Options of the Treatment in Steroid Resistant Nephrotic Syndrome in Children in Central Child Teaching Hospital-Baghdad

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ABSTRACT:

BACKGROUND:

The therapy of steroid resistant nephrotic syndrome (SRNS) is still a matter of controversy.

OBJECTIVE:

To assess the options of treatment in SRNS

PATIENT AND METHOD:

A retrospective study to 50 patients randomly selected in the Central Child Teaching Hospital during study period from Jan. 2006 to July 2008. The patients age were between 6 months.-18 years. All patients who had failed to achieve an improvement in proteinuria after minimum of 4 weeks (up to 8 weeks) of prednisolone (PDN) in a dosage 2 mg/kg/day were taken. Only the patients with idiopathic nephrotic syndrome (45 patients) were involved in the study but the patients with secondary nephrotic syndrome and congenital neprosis were excluded from the study. Each patient were individualized to the type of pathology and to the type of medication used.

RESULTS:

Forty five patients were included in the study, the age range between 6 months.-18 years. Twenty eight patients were male and 17 were female, M: F ratio 1.64: 1. Regarding the type of pathology, 20 patients with focal segmental glomerulosclerosis (FSGS), 11 patients with minimal change nephrotic syndrome (MCNS), 8 patients with diffuse mesangial proliferation (DMP) and 6 patients were unknown biopsy (not down biopsy). The drugs that used were methyl prednisolone (MP) in 17 patients, Every other day steroid (EODS) in 10 patients, cyclosporineA (CsA) plus EODS in 16 patients (10 patients as first option and 6 patients as second option), cyclophosphamide (CYS) used in 8 patients (6 patients as first option and 2 patients as second option) and chlorambucil were used in 2 patients only. The response was higher in patients who received EODS (50%), followed by the patients who received CsA plus EODS (25%) then the patients who received MP(23.5%) and the patients who received CYS(12.5%) and chlorambucil(zero%).

The response to treatment was higher in females than males, 11 out of 28 males (39.28%) responded to treatment while 7 of 17 female (41.17%) responded to treatment. The patients with early presentation responded to treatment higher than those with late presentation, so 12 of 19 patients (63.15%) presented early while 10 of 26 patients (38.46%) presented late.

According to histopathology, the patients with unknown etiology had higher rate of response, 3 out of 6 patients (50%) responded to treatment followed by 7 of 20 (35%) patients with FSGS, then 2 of 8 (25%) patients with DMP, then 2 of 11 (18.18%) patients with MCNS.

CONCLUSION:

The drugs used are the common drugs and EODS is preferable type of medication used in SRNS.

KEY WARDS: steroid resistant nephrotic syndrome (SRNS), methyl prednisolone (MP), every other day steroid (EODS), cyclosporineA (CsA)**.**

INTRODUCTION:

Idiopathic nephrotic syndrome (INS) is defined by the combination of massive proternuria, hypoalbuminemia, hyperlipidemia, and oedema, and histologic abnormalities of the kidney including minimal change NS (MCNS), focal segmental glomerulosclerosis (FSGS) and diffuse mesangial proliferation (DMP) [(1)]. About 85% of children with NS are INS. In children, the incidence of NS is 1-2 per 100000 children aged below 16 year [(2).] NS usually started between the ages of 2-7 years inspite of that can presented at

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first year of life or more than 7 years of age with male to female ratio of 2:1 [3].

Incidence: Of children with MCNS, 93% achieve complete remission with 8 weeks of oral steroid[4]. In addition, 30% of children with DMP and FSGS achieved complete remission [5].

