SINGLE VERSUS DIVIDED-DOSE STEROIDS IN TREATMENT OF NEPHROTIC SYNDROME

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ABSTRACT

Introduction*: Oral corticosteroids form the cornerstone for management of most children with nephrotic syndrome. Prednisolone should be administered at a dose of 60 mg/m²/day (maximum daily dose, 80 mg) for 4-6 weeks. Daily therapy may be either given, as a single morning or divided doses. We aim by this study to compare the regimen of giving steroids in a single daily dose with that of giving them in three-divided doses, as regard the compliance, response to treatment, and occurrence of complications.* ***Patients and methods****: The study was conducted on 30 patients having presumed steroid-responsive minimal change nephrotic syndrome. 15 patients were given prednisolone in a single daily dose. The other 15 patients were given prednisolone in three divided doses.* ***Results:*** *There was no significant statistical differences between the two groups of patients as regard the duration of treatment before remession or complications of nephrotic syndrome. No complications related to steroids were observed in any of our patients.* ***Conclusion:*** *Prednisolone, as a single morning dose is as effective as divided doses for inducing remission with no higher risk of complications. As single-dose steroid therapy is likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of nephrotic syndrome.*

INTRODUCTION

Nephrotic syndrome (NS) is a condition in which the glomeruli of the kidney leak protein from the blood into the urine. It results in hypoproteinaemia and general is edoedema (Elisabeth et al., 2010)

Nephrotic range proteinuria is defined as proteinuria exceeding 1000mg/m² per day or spot (random) urinary protein-to-creatinine ratio exceeding 2 mg/mg. The proteinuriain child-hood NS is relatively selective, constituted primarily by albumin. Estimates on the annual incidence of NS range from 2-7 per 100,000 children, and prevalence from 12-16 per 100,000 (Eddy and Symons, 2003).There is epidemio-logical evidence of a higher incidence of NS in children from south Asia (McKinney et al., 2001).

The condition is primary (idiopathic) in 95 per cent cases. An underlying disorder that might be identified in less than 5 per cent cases, includes systemic lupus erythematosus; Henoch Schonlein-purpura; amyloidosis; and infection with HIV, parvovirus B19,and hepatitis B and C viruses (Bagga and Srivastava, 2005).

More than 80 per cent patients with nephrotic syndrome show minimal change disease (MCD) characterized by normal renal histology on light microscopy. The remaining is contributed by focal segmental glomerulo sclerosis (FSGS) and mesangioproliferative glomerulo nephritis (Mes PGN). MCD and FSGS are often considered to represent the samepatho physiological process. Membrano-proliferative glomerulo nephritis and membranous nephropathy are uncommon conditions in childhood (Srivastava et al., 1975).

The age at initial presentation is useful in assessing the underlying etiology. NS presenting in the first three months of life (congenital NS) might be secondary to intrauterine infections, *e.g*., congenital syphilis, toxoplasmosis and cytomegalovirus disease (Niaudet, 2004). The usual age at the onset of symptoms in patients with MCD is between 2-6 yr; 30 per cent of the adolescents also show MCD. FSGS may occur throughout childhood, though the median age is usually below 8 yr (Bagga and Srivastava, 2005). Membrano-proliferative glomerulo nephritis is typically seen in older children and adolescents (Arvind & Mukta, 2005).

Common definitions for defining the course of NS are listed in Table I (Bagga and Srivastava, 2005).

Table (I): Common definitions to define the course of nephrotic syndrome.

Relapse: Urinary protein excretion >40 mg/m²/h; > 3+ by dipstick for 3 consecutive days
Remission: Urinary protein excretion <4 mg/m²/h; nil or trace by dipstick on spot sample for 3 consecutive days
Frequent relapses: Two or more relapses in 6 months of initial response; 4 or more relapses in any 12 month period
Steroid dependence: Occurrence of 2 consecutive relapses during steroid therapy or within 2 wk of its cessation

The pathogenesis of MCD is unclear, but there is a strong evidence of immune dysregulation, chiefly involving cell-mediated immunity (CMI). The tendency of NS to manifest and relapse after viral infections or an atopic episode, the association with HLA antigens and Hodgkin's lymphoma, and the therapeutic response to steroids and cyclosporine A (CsA) support this view. The occurrence of prolonged remissions following measles, which down regulates CMI further endorses this hypothesis. Abnormalities of T cell subsets and/or function have been variably reported in a number of patients with MCD (Arvind & Mukta, 2005). Most of the functional abnormalities that are described are not specific and might represent an effect (rather thana cause) of the disease (Grimbert et al., 2003).

