Pulse Methylprednisolone Therapy in Children with Resistant Nephrotic Syndrome

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Abstract:

This study was conducted on 26 children with steroid-resistant idiopathic nephrotic syndrome (NS), 14 males and 12 females, ranging in age at the start of pulse methylprednisolone therapy from 1 4/12 to 9 10/12 years, admitted to Alexandria University Children's Hospital starting from 1-4-1996. All cases of idiopathic NS admitted during this period were treated by prednisone 2 mg/kg/day divided into 3-4 doses. If the child continues to have proteinuria (2+ or greater) after one month of this treatment, the nephrosis was considered steroid–resistant and renal biopsy was indicated to determine the precise etiology of the disease. All the 26 cases were still edematous with nephrotic proteinuria after one month of prednisone therapy. The diagnoses were: minimal – change disease (MCD), 8 cases, diffuse mesangial proliferation (DMP), 12 cases, and focal segmental glomerulosclerosis (FSGS), 6 cases. All cases received multiple infusions of high dose intravenous methylprednisolone as described by Mendoza and Tune. Many of the children also received cyclophosphamide according to the criteria of the previous authors. The period of follow up (from the start of therapy till 30-6-99) ranged from 4to 38 months. At the last follow up, the results were as follows: In MCD, all cases responded with disappearance of edema and nephrotic–range proteinuria, 50% with complete remission and 50% with non-nephrotic proteinuria (partial response). All maintained normal GFR. In DMP, normal GFR was maintained in 75% (9 cases). Complete remission was found in 7 cases and partial response in 2 cases. End-stage renal failure (ESRF) occurred in one case and 2 cases died (one from septicemia and one from thromboembolic complications). In FSGS, GFR was normal in 50% (3cases), two cases with complete remission and one case with partial response. GFR was decreased in one case and ESRF developed in one case. One case died from septicemia. We concluded that pulse methyl prednisolone therapy with or without cyclophosphamide has better results than those reported for cyclophosphamide alone or cyclosporine. However, newer protocols are still needed to achieve better results.

Introduction:

Steroid-resistant nephrotic syndrome (NS) commonly progresses to renal failure.(1) Thus, the management of this disease is a major concern to pediatric nephrologists.

Steroid-resistant patients may respond to an extended (3-6 months) course of cyclophosphamide, pulse methyl prednisolone or cyclosporine (CSA).(2) Some of the patients with minimal change disease (MCD) will respond to cytotoxic therapy.(3,4) Alkylating agent therapy alone seemed ineffective in focal segmental glomerulosclerosis (FSGS).(5) CSA alone seems to be relatively ineffective in patients with MCD or FSGS.(1,6) So the aim of the present work was to study the value of pulse methylprednisolone therapy in steroid-resistant NS in children.

Subjects and Methods:

This study was conducted on 26 children with steroid-resistant idiopathic NS (14 males and 12 females) ranging in age at the start of the protocol of therapy from 1 4/12 to 9 10/12 years. This study was conducted on patients admitted to Alexandria University Children's Hospital starting from 1-4-96. The data presented in this paper are those reported until 30-6-99. The survivors are still followed up and their data will be presented in future papers. Consent was obtained from parents of all children.

The diagnosis of idiopathic NS depended on thorough history taking and full clinical examination and the following laboratory investigations: urine analysis and estimation of proteins in 24 hours urine (or protein / creatinine in random urine sample in young patients: nephrotic–range proteinuria >2),(5) serum albumin, serum cholesterol, blood urea, serum creatinine, creatinine clearance (using the height formula of schwartz and colleagues)(7) and serum complement 3 (C3). In addition, complete blood count (CBC), X-ray chest and tuberculin testing were done to all patients. To exclude relatively common diseases that may produce secondary NS in Egypt, the following investigations were done: antinuclear antibody (ANA) and anti-deoxyribonucleic acid (anti-DNA) antibodies to exclude systemic lupus erythematosus (SLE) (when clinically accepted), hepatitis B surface antigen (HBs Ag) and anti-hepatitis C (anti–HCV) antibodies as well as stool analysis, rectal snip and serology

for schistosomiasis for patients coming from rural area. All cases of idiopathic NS admitted during this period were treated with prednisone 2 mg/kg/day divided into 3-4 doses. If the child continues to have proteinuria (2+ or greater) after one month of this treatment, the nephrosis was considered steroid–resistant and renal biopsy was indicated to determine the precise etiology of the disease.[2] Out of large number of cases of idiopathic NS, only 26 cases were steroid–resistant (2 of them had responded to previous courses of prednisone i.e. they were late nonresponders and 24 cases were initial non-responders). All cases were edematous with nephrotic-range proteinuria.