Steroid Resistant Nephrotic Syndrome (SRNS): The treatment of children with SRNS remain un satisfactory [6]. Children who fail to response to oral steroid may be treated with high dose intravenous methylprednisolone (MP) or with immunosuppressive agents such as cyclophosphamide (CYS), chlorambucil or cyclocporine A (CSA) as a combination of these drugs or as isolated with different results[7,8,9,10] respectively. However SRNS may remit spontaneously or following courses of steroid longer than the standard two months, making assessment of response to treatment in nonrandomized studies difficult [6]. Other modality of treatment including azathioprine [11] plasmaphersis [12], LDL apharesis[13], tacrolimus [14] vincristin[15] other non-immunosuppressive agent including angiotensin converting enzyme inhibitors (ACEI) [16], non-steroidal anti inflammatory drug [17] and tuna fishoil [18]. There were many other controlled trials used to assess the benefits and harms of all intervention studies used in children with SRNS [6].

PATIENTS AND METHOD:

A retrospective study of 50 patients randomly selected in the Central Child Teaching Hospital during study period from Jan. 2006 to July 2008. The patients age were between 6 months-18 years. All patients how had failed to achieve an improvement in proteinuria after minimum of 4 weeks (up to 8 weeks) of prednisolone (PDN) in a dosage of 2 mg/kg/day, only the patients with idiopathic nephrotic syndrome (45 patients) were involved in the study but the patients with secondary nephrotic syndrome and congenital neprosis were excluded from the study. Each patient were individualized to the type of pathology and to the type of medication used.

Definition: N.S. was defined as edema, plasma albumin < 25g/L, proteinuria > 40 mg/m^2/hr or protein: creatinine ratio > 200mg/mmol. Steroid resistant: was defined as persisting proteinurea follow therapy for 4 weeks or more in a dose of 2 mg /kg /d or 60mg/m^2/d as persistence of proteinuria > 3+on dipstick, urinary protein > 40 mg/m^2/h and/or persistence of a edema. [1].

Outcome measures: children achieving complete remission during and following therapy when (urine protein ≤ 1 + on dipstick or < 4mg /m^2/h for 3 or more consecutive days), the children with partial remission when (proteinuria ≤ 2 + on dipstick, < 40mg/m^2/h).

Treatment options:

1- Pulse MP: as Mendoza protocol (30mg/kg/day) [7].
2- Cyclosporine A: 4-5mg/kg/day or 150-200mg/m^2/day for 1 year, alone or with PDN. 30mg/m^2/day for 1 month followed by EODS for 6 months.
3- Cyclophosphamide: 2.5-3 mg /kg /d for 8-12 week alone or with PDN 40mg/m^2 EOD for 1 year.
4- EODS: PDN 40 mg/m^2/EOD for 1 year.
5- Chlorambucil: 0.2mg/kg/day for 2-6 months.
6- IV cyclophosphamide: 500-750 mg/m^2/month for 6 months.

RESULTS:

Forty five patients were included in the study, the age range between 6month.-18years. Twenty eight patients were male and 17 were female, M: F ratio 1.64: 1.

The Distribution of SRNS patients according to age, sex, type of presentation and pathology shown in table (1).

Table 1: Distribution of SRNS patients according to age, sex, type of presentation and pathology.

	F SGN	MCNS	DMP	UN	Total
No. of patients	20	11	8	6	45
Age of presentation	6m.-13y.	3y-7y	8m.-9m.	3y-9y	6m.-13y
Age of diagnosis	2.5y-17y	4y-18y	8m.-3.5y	5y-15y	8-18y
Male sex	10	7	3	5	28
Female sex	4	2	5	6	17
Early Presentation	9	6	2	2	19
Late Presentation	11	5	6	4	26

FSGS: focal segmental glomeruloseclerosis
MCNS: minimal change nephritic syndrome
DMP: diffuse mesangial prolifrative
UN: unknown biopsy

The distribution of patients according to response to first option of treatment shown in table (2).

Table 2: Distribution of patients according to response to first option of treatment.

