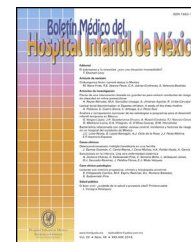




Boletín Médico del Hospital Infantil de México

www.elsevier.es/bmhim



RESEARCH ARTICLE

Comparative study of the conventional scheme and prolonged treatment with steroids on primary steroid-sensitive nephrotic syndrome in children[☆]



Miguel Liern^{*}, Paola Codianni, Graciela Vallejo

Nephrology Service, Children's General Hospital Dr. Ricardo Gutiérrez, Buenos Aires City, Argentina

Received 23 April 2016; accepted 25 July 2016

Available online 6 December 2017

KEYWORDS

Steroid-sensitive
nephrotic syndrome;
Steroid toxicity;
Remission time;
Number of relapses

Abstract

Background: In the steroid-sensitive nephrotic syndrome (SSNS), the prolonged treatment with steroids could decrease the frequency of relapses. A comparative study of a prolonged steroid scheme and the usual treatment of primary SSNS were conducted to assess the number of patients with relapses, the mean time to treatment initiation, until remission and until first relapse, total number of relapses, total cumulative dose of steroids, and the steroid toxicity.

Methods: Patients were divided into two groups: group A (27 patients) received 16- β -methylprednisolone for 12 weeks, reducing the steroid until week 24. Group B (29 patients) received 16- β -methylprednisolone for 12 weeks and placebo until week 24.

Results: The cumulative incidence rate of relapses (person/year) for group A was of 36/100 and for group B, 66/100 ($p=0.04$). The mean elapsed time to first relapse was 114 days for group A and 75 days for group B ($p=0.01$). The difference in time for the initial response to treatment and up to achieve remission between both groups was not significant. Total cumulative relapses were nine for group A and 17 for group B ($p=0.04$). Total patients with relapses were three for group A and seven for group B ($p=0.17$). The cumulative average dose per patient was 5,243 mg/m² for group A and 4,306 mg/m² for group B ($p=0.3$), and serum cortisol was 14 μ g/dl for group A and 16 μ g/dl for group B ($p=0.4$). There were no steroid toxicity differences between both groups.

Conclusions: The duration of the treatment had an impact on the number of relapses without increasing steroid toxicity.

© 2016 Hospital Infantil de México Federico Gómez. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

[☆] Please cite this article as: Liern M, Codianni P, Vallejo G. Estudio comparativo entre el esquema convencional y el tratamiento prolongado con esteroides en el síndrome nefrótico cortico-sensible primario en Pediatría. Bol Med Hosp Infant Mex. 2016;73:309–317.

^{*} Corresponding author.

E-mail address: jliern@yahoo.com (M. Liern).

PALABRAS CLAVE

Síndrome nefrótico
cortico-sensible;
Toxicidad esteroide;
Tiempo de remisión;
Número de recaídas

Estudio comparativo entre el esquema convencional y el tratamiento prolongado con esteroides en el síndrome nefrótico cortico-sensible primario en Pediatría

Resumen

Introducción: En el síndrome nefrótico cortico-sensible (SNCS), la corticoterapia prolongada podría reducir la frecuencia de recaídas. El objetivo de este trabajo fue la comparación de un esquema corticoide prolongado frente al tratamiento habitual del SNCS primario, con la evaluación de los siguientes parámetros: el número de pacientes con recaídas, el número total de recaídas, el tiempo medio transcurrido al iniciar el tratamiento, hasta la remisión y hasta la primera recaída, la dosis acumulada de corticosteroides y la toxicidad esteroide.

Métodos: La población se dividió en dos grupos: el grupo A (27 pacientes) recibió 16- β -metilprednisona durante 12 semanas, reduciendo la dosis hasta la semana 24; y el grupo B (29 pacientes) recibió 16- β -metilprednisona durante 12 semanas, y placebo hasta la semana 24.