Oral corticosteroids form the cornerstone for management of most children with NS. The commonly used preparations are prednisone (USA) or prednisolone (most other countries including India) (Arvind & Mukta, 2005).

Children with onset of uncomplicated NS between 1 and 8 yr of age are likely to have steroid-responsive minimal change NS (MCNS), and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features making MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 yr or >8 yr) should be considered for renal biopsy before treatment. In children with presumed MCNS, prednisone should be administered at a dose of 60 mg/m²/day (maximum daily dose, 80 mg) for 4-6 weeks. About 80-90% of children respond to steroid therapy within 3 weeks (Priya and Ellis, 2011). Daily therapy may be either given, as a single morning or divided doses (Arvind & Mukta, 2005). After the initial 6-wk course, the dose should be tapered to 40 mg/m²/day given every other day as a single dose for at least 4 wk. The alternate-day dose is then slowly tapered and discontinued over the next 1-2 mo (Priya and Ellis, 2011). Trials to determine the appropriate duration of initial corticosteroid therapy are in progress, including one by the British Association of Pediatric Nephrology. Based on current evidence and the need to reduce steroid toxicity, most specialists recommend that the initial episode be treated with prednisolone for 6 wk daily and 6-wk alternate day (total 12 wk therapy)(Eddy and Symons, 2003).

AIM OF THE WORK

The aim of this study is to compare the regimen of giving steroids in a single daily dose with that of giving them in three-divided doses in treatment of presumed steroid-responsive minimal change nephrotic syndrome (MCNS), as regard the compliance, response to treatment, and occurrence of complications.

PATIENTS AND METHODS

The study was conducted on 30 patients having NS, aged from 2 to 8 years, in Assiut University Children Hospital (AUCH) through 2014. Some of these patients had infrequently relapsing NS. Selection of these patients was accomplished as follow. Patients suspected clinically to have an initial or an infrequently relapsing NS for having polyurea, whitish frothy urine, edema of lower limbs, preiorbital edema, and/or as cites were subjected to the investigations including urinalysis, estimation of urinary proteins; plasma proteins; serum cholesterol; and C3 complement, and assessment of renal function (measurement of serum urea and creatinine) for confirmation of the dignosis and follow up of the treatment later on. Cases of steroid-resistant, steroid-dependent, and frequently relapsing NS and cases with features making MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 yr or >8 yr)were excluded from the study, which included only the presumed steroid-responsive minimal change nephrotic syndrome (MCNS) cases (no gross hematuria, normal blood pressure, no renal insufficiency, no hypocomplementemia, and ageranging from 1 to 8 yr).

Inclusin criteria:

1. Initial and infrequently relapsing NS.
2. Age from 1-8yr.
3. No gross hematuria.
4. Normal blood pressure.
5. Normal renal function.
6. Normal serum complement.

Exclusion criteria:

1. Cases of steroid-resistant, steroid-dependent, and frequently relapsing NS.
2. Age <1 yr or >8 yr.
3. Gross hematuria.
4. Hypertension.
5. Renal insufficiency.
6. Hypocomplementemia.

After confirming a negative PPD test 15 patients (group 1) were given prednisolone at a dose of 60 mg/m²/day (maximum daily dose, 80 mg) in a single daily dose for 4-6 weeks. Then, in responding cases only (clinical remission, diuresis, and urine trace

or negative for protein for 3 consecutive days), prednisolone was tapered to 40 mg/m²/day given every other day for 4 weeks, then tapered and discontinued over the next 1-2 mo. N.B Patients showing no response after 8 wk of daily steroid therapy are considered steroid resistant but, fortunately this did not occur during our study. Other lines of treatment (fluid restriction, salt restriction, diuretics, and 25% albumin) were given when indicated.

