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Original Article

Relapse episodes in childhood primary nephrotic syndrome treated by alternate or three consecutive daily dose prednisone therapy

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Abstract

Background Prednison is still the drug of choice for the treatment of nephrotic syndrome, especially for those with minimal change. Methods of treatment to optimize the effectiveness and efficacy are still in discussion.

Objectives To evaluate the episode of relapsing minimal change nephrotic syndrome patients who received prednisone therapy by alternate or by three consecutive dose methods.

Methods We performed a retrospective cohort study using medical records of the patients with primary nephrotic syndrome admitted to Division of Nephrology, Sardjito Hospital, Yogyakarta from January 1995 to January 2005. Subjects were divided into two groups, the first group treated with alternate days while the second group with three consecutive days prednisone program. Evaluation had been done to compare both treatment program (alternate days or consecutive days).

Results Relapse episodes after six month recovery periods with alternate days treatment was 33% while those with consecutive days was as high as 83% (P>0.01).

Conclusion Alternate dose group has a lower relapse event compared to three consecutive dose group in children with nephrotic syndrome. **[Paediatr Indones. 2008;48:338-41]**.

Keywords: *primary nephrotic syndrome, prednisone, alternate days, three consecutive days, relapse*

Nephrotic syndrome (NS) is a disease characterized by proteinuria over 40 mg/m^2 or 50 mg/kg, hypoalbuminemia below 2.5 g/dl, edema, and hypercholesterolemia over 250 mg/dl.[1] NS is classified into three groups: congenital (under one year of age), primary or idiopathic, and secondary NS. According to the study conducted in US, approximately 85-95% of primary NS cases are found in pediatric patients categorized as minimal change variant. Ninety percents of patients suffering from minimal change NS will respond to prednisone therapy, confirmed by decreased proteinuria.[2]

The episodes of relapse usually occur when daily maintenance doses were reduced because of prednisone side effects and/or toxicity. The risk for relapse is as high as 60-75% classified as frequent relapse (more than two events within six months or more than four events within a year) or infrequent

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relapse (less than two events within six months) according to Constantinescu's classification.

Two alternative prednisone administration NS programs during maintenance phase are alternate dose (AD) and three consecutive days (ID). Both methods are reported to be effective and tolerable for patients even with prolonged administration up to a year or longer.[5] Currently, data about prednisone administration program whether using AD or ID for maintenance dose during remission in pediatric NS is limited.[22] The purpose of this study was to evaluate the relapse episodes in patients given AD and in those given ID methods during remission.

Methods

We conducted a retrospective cohort study. Patients' data were obtained from the available medical records of patients admitted at Nephrology Division of Sardjito Hospital, Yogyakarta from January 1995 to February 2005 with the diagnosis of primary nephrotic syndrome. Informed consent was obtained before dividing the subjects into two groups, those who were treated with AD and those treated with ID prednisone program.

We collected complete medical records data including the diagnosis, initial treatment administered to achieve remission that was based on International Study of Kidney Disease in Children (ISKDC) standard using prednisone 60 mg/m^2/day with maximum dose of 80 mg/day given in three divided doses for four weeks. Primary NS in children was defined as massive proteinuria (>40 mg/m^2/hour or >50 mg/kg body weight/day), hypoalbuminemia (<2.5 mg/dl), edema and hypercholesterolemia (>250 mg/dl) which is responsive to initial dose of prednisone (2 mg/kg body weight/day or 60 mg/m^2/day).

AD prednisone administration was labeled as nominal scale, given at remission phase with the dose of 60 mg/m^2/day on alternate day for four weeks; ID prednisone administration was measured as nominal scale, given at remission phase with the dose of 60 mg/m^2/day in three consecutive days (per week for four weeks).