Resultados: La tasa de incidencia acumulada de recaídas (persona/año) fue de 36/100 en el grupo A y de 66/100 ($p=0.04$) en el grupo B. El tiempo medio transcurrido (días) hasta la primera recaída fue de 114 en el grupo A y 75 en el grupo B ($p=0.01$). Las diferencias de tiempo transcurrido al iniciar tratamiento y hasta la remisión no fueron significativas entre ambos grupos. El total acumulado de recaídas fue de nueve en el grupo A y 17 en el grupo B ($p=0.04$), y el total de pacientes con recaídas fue de tres (grupo A) y siete (grupo B) ($p=0.17$). La dosis media acumulada (mg/m^2) por paciente fue de 5,243 en el grupo A y de 4,306 en el grupo B ($p=0.3$), y el cortisol sérico ($\mu\text{g}/\text{dl}$) final fue de 14 en el grupo A y 16 en el grupo B ($p=0.4$). La toxicidad esteroide fue similar entre ambos grupos.

Conclusiones: La duración del tratamiento disminuyó el número de recaídas, sin incrementar la toxicidad esteroide.

© 2016 Hospital Infantil de México Federico Gómez. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Nephrotic syndrome is defined as the presence of proteinuria $>40\text{ mg}/\text{m}^2/\text{h}$ and serum albumin $<2.5\text{ g}/\text{mL}$. Hypercholesterolemia and the presence of edema are frequent findings but not required for diagnosis. In pediatrics, the incidence of its primary form is 2/100,000 children¹.

Initially, the International Study of Kidney Disease in Children (ISKDC) established a daily 8-week corticosteroid regimen. Later recommendations prolonged treatment up to 12 weeks^{2,3}. With these schemes, up to 53% of patients will suffer disease relapse at some point during their evolution^{4,5}, with the need of restarting glucocorticoid administration and the subsequent risk of developing associated adverse effects^{6,7}. For this reason, 6-month corticosteroid therapeutic schemes have been described⁸⁻¹⁰. In the present work, a comparative study between a prolonged corticosteroid scheme and usual steroid treatment for primary steroid-sensitive nephrotic syndrome (SSNS) was conducted. General objectives included evaluation of the following parameters:

- 1) The number of patients with relapses within 12, 24 and 36 months after completion of either treatment
- 2) Number of relapses throughout the duration of the study
- 3) The time from diagnosis to the initiation of therapy, the time from the initiation of therapy to the initial remission and the time from remission to the first relapse

- 4) The accumulated dose of corticosteroids

The specific objective was to evaluate the occurrence of steroid toxicity:

- Cushingoid appearance
- Increased HOMA index (>3)
- Decrease growth rate
- Arterial hypertension
- Acne, striae
- Cataract/increased intraocular pressure
- Osteoporosis/osteopenia

2. Methods

A controlled, randomized, double-blind (patients and physicians), non-inferiority clinical trial was implemented in patients with new-onset primary SSNS.

2.1. Patient criteria

2.1.1. Inclusion

- Patients from 1 year to 11 years-old, eutrophic and normotensive
- Serum creatinine within normal range for age and gender
- Urinary sediments without hematuria
- Normal renal ultrasound

- Approved informed consent. In adolescents, assent was required according to the basic principles of the Declaration of Helsinki

2.1.2. Exclusion

- Intolerance to corticosteroid therapy
- Contraindication to the use of steroids (e.g., acute or chronic active infections)

2.1.3. Suspension

- Patients who developed either steroid-dependent nephrotic syndrome (SDNS) or steroid-resistant nephrotic syndrome (SRNS), those who did not comply with the indications or did not attend to at least 80% of the programmed follow-up appointments, and those who developed uncontrolled steroid toxicity were removed from the study

2.2. Treatments

The total population was randomly divided into two groups. In group A, a prolonged steroid treatment with 16- β -methylprednisolone was administered at a dose of 48 mg/m²/day during 6 weeks; afterwards, a dose of 33 mg/m²/day on alternate days was administered for 6 weeks. As of week 13, the dose was reduced to 24 mg/m²/day on alternate days until week 16; thereafter, 18 mg/m²/day on alternate days until week 20; and finally, 9 mg/m²/day on alternate days until week 24.

In group B, the usual treatment consisting of 16- β -methylprednisolone at a dose of 48 mg/m²/day during 6 weeks was administered; afterwards, a dose of 33 mg/m²/day on alternate days was administered until week 12; and finally, placebo was given on alternate days until week 24 of treatment.