Steroid–resistant cases were subjected to renal biopsy using ultrasound–guided, automatic Tru-cut needles (14 or 18 gauge) under general analgesia and local anesthesia. The procedure was done by the author with no complications in any case. Specimens were examined by light microscopy and electron microscopy. The diagnoses were 8 cases of MCD, 12 cases of diffuse mesangial proliferation (DMP) and 6 cases of FSGS.

All steroid–resistant cases received multiple infusions of high-dose intravenous methyl prednisolone as described by Mendoza et al. [8] and Tune et al. [9] (table I).

Table I. Treatment protocol for children with steroid–resistant NS.

Week	Methyl prednisolone	Prednisone
1-2	30 mg / kg q o d	None
3 –10	30 mg /kg weekly	2 mg /kg q o d
11- 18	30 mg /kg q o week	± taper
19-52	30 mg /kg monthly	slow taper
53-78	30 mg / kg q o month	slow taper

If patients improved consistently throughout the treatment they did not receive cyclophosphamide; however, many of the children also received cyclophosphamide. The criteria for the addition of cyclophosphamide were: [1] persistent nephrotic–range proteinuria (urine protein / creatinine >2) after the first 10 weeks of methylprednisolone therapy; or [2] initial improvement with a subsequent significant rise in proteinuria. In either case, the protocol was restarted and cyclophosphamide (2mg/kg/day) given for 12 weeks with continued weekly methylprednisolone infusions. Less frequent methylprednisolone infusions were then given and oral prednisone tapered, as described in table I. Out of 26 cases, 15 received one course of cyclophosphamide.

The period of follow up (from the start of the protocol till 30-6-99 ranged from 4-38 months. The follow up included thorough periodic history taking and clinical examination including measurement of blood pressure and height (or length) and periodic ophthalmologic examination (for cataract) and regular investigations especially for proteinuria, renal functions and WBCs.

Results:

The data of the cases with steroid-resistant NS are shown in tables II to IV. Out of 26 cases, 15 cases received one course of cyclophosphamide. Repeated courses were not used in any case for fear of exceeding the presumed threshold for gonadal toxicity. Out of these 15 cases, 6 developed leukopenia (<4000 WBCs/cmm) which was transient (resolved when the drug was held) and the courses were completed. No other acute complications occurred (alopecia, hemorrhagic cystitis, anorexia, abdominal pain, nausea and vomiting). [10,11]

The period of follow up ranged from 4-38 months. Out of 26 cases, 7 were still receiving methyl prednisolone and the remaining cases have completed the course. At the end of the period of follow up: 13 were in remission (2 of them were still receiving methyl prednisolone). After complete remission, no one relapsed again till now. Seven cases had non-nephrotic proteinuria with normal GFR (one of them still receiving methyl prednisolone). One case had nephrotic-range proteinuria with decreased GFR (still receiving methylprednisolone), Two cases had ESRF. Three cases died [2 from septicemia and one from thromboembolic complication (TEC)], all were still receiving methylprednisolone, 2 of them received cyclophosphamide but they were not leukopenic. As regards side effects of methyl prednisolone, five patients suffered from nausea. No one had cataract. Seven cases developed hypertension, which was easily controlled with medication and resolved when steroids were discontinued. One case had decreased growth (this case had ESRF).

Table II. Data of cases with steroid-resistant MCD

Case Number	Age at start of protocol (years)	Sex	Cyclophos-phamide	Period of follow-up	Status of patients At last follow-up
1	3 4/12	male	+	35	Proteinuria, Normal GFR
2	1 7/12	male	+	34	Remission
3	2	male	-	30	Remission
4	2 6/12	female	+	36	Proteinuria, Normal GFR
5	3 2/12	male	+	32	Proteinuria, Normal GFR
6	3	male	+	26	Proteinuria, Normal GFR
7	2 8/12	Male	-	32	Remission
8	1 10/12	female	+	28	Remission
Range	1 7/12-3 4/12			26 – 36	
Mean	2.51			31.63	
SD	0.65			3.46	

Table III. Data of cases with steroid-resistant DMP

Case Number	Age at start of protocol (years)	Sex	Cyclophos-phamide	Period of follow-up	Status of patients At last follow-up
1	5 7/12	Female	+	34	Remission
2	2 4/12	Female	+	37	Proteinuria, Normal GFR
3	1 6/12	Male	-	17	Remission
4	4	Male	-	12	Died (Septicemia)
5	9 10/12	Female	-	38	Proteinuria, Normal GFR
6	2 2/12	Male	-	22	Remission
7	3 2/12	Male	+	26	Remission
8	2 8/12	Female	-	30	Remission
9	2 6/12	Male	+	31	Remission
10	3 4/12	Female	-	33	Remission
11	4	Male	+	15	Died (Thromboembolic Complications) (TEC)
12	3 11/12	Female	-	22	End-stage renal failure (ESRF)
Range	1 6/12- 9 10/12			12 – 38	
Mean	3.06			26.25	
SD	2.2			8.77	