Primary nephrotic syndrome patients who responded to initial dose steroid (prednisone 60 mg/m^2 per oral for four weeks) were selected. During remission phase defined by dipstick negative the treatment continued by 40 mg/m^2/day. AD prednisone was given for four weeks or 40 mg/m^2/day three consecutive day prednisone for four weeks.

Relapse was measured as nominal scale, manifested as edema and proteinuria showed by dipstick showing negative or trace proteinuria in three consecutive days, or protein excretion <40 mg/m^2/hour and dipstick positive 2 or more in three consecutive days, or protein excretion exceeded 40/m^2/hour during the first six weeks of prednisone administered in remission phase.

Results

From January 1995 to February 2005, there were 38 ID and 64 AD patients. The subject's characteristics are shown in **Table 1**. Ratio between male and female was 2:1. The means of age of nephrotic syndrome patients with AD and ID were 4.86 (SD 3.15) and 9.07 (SD 4.05) years, respectively (**Table 1**).

Relapse in AD and ID group were 21 and 33 respectively (P<0.001). Frequent relapse of patients treated with alternate days was lower than that of those who were treated with prednisone for three consecutive days (**Table 2**).

Table 1. Characteristics of primary nephrotic syndrome (NS) patients of both groups

Variable	AD subject n= 64	ID subjects n= 38	Total
Gender:			
Male	42	21	63
Female	22	17	39
Age (years), mean (SD)	4.9 (3.15)	9.1 (4.05)	
Nutritional status:			
Good	61	31	92
Poor	31	7	10
Parent's educational degree:			
Elementary School	21	20	41
Junior High School	19	11	30
Senior High School	16	7	23
Scholar	8	0	8
Parent's salary/month			
<500.000	21	21	42
500.000-1 million	24	14	38
>1 million	19	3	22

Table 2. Incidence of relapse in primary NS with AD versus three ID treatment.

Variable	AD Group	ID Group	Total	P
No relapse	43	5	48	
Relapse	21	33	54	0.01
Total	64	38	102	

Notes: ID: three consecutive days; AD: alternate days; NS: nephrotic syndrome

Discussion

In 1950, adrenocorticotropin hormone (ACTH) was first introduced for the treatment of NS. Steroid has become the main drug of choice in the management of pediatric patients suffering from NS to combat immunological reaction.[3]

In certain condition of NS, the levels of antibodies are greater compared to that of antigen, resulting in one antigen bounded by multiple antibodies. This excessive amount of antibodies will then bind nonspecific antigens. Consequently, a large amount of antigen-antibody complexes are then released into circulation. These immune complex aggregates build up to be large enough and then easily undergo phagocytosis.[4]

Another extreme condition caused by excessive antigen was the production of very small immune complexes. These complexes consist of one bivalent antibody molecule bound to two antigen molecules. These complexes are not attached to complement and therefore incapable of inducing inflammation. Immune complexes that capable of inducing pathologic abnormality are those produced by non-excessive antigen, consist of medium-sized molecule in soluble state, do not undergo phagocytosis too early, but large enough to bind complement and therefore easily induce inflammation.[4]

Immune complexes with medium-sized molecule which are not phagocytosized will be entrapped in mesangial cells located between the neck and capillary of glomerulus. Mesangial cells may serve as cell with phagocyte feature. Consequently, its phagocytosis activity will induce hypertrophy and proliferation in that area. The proteoglycan heparin sulphate which creates negative charge in internal and external layers is the main barrier to prevent the leak of negative-charged molecule such as albumin. Damage of this barrier mechanism will cause proteinuria.[5]

Study of NS in Dr. Sardjito Hospital Yogyakarta based on histopathologic features finds that most of the patients belong to minimal change lesion (46%), focal segmental glomerulosclerosis (36%), membranous glomerulonephritis (7%), mesangial proliferative glomerulonephritis (7%), and membranoproliferative glomerulonephritis (4%).[6] Therefore it is estimated that at least more than 50% are prednisone responsive NS cases. Hospital data shows pediatric NS is increasing from 15 in 1995 to 65 relapsed and or readmitted cases in 2004.