Placebo properties regarding flavor, external appearance and presentation were similar to 16- β -methylprednisolone.

Steroid doses were prescribed once daily, during the morning, on an empty stomach and not exceeding 60 mg/day. Adherence to treatment was controlled by counting the medication at each visit, excluding patients who did not comply with the indications.

The dose of 48 mg/m²/day of 16- β -methylprednisolone is equivalent to 60 mg/m² of prednisone, and the dose of 33 mg/m² of 16- β -methylprednisolone is equivalent to 40 mg/m² of prednisone.

In both groups, vitamin D at 1,500 IU/day, calcium carbonate at 50 mg/kg/day (maximum dose of 2 g/day) and a hyposodic diet were prescribed during the 24 weeks of treatment.

2.3. Blinding and randomization

Both corticoids and placebo were given as tablets in indistinguishable submissions. Outside the group of investigators, one medical professional knew the content of these drugs (with this specific function previously delegated), who gave the tablet to each patient according to their assigned

number with the randomization sequence. Randomization was obtained with the statistical program *GraphPad InStat*.

2.4. Controls

2.4.1. At admission

- Data as weight and height with growth rate calculation, blood pressure control (oscillometric and auscultatory methods), pubertal development stage (Tanner), evaluation of bone age (left hand radiograph) and ophthalmologic control (eye funduscopy, tonometry) were registered
- Renal ultrasound and Mantoux-PPD reaction
- Control blood tests included VDRL, serology for HIV, hepatitis A, B, C, toxoplasmosis and Chagas, and serum complement (C3 and C4)
- Uremia, venous acid-base status, protein electrophoresis, total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, ionogram, blood calcium, phosphorus, alkaline phosphatase (ALP), uric acid, glycemia, and basal insulin levels
- 25-OH vitamin D levels (cholecalciferol)
- Urine 24 hour-protein determination (expressed in mg/m²/h) or the proteinuria/creatininuria index in a single sample (normal value <0.2) were performed. For operative purposes, reactive strips were delivered to the patient's proxy to measure urine protein; they were instructed to be able to communicate with the researcher
- Calculation of the estimated glomerular filtration rate was used, expressed as the creatinine/height index and Barrat's constant according to gender and age
- Calculation of the growth rate obtained from the measure of height in cm. For operative reasons, the first measure corresponded to the first nephrologic control, and the following measures to the annual height until the end of the study. To calculate growth rate, results were expressed as cm/year
- In stool samples, a full parasitoscopic study was performed (direct, serial, and Graham's test)

2.4.2. Monthly controls

- Clinical follow-up including blood pressure measurement
- Blood protein electrophoresis, total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, ionogram, calcium, phosphorus, alkaline phosphatase, glycemia and basal insulin were performed

2.4.3. Biannual follow-up until completion of the study

- Growth rate percentile, cardiovascular evaluation, ophthalmologic follow-up

2.4.4. Annual follow-up until completion of the study

- Bone age. In patients older than 6 years, a dual-photon absorptiometry was indicated (lumbar spine bone mineral densitometry) to measure bone mineral content (g/cm²) and a Z score. The registered values for this population, which were provided by studies conducted in local controls, were employed for the calculations. The interpretation of data was based on the comparison of the results with normal values adjusted for gender, age and stage of puberty¹¹

- At the end of the study, morning serum cortisol level (08:00 AM) was measured
- A renal biopsy was performed in patients with SDNS and SRNS

The duration of the study was 36 months.

The independent variables evaluated were gender, age at onset of the nephrotic syndrome (years), time until the beginning of treatment (from the onset of therapy until remission and from remission to the first relapse).

The dependent variables evaluated were accumulated steroid dose, number of diagnosed relapses, adherence to treatment, final serum cortisol level, steroid toxicity.