The other 15 patients (group 2) were given prednisolone at a dose of 60 mg/m²/day (maximum daily dose, 80 mg) inthree divided doses for 4-6 weeks. the rest of course of treatment was accomplished in a similar manner to the previous 15 patients. Again, Patients showing no response after 8 wk of daily steroid therapy are considered steroid resistant but, fortunately this did not occur during our study.

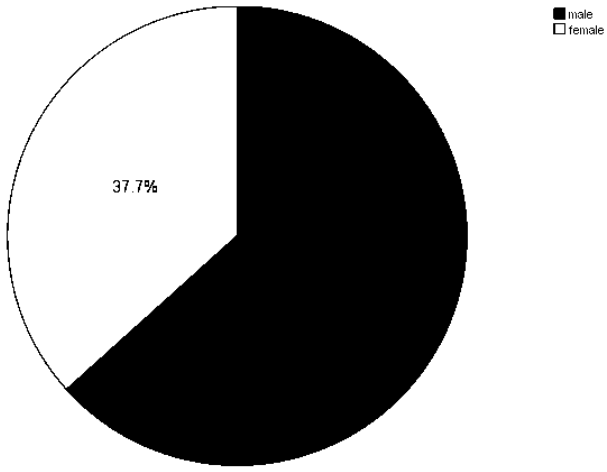
Ethical considerations: The study was approved by the ethical committee, Faculty of Medicine, Assiut University.

RESULTS

The study included 19 (63.3%) males and 11 (37.7%) females, figure 1. The ages of patients ranged from 2 to 8 (mean± SD: 5.35 ± 1.7) years. The 15 patients, given the single-dose regimen, included 9 males (60%) and 6 females (40%), while the 15 patients, given the divided-dose regimen, included 10 males (66.7%) and 5 females (33.3%). Table 2 shows a comparison between ages and sex distribution of the two groups of patients. There is no significant statistical differences between the two groups of patients as regard ages and sex distribution.

18 patients had past H/O nephrotic syndrome (60%), ten in group1 and eight in group 2, while only one patient had family H/O nephrotic syndrome (3.3%). This patient was related to group 2, table 2.

Figure 1: Sex distribution of the patients



All patients had bilateral lower limb edema. Ascites was present in 22 patients (73.3%), 11 in each group, while periorbital edema was present in 25 patients (83.3%), 12 in group1 and 13 in group 2. Table 3 shows that there is no significant statistical differences between the two groups of patients as regard the clinical manifestations.

Table (2): Demographic criteria of the two groups of patients.

	Group 1	Group 2	P value
Age(y):			
Range	2-7 y	2-8 y	0.64(ns)
Mean±SD	5.5±1.59	5.2±1.86	
Sex (n&%):			
Male	9 (60%)	10 (66.7%)	1.00 (ns)
Female	6 (40%)	5 (33.3%)	
Past H/O NS (n&%)	10 (66.7)	8 (53.3)	0.71(ns)
Family H/O NS (n&%)	0 (0.0)	1(6.7)	1.00 (ns)

ns = non significant. SD = standard deviation.
n = number.

Table (3): Clinical manifestations in the two groups of patients.

	Group 1		Group2		P-value
	No.	%	No.	%	
Ascites	11	73.3	11	73.3	1.00(ns)
Periorbital edema	12	80.0	13	86.7	1.00 (ns)

Fisher's Exact test. NS= nephrotic syndrome.

Microscopic haematuria was found in only one patient (3.3%), related to the first group. All patients had heavy proteinurea, urinary proteins ranged from 1000 to 1600 (1205 ± 164.6) mg/m²/24 h; hyportoteinemia, plasma proteins ranged from 1.5 to 4.4 (2.9 ± 0.7) gm/dl; hypercholesterolemia, serum cholesterol ranged from 230 to 673 (444±136) mg/dl; normal serum urea (3.5±1.1 mmol/L); normal serum creatinine (37.1±10.5 µmol/L); and normal serum C3 complement (124±19 mg/dl). Table 5 shows that there is no significant statistical differences between the two groups of patients as regard these investigatory findings.

Duration of treatment before remission ranged from 2 to 7 (3±1) weeks. Complications of nephrotic syndrome occurred in only one patient related to group 2, who had impetigo (3.3%). There was no significant statistical differences between the two groups of patients as regard the duration of treatment before remession and the complications of nephrotic syndrome, table 4. No complications related to steroids were observed in any of our patients.

