse effects.

Angiotensin converting enzyme inhibitor (ACE inhibitor) such as enalapril has been used to decrease proteinuria, by preventing the activity of
local ACE in arteriole wall and decrease vaso-constriction caused by angiotensin.\textsuperscript{8}

Recent studies on antiproteinuria effect of ACE inhibitor drugs show that ACE inhibitor can decrease proteinuria significantly.\textsuperscript{9-11} This study aimed to establish the effect of enalapril in reducing proteinuria in children with steroid resistant nephrotic syndrome.

## Methods

This was a randomized double blind controlled trial comparing two interventions in steroid resistant nephrotic syndrome children. The first group received combined prednisone and enalapril (Enalapril Group), while the second one received combined prednisone and cyclophosphamide (CPA Group). Subjects were children with steroid resistant nephrotic syndrome treated at the Nephrology Division, Department of Child Health, Dr. Sardjito Hospital.

To be included in this study, a child with nephrotic syndrome must have received prednisone therapy for 4 weeks but showed no response. Nephrotic patients with other systemic diseases such as systemic lupus erythematosus, diabetes mellitus, Henoch Schonlein purpura, malaria, hepatitis, amiloidosis, kidney failure or those who refused to participate in this study were excluded. Allocation of subjects into either treatment group was performed using block randomization technique.

Urine protein was measured by dipstick (qualitative method), then the results were converted into quantitative result: trace (±) = 10 mg/dl; +1 = 30 mg/dl; +2 = 100 mg/dl; +3 = 300 mg/dl; dan +4 = 1000 mg/dl.\textsuperscript{10,12}

For monitoring compliance to therapy, the parents were provided a form that had to be marked if the medicine had been taken. The parents were given explanation for duration of medication, how to take the medicine, possible side effects and the importance of compliance. Study participants were asked to visit every two weeks, where they were examined for their proteinuria level.

Sample size was calculated with formula of sample size estimation for hypothesis for two independent means.\textsuperscript{13} Based on the result of study by Sasinka \textit{et al}\textsuperscript{9}, the average proteinuria level in steroid resistant nephrotic syndrome patients with prednisone and enalapril therapy was 0.52 g/day. The difference of average proteinuria level between both groups was expected to be 20% value. The sample size for each group was 31 people.

Data were analyzed using student-t test for numerical data, and chi square for categorical data. \( P < 0.05 \) was considered statistically significant; 95% confidence intervals were supplied where appropriate. We used SPSS for Windows release 11.0 for data analysis.

## Results

The study was conducted from January 2004 to October 2005. Fifty-four children met the criteria but one child from CPA Group was dropped out, giving 53 patients completed the study; 27 patients in CPA Group and 26 in Enalapril Group. \textbf{Table 1} shows basic characteristics of study subjects.

After therapy period for eight weeks, it was found that in Enalapril Group 25 children experienced remission (96.2%), whereas in CPA Group there were only 22 children showed remission (82%). This difference was not statistically significant (\( P = 0.092 \)).

Multivariate analysis, using logistic regression toward pretreatment factors that have possibility to influence the remission, showed that there was no significant difference in case of patients age, sex, parent education, serum albumin level, serum cholesterol level, Esbach proteinuria level, serum BUN level, serum creatinin level between remission group and non remission group (\textbf{table 3}).

Proteinuria level monitoring was performed on all of research subjects every two weeks for eight weeks. The reduction of proteinuria level in both groups was almost similar. The most rapid reduction occur in first two weeks of therapy period (\textbf{figure 1}).

There was no significant difference in a decrease of proteinuria level between combined prednisone and enalapril therapy group and combined prednisone and cyclophosphamide therapy group that monitored every two weeks (\textbf{table 4}).

Drug adverse effects in both groups were also monitored and the results are presented in \textbf{Table 5}. This monitoring was based on physical examination of every visit and laboratory examination at the end of treatment period. Odds ratio (OR) for overall adverse effects occurred in combined prednisone and
enalapril therapy group compared to combined prednisone and cyclophosphamide therapy group was 0.29 (CI 95% 0.17-0.41).

**Discussion**

After therapy period of eight weeks, there were 25 children of combined prednisone and enalapril therapy group and 22 children of combined prednisone and cyclophosphamide therapy group who showed remission. The difference was not statistically significant.

The average difference of proteinuria reduction monitored every two weeks between combined prednisone and enalapril therapy group and combined prednisone and cyclophosphamide therapy group was not
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significant (P>0.05). Decrease of proteinuria level in enalapril and prednisone therapy group from beginning to the end of therapy was 606.92 mg/dL (98.63%) whereas in cyclophosphamide and prednisone therapy group was 712.97 mg/dL (98.8%).