2.5. Diagnosis and treatment definitions

- 1) New-onset or early primary nephrotic syndrome. First episode with proteinuria greater than 40 mg/m²/h, serum albumin less than 2.5 g/ml and, eventually, hypercholesterolemia above the percentile 95, without an infectious or immune concurrent disease.
- 2) Relapse. Proteinuria >40 mg/m²/h during three consecutive days (ISKDC).
- 3) Relapse treatment. With 48 mg/m²/daily of 16- β -methylprednisolone until achievement of remission during three or more consecutive days, followed by four weeks of 16- β -methylprednisolone.
- 4) Frequent relapses. Two or more relapses within six months or four relapses within 12 months (ISKDC).
- 5) Partial remission. Proteinuria of <2+, proteinuria-creatinuria index of >0.2 and <3.5 g/mg or >4 mg/m²/h and <40 mg/m²/h and an increment of serum albumin levels of >2.5 g/ml (ISKDC).
- 6) Complete remission. Absence of edema and proteinuria <1+ on a urine test strip, proteinuria-creatinuria <0.2 g/mg or <4 mg/m²/h during three consecutive days.
- 7) Steroid-dependent nephrotic syndrome. Reappearance of proteinuria >40 mg/m²/h with a reduction of the steroid dose during or within 20 days of completion of treatment.
- 8) Steroid-resistant nephrotic syndrome. Persistence of proteinuria >40 mg/m²/h or >3.5 g/mg after two series of steroid administration of at least 12-weeks duration each, or after four weeks of daily methylprednisolone treatment plus three consecutive methylprednisolone pulses.
- 9) Steroid toxicity. Diabetes, gastrointestinal bleeding, cerebral edema, glaucoma, hypertension, fluid retention, obesity, insulin resistance, growth retardation, increased intra-ocular pressure, cataract, psychological and behavioral changes, cushingoid habitus (dorso-cervical fat pad, abdominal striae, skin thinning, ecchymosis, hirsutism, acne).

2.6. Statistical methodology

The statistical test suite EPIDAT 3.0 was used for subject simple randomization and assignment (two groups), randomization was done in a 1:1 ratio.

To evaluate the number of relapses in nephrotic syndrome, a percentage between 30-50% during the first three

years was assumed. The sample size calculation was performed considering a desired potency of 80% for a two-tailed $\alpha = 0.05$ (a confidence Z value of 1.65) and an estimated SE of 10% of 22 patients. Anticipating 20% of patient loss, a total sample 27 patients was planned for recruitment. To avoid selection bias, both groups were arbitrarily stratified according to age groups: 1-year-old to 6 years, 11 months and 29 days old; and 7-years-old to 11 years, 11 months and 29 days old.

Cumulative incidence rate (CIR) was used to evaluate the proportion of individuals with an event (relapse) during the entire follow-up period (person-time).

The heterogeneity of the final accumulated dose was analyzed with a non-paired t-test with Welch correction.

Relative risk (RR) was used to evaluate the appearance of steroid toxicity related to both treatments.

Considering sample size and the number of events, Fisher's exact test was used to evaluate if the total cohort was behaving as two distinct populations regarding the total accumulated relapses and the total number of patients with relapses.

A logarithmic ordinal calculation (log-rank) was used to compare the distribution for the actuarial survival between patients in group A and B.

A *p* value of <0.05 was established as statistically significant.

An intention-to-treat strategy was used to analyze the results.

The results are presented as mean $\pm$ SD and the statistical packages GraphPad InStat and EPIDAT 3.0 were used.

The protocol was approved by the Ethics and Research Committee of the Children's Hospital Ricardo Gutiérrez.

3. Results

Of the initially included 56 patients, 41 completed the 36-month duration of the study and were distributed in the following fashion: 27 patients in group A, of which 11 were women (median age 4 years, *r*: 2-10 years); and 29 patients in group B, of which 13 were women (median age 3 years, *r*: 2-11 years) (Table 1). Adherence to treatment in the total population was 73%; therapeutic adherence by group was 74% in group A and 72% in group B (*p* = 0.04) (Figure 1).

The mean time of control of the disease for the total population was 36 months (*r*: 34-38 months). During the entire protocol, the presence of edema coincided with relapses, although its magnitude and, eventually, its disappearance had no relationship with disease control, and did not always coincide with remission.