Table IV. Data of cases with steroid-resistant FSGS

Case Number	Age at start of protocol (years)	Sex	Cyclophos-phamide	Period of follow-up	Status of patients At last follow-up
1	1 10/12	Female	-	4	Remission
2	2	Female	+	14	Proteinuria, Normal GFR
3	4 2/12	Male	-	28	Remission
4	3 2/12	Male	+	16	Proteinuria (nephrotic-range), Decreased GFR
5	2 10/12	Female	+	26	End-stage renal failure (ESRF)
6	1 4/12	Female	+	12	Died (Septicemia)
Range	1 4/12- 4 2/12			4 – 28	
Mean	2.56			16.67	
SD	1.04			8.82	

Discussion:

Patients who do not respond to the initial course of prednisone (early non-responders) should have a renal biopsy .A large proportion of them, especially those six years old or younger, will have MCD.[12] In our study, 8 out of 24 cases who did not respond to the initial course of prednisone had MCD. About 60% of initial non-responders have partial responses to steroid therapy, with disappearance of the NS but persistence of proteinuria.[13,14] They generally become asymptomatic and therefore do not require therapy for edema. It is unclear whether continuation of alternate day steroids will hasten the disappearance of proteinuria. In about 40% of initial non-responders edema and its accompanying symptoms persist despite corticosteroid therapy, [14,15] presenting difficult therapeutic problems. All

our cases were still edematous one month after prednisone therapy.

In our study, all cases of MCD responded to methylprednisolone with disappearance of edema and nephrotic–range proteinuria. Four cases (50%) had complete remission with no relapses till now. Four cases (50%) had non-nephrotic proteinuria. All cases had normal estimated GFR. We did not find similar studies using methylprednisolone in MCD to compare with our results.

In other studies, some patients with MCD responded to cytotoxic therapy.[3,4] A collaborative study from France reported the response to CSA therapy in 65 children, 45 with MCD and 20 with FSGS.[1] The rate of complete remission was 42% (27 of 65), and partial remission was seen in 6% (4 of 65); the treatment was unsuccessful in 52% (34 of 65). After a mean follow–up evaluation of 38 months after the treatment was started, 23 patients were in complete remission, 8 have had a steroid–sensitive relapse, 3 were in a partial remission, 18 remained nephrotic, and 13 (20%) had ESRF. Although the outcome seemed somewhat worse in children with FSGS than in children with MCD, this difference was not dramatic. So, methylprednisolone seems better than cytotoxic therapy and CSA in children with MCD.

Mesangial hypercellularity may reflect a more severe degree of glomerular injury than does MCD without mesangial hypercellularity, and the greater the proliferation, the greater the glomerular injury.[12] Mesangial hypercellularity has been associated in some studies with decrease in responsiveness to steroids [16,17] and progression to renal failure. [18,19] Good outcomes have also been reported. [20-22]

In our study, 12 out of 26 cases had DMP, 2 of them were late non-responders (responded to previous courses of prednisone). Nine cases had responded, 7 were in complete remission (with no relapses till now) and 2 had non-nephrotic proteinuria and normal estimated GFR. One case had ESRF and 2 cases died (one from septicemia and one died suddenly, most probably from TEC). No similar studies were done to compare with our results.

Although FSGS is relatively uncommon, it is the most frequent progressive glomerular disease in children and is second only to congenital anomalies as a cause of pediatric ESRF.[5]

In our study, 3 out of 6 (50%) patients have a normal estimated GFR. Of these, two have cleared their proteinuria (one still receiving therapy and one receiving no therapy with no relapse till now). The remaining one has non-nephrotic proteinuria. Two patients out of the 3 with persistent nephrotic–range proteinuria developed a decreased GFR, one of them progressed to ESRF. The remaining patient died from septicemia (she died after 12 months of starting the protocol. She had nephrotic–range proteinuria despite receiving a course of cyclo-phosphamide in addition to methylprednisolone).

During the past 15 years, Mendoza et al. have treated children with FSGS with a protocol involving multiple infusions of high–dose intravenous methylprednisolone, often in combination with oral alkylating agent therapy.[8,9] In their study, after a period of follow–up of 76 $\pm$ 8months, 24 of 32 (75%) have a normal estimated GFR. Of these 21(66%) have cleared their proteinuria (protein–to–creatinine ratio $\leq$ 0.20) and are receiving no therapy. The remaining 3 have non-nephrotic proteinuria. No relapses have occurred in the great majority of patients who achieved a complete remission with methylprednisolone infusion therapy. The few who have relapsed have responded well to additional therapy. Thus, children who have cleared their proteinuria and completed the protocol seem to be at little risk of developing progressive renal failure. Eight patients with persistent nephrotic proteinuria developed a decreased GFR, and 3 of these (9%) progressed to ESRF. All of the patients who continued to exhibit nephrotic-range proteinuria after receiving the methylprednisolone and alkylating agent therapy eventually developed a decreased GFR.