The standard of management using prednisone was developed by International Study of Kidney Disease in Children (ISKDC) and Arbeitsgemeinschaft fur Paediatrische Nephrologic (APN) which included the four weeks of initial prednisone therapy followed by another four weeks of three consecutive days or alternate days therapy programs.[7] Immunological abnormalities found in nephrotic syndrome result from reaction of antibodies with endogen glomerular antigens placed in basal membrane, thus creating deposits.[8]

Corticosteroid is classified into two large groups, namely glucocorticoid and mineralocorticoid. The main effects of glucocorticoid are liver glycogen storage build up and anti-inflammatory effect, while its influence over fluid and electrolytes balance is minimal. The prototype of this group is cortisol. On the other hand, the main role of mineralocorticoid group is to maintain fluid and electrolytes balance

Prednisone is a synthetic hormone which possesses features similar to the hormone hydrocortisone produced by adrenal gland. Among the adverse effects of prolonged prednisone treatment are sodium retention, increased appetite, increased lipid storage, increased hair growth, increased gastric acidity, excessive sweating mostly at night time, acne growth over the face, back, and chest, bone problems, growth problems, increased blood glucose level, inhibited wound healing, decreased immune system against infection, and fungus growth in the mouth.[7] Prednisone serves as immunosuppressant for the management of autoimmune abnormalities. It prevents inflammatory process by increasing capillary permeability and suppressing polymorphonuclear cell activity. Abrupt discontinuation of its ongoing treatment may result in adrenal crisis, edema, osteonecrosis, myopathy, and hypokalemia.[3]

Current study results showed that prednisone administration in pediatric patients suffering from primary nephrotic syndrome using alternate day prednisone therapy induced less relapse event compared

with those using three consecutive days prednisone therapy. Alternate day therapy is proven to be more effective in preventing relapse event in pediatric patients suffering from primary NS. Employing one day interval administration soon after the patients achieve remission resulted in significant decrease of the incidence of relapse. Alternate day dose administered in the morning will result in more improvement for the patient. Prolonged-alternate-day therapy keeps adverse effect of prednisone such as suppression effect on hypothalamus-hypophysis axis, Cushingoid condition, and inhibition of patient's growth at minimal level. The rationale for these are: 1) Therapeutic effect or antiinflammatory effect of prednisone will still exist if the drug administered routinely within a long run in an alternating manner, e.g. one day taking the drug and one day suspending, however, the drugs' adverse effect will be kept minimal; 2) Administration of prednisone every alternate morning will keep the normal activity of hypothalamus-hypophysis and adrenal axis, this condition maintains the normal physiologic process. A low blood level of cortisol at night will send a feed back signal to hypophysis through hypothalamus to produce corticotropin hormone. In a normal state, hypothalamus-hypophysis-adrenal axis system follows a diurnal rhythm. Serum ACTH level will reach its lowest level in the midnight approximately at 22.00 and oscillate back to its highest level in the morning at 06.00. Maximum level of the increasing plasma cortisol will be attained at 02.00 and 08.00 in the morning. The increased cortisol level will reduce ACTH production and return the adrenocortical activity. Three consecutive days prednisone will suppress the adrenal cortex activity in inducing ACTH production if administered continuously. One time prednisone administrated by this method, adrenocortical activity suppressed up to two weeks or several days, therefore ID or AD are beneficial. In this study AD are superior compared to ID.[9]

In conclusion, most of pediatric primary nephrotic syndrome still respond to initial dose of steroid therapy and AD prednisone exhibits less relapse episode than ID prednisone during remission.

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EDITOR'S NOTE

Difference in the characteristics of the study subjects in AD Group and ID Group has to be accounted in the conclusion of this retrospective study. Table 1 only shows some factors and ignores other factors such as severity / duration of the disease. Confounding by indication may play an important role in this case.