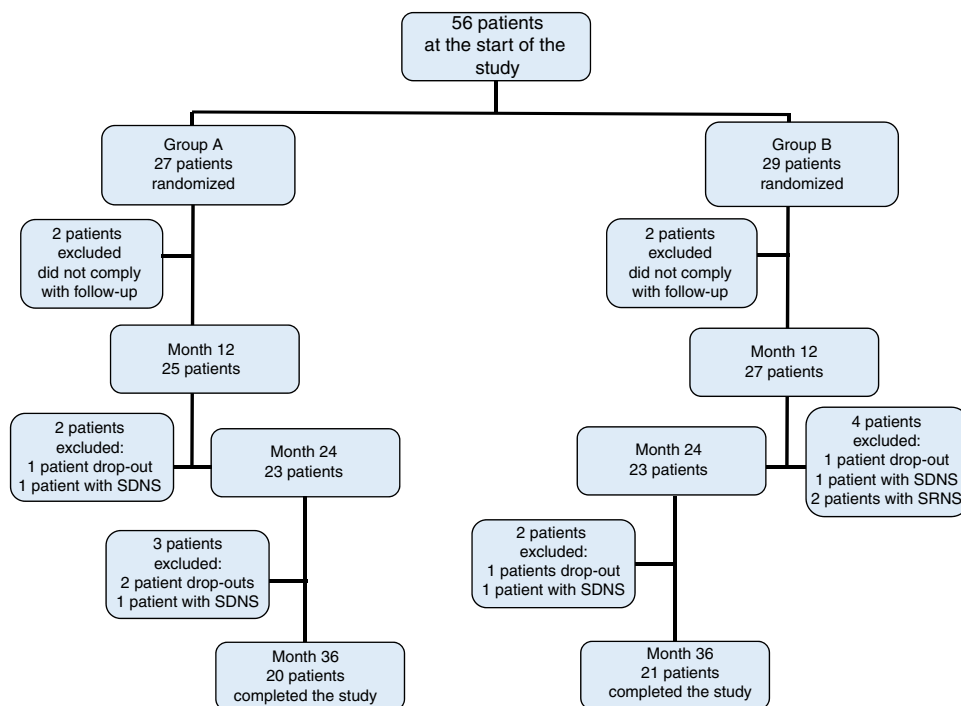
Mean age of onset of nephrotic syndrome in group A was 3.7 years (SD 1.6) and relapse CIR was 36/100 person/year. In group B, mean age of onset was 4.2 years (SD 2.1) and relapse CIR was 66/100 person/year (*p* = 0.04).

In group A, the mean time between the diagnosis of nephrotic syndrome and the onset of treatment was 10 $\pm$ 3 days and in group B was 13 $\pm$ 2 days (*p* = 0.07). At the same time, the mean time between the onset of treatment and remission in group A was 14 $\pm$ 3 days and 11 $\pm$ 2 days in group B (*p* = 0.08). Finally, the mean time since completion of the initial treatment until first relapse in group A was 114 $\pm$ 7 days for the total population and 102 $\pm$ 5 days for those > 7

Table 1 Characteristics of the population during the study.

Patients	Group A	Group B	<i>p</i>
Number of patients	27	29	0.08
Age (median in years)	4 (2-10)	3 (2.2-11)	0.31
Age < 7 years	18	19	0.09
Age > 7 years	9	10	0.07
Gender (F/M)	11/16	13/16	0.08
Basal Proteinuria (mg/m ² /h)			
• Massive	67 (SD 11)	79 (SD 9)	0.31
• In remission	1.4 (SD 1.8)	1.6 (SD 2)	0.43
Basal value of serum albumin (g/dl)			
• With massive proteinuria	1.0 (SD 0.8)	0.8 (SD 1.2)	0.20
• In remission	3.2 (SD 0.7)	3.6 (SD 0.9)	0.33
Basal cholesterol levels (mg/dl)			
• With nephrotic syndrome	532 (SD 125)	447 (SD 209)	0.08
• In remission	209 (SD 52)	189 (SD 27)	0.07
Basal BMI (kg/m ²)	20 ± 0.2	21 ± 0.1	0.42
MAP (mmHg)	64 ± 6	67 ± 9	0.44

F, female; M, male; BMI, body mass index; MAP, mean arterial pressure; SD, standard deviation.

**Figure 1** Study flow diagram.

SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.

years old, and in group B it was 75 ± 9 days for the total population and 67 ± 3 for those > 7 years old ($p = 0.01$).