Table (4): Outcome of treatment in studied patients.

	Group 1	Group 2	P-value
Duration before remession (mean±SD)	3.2±0.77 weeks	3.3±1.35 weeks	0.77(ns)**
Complications (n&%)	0 (0%)	1(6.7%)	1.00 (ns)*

*Fisher's Exact Test **T-test

Table (5): Investigatory findingsfound in the two groups of patients.

	Group 1	Group 2	P-value
Microscopic haematuria (n&%)	1(3.3%)	0 (0%)	1.00 (ns)*
Urinary proteins (mean±SD)	1225±175.9 mg/m²/24h	1185±155.9 mg/m²/24h	0.51(ns)**
Plasma proteins (mean±SD)	2.89±0.79 gm/dl	2.94±0.73 gm/dl	0.87(ns)**
Serum cholesterol (mean±SD)	452.9±120.8 mg/dl	434.7±153.6 mg/dl	0.72(ns)**
Serum urea (mean±SD)	3.5±0.9 mmol/L	3.49±1.3 mmol/L	0.98(ns)**
Serum creatinine (mean±SD)	37.1±10.9 µmol/L	37.06±10.5 µmol/L	0.99(ns)**
C3 complement (mean±SD)	124.7±16.7 mg/dl	123.8±22.2 mg/dl	0.90(ns)**

*Fisher's Exact Test **T-test

DISCUSSION

Our results showed that there was no significant statistical differences between patients who received prednisolone as a single morning dose and those who received it in three-divided dose as regard the duration of treatment before remission or complications of nephrotic syndrome. Moreover no complications related to steroids were observed in any of the two groups of patients. So our results shows that prednisolone, as a single morning dose is as effective as divided doses for inducing remission with no higher risk of complications. As single dose steroid therapy is convenient and likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of nephrotic syndrome.

Elisabeth et al., 2010 found that during daily therapy, prednisone is as effective when administered as a single daily dose compared with divided doses. Our results are also in accordance with results of Arvind & Mukta (2005) who found that prednisolone, as a

single morning dose was as effective as divided doses for inducing remission with no higher risk of gastrointestinal adverse effects. Our results are also in accordance with Guidelines for the Management of Nephrotic Syndrome issued by Renal Unit of Royal Hospital for Sick Children, November, (2005).

A study from India failed to show any advantage of divided daily doses over single morning dosage in the time to remission, and an advantage of morning administration of steroids is that suppression of the pituitary-adrenal axis is minimized (Ekka et al., 1997).

Our results showed that 63.3% of our patients who had idiopathic nephrotic syndrome were males and male to female ratio was nearly 2:1. This is consistent with the well-known fact on idiopathic nephrotic syndrome that it is more common in boys than in girls (2:1) (Priya and Ellis, 2011).

Regarding the clinical manifestations, all patients had bilateral lower limb edema and periorbital edema was present in 83.3%. Ascites was present in 73.3%. Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusion, and genital edema(Priya and Ellis, 2011).

Microscopic haematuria was found in only 3.3% of our patients, while all patients had normal serum urea and creatinine. Microscopic hematuria is present in 20% of children with nephrotic syndrome. The serum creatinine value is usual lynormal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume (Priya and Ellis, 2011).

Children with untreated nephrotic syndrome are at increased risk of bacterial infection, characteristically resulting in peritonitis, cellulitis or septicaemia, of thromboembolic phenomena and of protein caloriemal nutrition. Before antibiotics became available, two thirds ofchildren with nephrotic syndrome died (Elisabeth et al., 2010). As regard complications of NS, only one patient (3.3%) had a complication (impetigo).This patient was related to group 2 (the group given steroids in divided doses). There was no significant statistical

differences between the two groups of patients as regard the complications of nephrotic syndrome, table 4. Thus giving steroids as a single dose is not associated with increased risk of complications related to NS.

Complications related to corticosteroid toxicity (cushingoidappearance, hypertension, cataracts, and/or growth failure) did not occur in any of our patients. This indicates that giving steroids as a single morning dose is not associated with increased risk of complications related to steroids.

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older (Priya and Ellis, 2011). Whether the single-dose steroid therapy is associated with a higher, a lower, or the same rate of relapse as the divided-steroid therapy needs further patient prolonged studies.