	RS /FSGS	RS/MCNS	RS /DMP	RS /UN	RS /Total
Methyl PDN	2/8	0/5	1/2	1/2	4/17
CsA+EOD PDN	2/3	0/2	0/3	1/2	3/10
EOD PDN	2/7	1/1	1/1	1/1	5/10
Cyclophosphamide	0/2	1/1	0/2	0/1	1/6
Chlorambucil	0/0	0/2	0/0	0/0	0/2
Total	6/20	2/11	2/8	3/6	13/45

The distribution of patients according to response to second option of treatment shown in table (3).

Table 3: Distribution of patients according to response to second option of treatment

	RS /FSGS	RS/MCNS	RS /DMP	RS /UN	RS /Total
Methyl PDN	0/0	0/0	0/0	0	0
CsA+EOD PDN	1/4	0/2	0		1/6
EOD PDN	0/0	0/0	0/0	0	0
Cyclophosphamide	0/2	0	0	0	0/2
Chlorambucil	0/0				
Total	1/6	0/2	0	0	1/8

The degree of response to treatment in relation to sex, type of presentation and histopathology shown in table (4).

Table 4: Degree of response to treatment in relation to sex, type of presentation and histopathology.

	SRNS			
	response	No response	total	%
Male	11	7	28	39.28
Female	7	10	17	41.17
Early presentation	12	7	19	63.15
Late presentation	10	16	26	38.46
FSGS	6	14	20	23.07
MCNS	2	9	11	18.18
DMP	2	6	8	25
UN	3	3	6	50

The degree of response to type of medication used shown in table (5).

Table 5: Degree of response to type of medication used.

	Response		No response		Total
	No.	%	No.	%	
Methyl PDN	4	23.5	13	76.5	17
CsA+EOD PDN	4	25	12	75	16
EOD PDN	5	50	5	50	10
Cyclophosphamide	1	12.5	7	87.5	8
Chlorambucil	0	0	2	100	2

DISCUSSION:

No generally accepted treatment regimen is available for patients with SRNS. For this reason, a numbers of studies have been performed with immunsuppressive intervention as steroid (MP, EODS), CYS, chlorambucil CSA, Tacrolimus and plasmapharesis or immunoadsorpant [7, 8,9,12, 13, 14, 32, 33]

but there is no clear cut evidence in favor of any kind of treatment [19].

The result of this study was affected by two factors, the availability of medication and equipment and the compliance of the patients and the family.

Medication used as shown in table 2, 3 and 5 is the

common one similar to the medication as option of treatment but the result affected by small numbers of patients.

1-MP used in 17 patients, the response was 23.5% which is far away from other studies done by Murnaghan et al [23], Waldo FB et al [24], Sangwicz et al [21], Yorgin et al [20], Griswold et al [26], all these with results more than 50%. The reason of that mostly related to compliance of patients because the patients must come and admitted to the hospital every other day for 2 weeks, the second reason could be the dosage of MP used they take the lower limit as 20 mg/kg/d to that reason Tune et al [8] provide strong evidence of benefit of high dose MP and sometimes triple therapy of MP, with EODS, +/- alkylating agents.

2-CSA used in 16 patients, the response was 25%. The response was less than other studies done by Sangwicz et al [21] (5/6 response), Hyme LC et al [9] (11/14) and Cattran DC et al [10] (70% response). The other factors were the dosage used (4 – 5 mg/kg/d) and un availability of trough level measurement which appear more significant to give higher response rate as in Hyme LC et al [9]. Also the complication of the patient especially to the type of CSA available (tablet or syrup).

3-CYS used in 8 patients, the response was 1/8 (12.5%). The CYS is drug of variable result could be agood one as Siegel et al [27], Bergstrand et al [28] and Srivastava RN et al [25] range between 77%-90% while Cameron et al [29] show no response to CYS, the reason of this result is that 50% of cases treated was FSGS and Tarshish et al [30] concluded that there was no beneficial effect of CYS in these patients and EODS for 12 months is more effective.