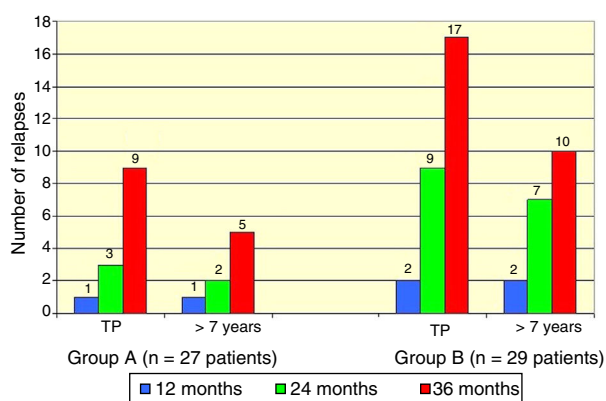
There was a total of nine cumulative relapses in group A and 17 in group B (Fisher's exact test, $p = 0.048$). In both groups, patients > 7 years old were the most commonly affected (Figure 2).

The total number of patients with relapses was lower in group A (three patients) than group B (seven patients), but this difference was not statistically significant (Fisher's

exact test, $p = 0.18$). Once again, patients > 7 years old were the most commonly affected (Figure 3).

Logarithmic ordinal calculation ($\chi^2 = 4.1$, $p < 0.05$) showed significant differences in the distribution of relapses for patients in group A vs. group B (Table 2).

Upon study completion, the mean accumulated total dose per patient in group A was $5,243 \text{ mg/m}^2$ and $4,306 \text{ mg/m}^2$ ($p = 0.3$) in group B, adding the administered steroid during the initial scheme (group A, $4,802 \text{ mg/m}^2$ and group B,



TP, total population
The total number of patients with relapses after 36 months of the protocol was significantly greater in group B.
In both groups, patients older than 7 years were the most affected.

Figure 2 Cumulative number of relapses throughout the duration of the study.

3,402 mg/m²) and the treated relapses (group A, 441 mg/m² and group B, 904 mg/m²).

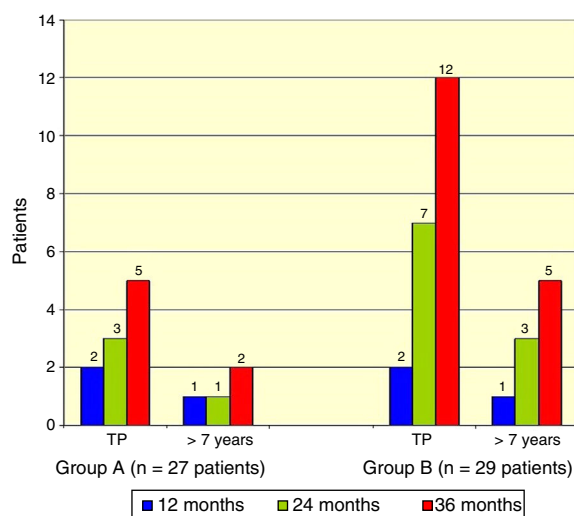
The final value of morning serum cortisol was 14 µg/dl in group A and 16 µg/dl in group B ($p=0.4$).

In group A, a renal biopsy was performed in three children. From these patients, two with SDNS were histopathologically diagnosed with minimal change disease (MCD), while the third patient with SRNS was diagnosed with mesangial proliferation.

In group B, renal biopsy was performed to four children: in two patients with SRNS, the histopathological diagnosis was focal and segment sclerosis, and mesangial proliferation, respectively. In the other two patients with SDNS, the histopathological diagnosis was MCD.

The risk of developing steroid toxicity was low and there were no significant differences between both groups (Table 3).

Phosphate/calcium metabolic derangement were not significant: for group A, calcium levels were 7.9 ± 0.9 mg/dl,



TP, total population
The total number of patients with relapse after 36 months of the protocol was greater in group B (no statistical significance).
In both groups, patients older than 7 years were the most affected.

Figure 3 Cumulative number of patients presenting relapses in both groups.

Table 2 Calculation for the logarithmic ordinal tests (log-rank) for comparison of actuarial survival distributions between patients in group A and group B.