These results support previous studies. Hogg et al.\(^{10}\) reported that enalapril can decrease protein excretion level to 50% in steroid resistant nephrotic syndrome patients. Sasinka et al.\(^{9}\) reported that enalapril can reduce proteinuria in normotensive children with proteinuria, but it had no influence on arterial blood pressure. They also found that the addition of enalapril to prednisone could accelerate proteinuria level reduction. Delucchi et al.\(^{11}\) reported that combined prednisone and enalapril therapy can increase plasma protein level. Average total plasma protein increased from 4.7 g/dl to 5.43 g/dl (P<0.01).

Our data show that the effectiveness of combined prednisone and enalapril was similar to that of combined prednisone and cyclophosphamide. However other factors including adverse effect and drug cost should be considered to determine the treatment. Adverse effects of combined prednisone and enalapril was lower than those of prednisone and cyclophosphamide, and also drug cost for combined prednisone and enalapril is less than that for prednisone and cyclophosphamide.

The drawback of this study is that the power study only 75%. Other drawback was proteinuria level monitoring by qualitative method; quantitative method for proteinuria measurement was not performed due to difficulty in collecting 24-hour specimen for children, especially for outpatients.

### References

1. Alatas H, Tambunan T, Trihono PP, Pardede SO. Konsensus tata laksana sindrom nefrotik idiopatik pada anak. Unit Kerja Koordinasi Nefrologi Ikatan Dokter Anak Indonesia, 2005.
2. Haycock G. The child with idiopathic nephrotic syndrome. In: Webb, NJA & Postlethwaite, RJ, editors. Clinical Paediatric Nephrology. 3rd ed. New York: Oxford University Press; 2003. p. 341-65.
3. Hodson EM, Knight JF, Willis, NS, Craig JC. Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trial. Arch Dis Child 2000;83:45-51.
4. Damanik MP. Clinical features of nephrotic syndrome in children. Paediatr Indones 1997;37:13-9.
5. Roth KS, Amaker BH, Chan, JCM. Nephrotic syndrome: pathogenesis and management. Pediatrics in review 2002; 23:237-47.
6. Tarshish P, Tobin JN, Bernstein J, Edelmann CM. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol 1996;10:590-3.
7. Latta K, Schmakenburg CV, Ehrich JHH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syn-

### Table 4. The difference in decrease of proteinuria level every 2 weeks between combined prednisone and enalapril therapy group and combined prednisone and cyclophosphamide therapy group

| Proteinuria reduction | prednisone-enalapril group, mg/dL (mean, SD) | prednisone-cyclophosphamide group, mg/dL (mean, SD) | p value |
|------------------------|--------------------------------------------|-------------------------------------------------|---------|
| Reduction in 0-2nd week | 425.00 (359.79) | 457.04 (369.20) | 0.75 |
| Reduction in 2nd-4th week | 133.46 (190.22) | 157.04 (300.24) | 0.75 |
| Reduction in 4th-6th week | 28.46 (27.81) | 27.81 (84.64) | 0.13 |
| Reduction in 6th-8th week | 20.00 (43.33) | 45.08 (77.31) | 0.19 |

### Table 5. Adverse effects that occur in both groups

| Adverse effects | prednisone-enalapril group (%) | prednisone-cyclophosphamide group (%) |
|----------------|-------------------------------|---------------------------------------|
| Leucopenia     | 0                             | 2 (7)                                 |
| Anemia         | 0                             | 0                                     |
| Thrombocytopenia | 0                            | 0                                     |
| Skin eruption  | 0                             | 0                                     |
| Hypotension    | 0                             | 0                                     |
| Dry cough      | 2 (8)                         | 0                                     |
| Taste disturbance | 0                           | 0                                     |
| Appetite reduction | 0                           | 4 (15)                               |
Enalapril effectiveness in childhood steroid resistant primary nephrotic syndrome in children. Pediatr Nephrol 2001;16:271-82.

8. Balfe JW, Levin L, Radde IC. Hipertensi dan terapinya. In: Masyrof M, editor. Farmakologi dan terapi pediatri. 2nd edition. Jakarta: Hipokrates; 1999. p. 751-75.

9. Sasinka MA, Podracka L, Boor A, Jurkovic I, Mitro A, Kovacs L. Enalapril treatment of proteinuria in normotensive children. Bratisl Lek Listy 1999;100: 476-80.

10. Hogg RJ, Portmann RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephritic syndrome in children: recommendation from a pediatric nephrology panel established at the National Kidney Foundation Conference on proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). Pediatrics 2000;105:1242-49.

11. Delucchi A, Cano F, Rodriguez E, Wolff E, Gonzalez X, Cumsille MA. Enalapril and prednisone in children with nephrotic-range proteinuria. Pediatr Nephrol 2000;14: 1088-91.

12. Wirya IGNW. Sindrom nefrotik. In: Buku ajar nefrologi anak. 2nd edition. Jakarta: Balai Penerbit Fakultas Kedokteran UI; 2002. p. 381-422.

13. Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Besar sampel dalam penelitian kesehatan. Yogyakarta: Gadjah Mada University Press; 1997. p. 50-2.