4-EODS used in 10 patients, the response was 50%. EODS, used in different studies as Abramowicz M, et al [11], Tarshish et al [30] with azathioprine, CSA and CYS respectively and other studies from analysis of these studies done by Dooa H et al[6], the study mention that, although the majority of patients of NS who eventually respond to prednisone therapy do so within 8 weeks, regardless of underlying pathology, additional patients may enter remission after longer periods of treatment. It has been recommended that the patients should receive up to 6 months of prednisone before determining that the patients have SRNS. So our result with its simplicity can be supported by Dooa et al study [6].

5-Sex, type of presentation & the Histological finding. The result show no significant difference mostly due to small number of patients also Sarivastava et al[25], from his observation that patients with late SRNS comprise aheterogenous group of MCNS, FSGS and DMP, he hypothesized that the different pathologies in SRNS would influence the response to the immunosuppressive agents and that patient with MCNS would be more likely to respond to treatment than patient with FSGS. However no difference in efficacy in patients with MCNS or FSGS could be demonstrated, these result observed also by Dooa et al study [6].

CONCLUSION:

The drugs used are the common drugs and EODS is preferable type of medication used in SRNS.

REFERENCE:

1. Ellis D. Avner, William E. Harmon, Patrick Niaudet. Pediatric Nephrology. 5th ed. Section V steroid resistant Idiopathic Nephrotic syndrome in children 2003; 557-68.
2. Habib R, Churg J. Minimal change, mesangial proliferative glomerulonephritis and focal sclerosis, individual entities or a spectrum of disease. In: Robinson R, ed. Nephrology Today. Proc 9th Conger. Nephrol, Los Angels. New York: Springer 1984.
3. Schlesinger ER, Sultz HA, Mosher WE, Feldman JG. The NS: its incidence and implications for the community. Am J child. 1968;116: 623-32.
4. International study of kidney disease in children. The primary NS in children identification of patients with MCNS from intial response to prednisone. J pediatr. 1981;98:561-64.
5. International study of kidney disease in children. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial proliferation kidney int 1981;20:765-71.
6. Dooa H, Elesabth M, Hodsen JC, Craig. Intervention for SRNS: a systematic review. Pediatr Nephrol 2003; 18:906-12.
7. Mendoza SA, Reznik VM Giswold W, et al. Treatment of steroid resistant focal segmental glomerulosclerosis with pulse methyl perdnisolone and alkylating agents. Pediatr nephrol 1999;4: 303-7.
8. Tune BM, Kirpekar RK, Reznik VM, et al. Intravenous methylprednisolone and oral alkylating agent therapy of prednisolone-resistant pediatric focal segmental glomerulosclerosis: along term follow up. Clinical neph. 1995;43:84-88.
9. Hyme LC. Steroid resistant cyclosphorine responsive, relapsing nephritic syndrome, Pediatric Nephrology 1995;9:137-9.

10. Cattran DC, Appl GB, Hebert LA, etal. A Randomized trial of CSA in patients with SRNS North America NS study group, Kidney Int. 1999; 55:2220-6.

11. Abramowicz M, Barnett HL, Edemann CM Jr, etal. Controlled trial of azathioprine in children with nephritic syndrome. A report for the international study of kidney disease in children. Lancet I: 1970 ; 959-61.

12. Ginsbug DS Dan P. Plasmapharesis treatment for patients with steroid resistant FSGS. Clin Nephrology 1997; 48:282-7.

13. Muse E, Mune M, Fujii Y etc. Significantly rapid relieve from SRNS by LDL apharesis compaired with steroid monotherapy. Nephron Dec.;89: 408-14.

14. Schweda F, Liebl R, Riegger GA, Kramer BK. Tacrolimus treatment for steroid and cyclosporine-resistant minimal-change nephritic syndrome. Nephrol Dial Transplant 1997; 12: 2433-5.

15. Almeida MP, Almeida HA, Rosa FC. Vincristine in steroid resistant nephritic syndrome pediatr Nephrol. 1994 ; 8: 79-80.