The remission rate reported by Mendoza et al. was considerably higher than that reported in other series of children with FSGS.[9] There has been one other report of the use of intravenous methylprednisolone in the treatment of steroid – resistant NS.[23] The children in that series had a much less favorable response to therapy which the authors attributed to the fact that many of their patients were of African descent. In addition several details of the present protocol were not followed. Therefore whether the difference in outcome in the two series was caused by a difference in the race of the patients, the treatment protocol , or some other variable is not clear .

In our study, we have followed the details of the protocol of Mendoza (except the repeated courses of alkylating agent therapy, we used one course only). However, our patients are few (only 6 patients) and are different from those of Mendoza (they are Egyptians). This may explain the difference in the results.

Cyclophosphamide appears to be no better than prednisone in inducing remission in children with FSGS.[24] Similar results have been reported with chlorambucil.[25]

Several authors have treated steroid–resistant FSGS with CSA. CSA alone seems to be relatively ineffective in these patients. The limited experience reported on the use of CSA in patients with FSGS unresponsive to steroid therapy has not been encouraging.[26-32] In the six patients reported by Waldo and Kohaut,[32] only one had a decrease in proteinuria. In the four patients of Garin et al. [27] treated with a dose of 5 mg/kg/day there was no change in proteinuria or in hypoalbuminemia. Of the 13 patients of Brodehl et al.,[26] four experienced a complete remission and two had an increase in serum albumin, but the remaining seven children showed no response. Niaudet and Habib [6] recently reviewed seven series of children with steroid–resistant NS. Only 12 out of the 60 children achieved a complete remission with CSA alone. Somewhat better results have been reported when a combination of CSA and prednisone is used in steroid–resistant NS. A collaborative study from France reported the response to CSA therapy in 65 children, 45 with MCD and 20 with FSGS.[1] The results were mentioned earlier. So, methylprednisolone therapy in children with FSGS is generally better than cytotoxic therapy and CSA despite the difference in results among different populations.

We did not find a significant difference between the patients who responded to methyl prednisolone and the patients who did not respond as regards pretreatment proteinuria, serum albumin concentration or estimated GFR (taking the patients together, not each group separately because of the small numbers). Other authors reported that the magnitude of pretreatment proteinuria, serum albumin concentration, or estimated GFR did not predict which patients with FSGS would respond to the protocol with a complete remission.[5] These authors are currently reviewing their patients further with the hope of defining a subgroup that is unlikely to respond to this treatment.

In our study, five patients suffered from nausea during or immediately after the infusion. This was most severe when the interval between infusions was one month or longer. No one had cataract. Seven cases developed hypertension which was easily controlled with medication and resolved when steroids were discontinued. One case had decreased growth (this case had ESRF).

Other workers reported that, despite the fact that the protocol involved large doses of intravenous steroids administered over a long period of time, the treatment was well tolerated.[5] The most common adverse effect was nausea during and immediately after a methylprednisolone infusion. This was most severe when the interval between infusions was one month or longer. Steroid cataracts developed in 22% of the children but were generally small and did not affect vision in any case. The cataracts disappeared in one child after he went into remission and treatment was discontinued. Decreased growth was seen in 17% of these patients. One of these children had catch–up growth at the end of protocol, but the remaining children did not. Hypertension developed during the protocol in 17% of the patients but was easily controlled with medication and resolved when steroids were discontinued.

In our study, 40% developed leukopenia which was transient and the courses were completed. No other acute complications occurred (alopecia, hemorrhagic cystitis, anorexia, abdominal pain, nausea and vomiting).[10,11] Other authors reported that 19% of the children with FSGS who received an alkylating agent therapy developed WBC counts of < 4000 cmm. Leukopenia resolved when the drug was held and the full course of alkylating agent therapy was completed.[5]

In conclusion, in cases of MCD, all patients responded to methylprednisolone, 50% with complete remission and 50% with non-nephrotic proteinuria. All had normal estimated GFR. In DMP the response was less favorable. Normal estimated GFR was found in 75%. Complete remission was achieved in 58% and partial response in 17%. In FSGS, 50% had normal estimated GFR. Complete remission was achieved in 33.3% and partial response was obtained in 16.7%. In general, these results could not be obtained with alkylating agents or with cyclosporine. However newer protocols are needed to achieve better results in resistant NS to prevent mortality and morbidity especially progression to ESRF.

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