CONCLUSION

Prednisolone, as a single morning dose is as effective as divided doses for inducing remission with no higher risk of complications. As single dose steroid therapy is likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of nephrotic syndrome.

REFERENCES

1. **Arvind Bagga & Mukta Mantan.** Nephrotic syndrome in children**.** Indian J Med Res 122, July 2005, pp 13-28

2. **Bagga A, and Srivastava RN. Nephrotic syndrome.** In: Srivastava RN, Bagga A, editors. *Pediatric Nephrology*. 4th ed. New Delhi: Jaypee; 2005 p. 159-200.

3. **Eddy AA and Symons JM.** Nephrotic syndrome in childhood. *Lancet* 2003; *362* : 629-39.

4. **Ekka BK, Bagga A, Srivastava RN.** Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatr Nephrol 1997;11:597-9.

5. **Elisabeth M Hodson, Narelle S Willis, and Jonathan C Craig.** Corticosteroid therapy for nephrotic syndrome in children. The Cochrane Collaboration, 2010, Issue 4.

6. **Grimbert P, Audard V, Remy P, Lang P, and Sahali D.** Recent approaches to the pathogenesis of minimal-change nephrotic syndrome. *Nephrol Dial Transplant* 2003; *18*: 245-8.

7. **McKinney PA, Feltbower RG, Brocklebank JT, and Fitzpatrick MM.** Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol* 2001; *16*:1040-4.

8. **Niaudet P.** Genetic forms of nephrotic syndrome. *Pediatr Nephrol* 2004; *19*:1313-8.

9. **Priya Pais and Ellis D.** Avner. Idiopathic nephrotic syndrome in: Nelson Textbook of Pediatrics, 19th Ed., R. E. Behrman and R. M. Kliegman, editors, W. B. Saunders Company, publishers, P: 179-188, (2011).

10. **Renal Unit of Royal Hospital for Sick Children**: Guideline for the Management of Nephrotic Syndrome, November, (2005).

11. **Srivastava RN, Mayekar G, Anand R, Choudhry VP, Ghai OP, and Tandon HD.** Nephrotic syndrome in Indian children. *Arch Dis Child* 1975; *50* : 626-30.

مقارنة بين الستيرويدات ذات الجرعة الواحدة والمقسمة فى علاج متلازمة النفروزز

تعتبر الستيرويدات التى تؤخذ عن طريق الفم حجر الزاوية فى علاج متلازمة النفروزز، حيث يعطى البريدنيزولون بمعدل 60مجم/كجم/يوم بحد أقصى 80 مجم يومياً لمدة من 4 إلى 6 أسابيع. وهذا العلاج اليومى يمكن أن يعطى كجرعة واحدة فى الصباح أو كجرعات مقسمة.

ونهدف من وراء هذه الدراسة إلى المقارنة بين إعطاء الستيرويدات فى جرعة يومية واحدة وإعطائها على هيئة جرعة مقسمة على ثلاث مرات من حيث الالتزام بتناول الدواء والاستجابة له وحدوث المضاعفات.

أجريت هذه الدراسة على 30 من الأطفال المرضى المصابين بمتلازمة النفروزز التى يتوقع أن تكون من النوع الذى يستجيب للستيرويدات. خمسة عشرة من هؤلاء الأطفال أعطوا البريدنيزولون على هيئة جرعة واحدة يومياً، بينما أعطى البريدنيزولون للخمشة عشرة الباقين فى جرعة مقسمة على ثلاث مرات.

وقد وجد أنه لا يوجد اختلاف إحصائى معتبر بين مجموعتى المرضى بالنسبة لمدة العلاج وحدوث المضاعفات. كذلك لم تحدث آثر جانبية للستيرويدات فى أحد من المرضى.

نستنتج من هذا أن البريدنيزولون حينما يعطى على هيئة جرعة صباحية له نفس الفاعلية عندما يعطى فى جرعات مقسمة من حيث الشفاء وحدوث المضاعفات. ولأن إعطاء الستيرويدات فى جرعة واحدة يسهل على المريض الانتظام فى أخذ العلاج فإننا نوصى بأن يكون الطريقة محل الاختيار لعلاج متلازمة النفروزز.