16. Bagga A, Mudigouder BD Vasudev V, Hari P. Low versus high dose enalapril therapy in SRNS Seven Asian Cong. Of pediatric nephrology, 2000:4-6 November, Singapore.

17. Low CL, McGoldrick MD, Bailie GR. Successful management of steroid resistant nephritic syndrome using ibuprofen. Clin Nephrol. 1997; 47: 60-2.

18. Chongviriyaphan N, Tapaneya Olarn Csuthutvoravut U. Effect of tuna fish oil on hyperlipidemia and protenuria in children NS.J Med AssocThai 1999;82(suppl): 122-28.

19. Peter H, Norbert B, Reinhard MKatrin IIngeborg Z. Cyclospo. A & Chlorambucil in treatment of idiopathic FSGS. America J of kidney Dis. 2003; 43:10-17.

20. Yorgin PD, Krasher J, AL-Uzri AY. Pulse methylprednisolone treatment of idiopathic steroid resistant nephritic syndrome. pediatr Nephrol. 2001;16: 245-50.

21. Sangwicz-Pack K, Slowiaczek E, Nawrotek G. A comparison of the efficacy of cyclosporine and methylprednisolone in treatment of steroid resistant nephritic syndrome in children. Przegl Lek. 1995; 52: 436-9.

22. Ingulli E, Singh A, Baqi N, Ahmad H, Moazami S, Tejani A, Aggressive, long-term cyclosporine therapy for steroid resistant focal segmental glomerulosclerosis. J Am Soc Nephrol. 1995;5: 1820-5.

23. Murnaghan K, Vasmant D, Bensman A. pulse methylprednisolone therapy in severe idiopathic childhood nephritic syndrome. Acta Paediatr Scand. 1984; 73:733-9.

24. Waldo FB, Benfield MR, Kohaut EC. Methylprednisolone treatment of patients with steroid resistant nephritic syndrome Pediatr Nephrol. 1992;6:503-5.

25. Srivastava RN, Agarwal RK, Moudgil A, Bhuyan UN. Late resistance to corticosteroids in nephritic syndrome J Pediatr. 1986 Jan; 108(1): 66-70.

26. Griswold WR, Tune BM, Reznik VM, Vazquez M, Prime DJ, Brock P, Mendoza SA. Treatment of childhood prednisone resistant nephritic syndrome and focal segmental glomerulosclerosis with intravenous methylprednisolone and oral alkylating agents. Nephron. 1987; 46: 73-7.

27. Siege INJ, Gur A, Krassner LS. Minimal lesion nephritic syndrome with early resistance to steroid therapy. J Pediatr. 1975; 87: 377-80.

28. R martinelli, L.J. Pereira, O.M.M. silva, A.S. Okumura and H. Rocha. Cyclophosphamide in the treatment of focal segmental glomerulosclerosis. Brazilian Journal of medical and Biological Research 37: 2004 :1365-72.

29. Cameron JS, Chantler C, Ogg CS, et al. AL-Along term stability of remission in NS after treatment with CYS. BJM 1996; 4: 7-11.

30. Tarshish JN, Bernstein J, etal. Cyclophosphamide dose not benefit patients with focal segmental glomerulosclerosis. A report of the international study of kidney disease in children. Pediatr Nephrol 1996; 10: 590-93.

31. Burgess E, Management of FSGS, evidence-based recommendations. Kidney Int. 1999;55 (suppl 70): S25-S32.

32. Jochen H. H. Ehrich, christoph Geerlings, Miroslav Zivicnjak et al . Steroid resistant idiopathic childhood nephrosis: overdiagnosed and undertreated . NDT 2007;15:1090-93.

33. Gipson Ds, Gibson K, Gipson PE,et al. Therapeutic approach to FSGS in children. Pediatr. Nephrol 2007; 22:28-36.