Time since the initiation of the treatment (months)	Number of patients		Total	Number of patients with documented relapses		Total	Number of patients with expected relapses		Total
	A	B		A	B		A	B	
3	27	29	56	0	0	0	0.48	0.51	0.99
9	27	29	56	2	5	7	0.96	2.58	3.46
12	25	24	49	0	0	0	0.50	0.48	0.98
18	25	24	49	1	2	3	0.50	0.97	1.47
24	24	22	49	0	0	0	0.48	0.44	0.98
30	24	22	49	0	0	0	0.48	0.44	0.98
36	24	22	49	0	0	0	0.48	0.44	0.98
Total			3	7	10	3.88	5.86	9.74	

$\chi^2 = 4.1$ ($p < 0.05$). The decimal extension explains the minimal difference among the totals.

Table 3 Steroid toxicity in both groups.

Adverse events	Group A (n/total)	Group B (n/total)	RR
Overweight/obesity	6/27	4/29	1.5 (CI 95% 0.7-1.3)
HOMA > 3	2/27	1/29	1.5 (CI 95% 0.6-3.9)
Increase in MAP*			
Stage I	4/27	3/29	2.1 (CI 95% 0.8-4.1)
Stage II	2/27	1/29	1.5 (CI 95% 0.6-3.9)
Cushingoid habitus	9/27	12/29	1.0 (CI 95% 0.5-1.4)
Cutaneous striae	7/27	5/29	1.7 (CI 95% 0.7-4.1)
Acne	2/27	3/29	0.8 (CI 95% 0.2-4.1)
Pathological IOP (> 25 mmHg)	2/13	1/29	1.5 (CI 95% 0.6-3.9)
Cataract	2/27	1/29	1.5 (CI 95% 0.6-3.9)
Growth rate (cm/year)	5.5	5.3	1.94 (CI 95% 0.2-18)

HOMA, homoeostasis model assessment; MAP, mean arterial pressure; IOP, intraocular pressure; RR, relative risk.

* Blood pressure was standardized with the use of nifedipine in all patients.

and for group B, 8.2 ± 2.1 mg/dl ($p=0.6$). Phosphate levels in group A were 4.8 ± 1.1 mg/dl, and 5.2 ± 1.8 mg/dl in group B ($p=0.09$).

In group A, alkaline phosphatase levels were 339 ± 132 mg/dl; in group B, 430 ± 112 mg/dl ($p=0.06$).

Parathyroid hormone (PTH) levels in group A were 41 ± 16 pg/ml and 32 ± 11 pg/ml in group B ($p=0.08$). In group A, the concentration of 25-OH vitamin D was 26 ± 4 ng/ml, and 29 ± 5 ng/ml in group B ($p=0.29$).

Finally, bone mineral content was 0.76 ± 0.11 g/cm² with and Z score of 1 ± 1 in group A (nine patients), and in group B, the bone mineral content was 0.80 ± 0.08 g/cm² ($p=0.26$) with a Z score of -1 ± 0.5 ($p=0.9$). Specific genetic studies were not evaluated in any patient.

4. Discussion

The rationale behind this research was to justify the use of a prolonged therapeutic scheme by comparing it with the usual treatment. It was shown that patients in group A presented fewer relapses, without a significant increase in the accumulated doses of corticosteroids. Although no significant differences were observed regarding the number of patients with relapses between the two randomized populations, the final value of serum cortisol in both groups indicated an adequate steroid suppression¹².

The ISKDC established a daily 8-week regimen of corticosteroids. Later schemes were extended for up to twelve weeks^{13,14}, and although no consensus has been reached regarding treatment duration¹⁵, it was observed in this work that a prolonged scheme of more than 3 months reduces relapse rate, which coincides with the reports from Bagga et al. (1999)¹⁶ and Hiraoka et al. (2000)¹⁷. Furthermore, according to Ueda et al.¹⁸ and Ksiazek and Wyszynska¹⁹, a significant remission index was achieved since the first episode. Interestingly, although the follow-up in the studies of Sinha et al.²⁰, Yoshikawa et al.²¹ and Hoyer²² was different to those established in the present work, the variation in the size of the studied sample could be responsible for the discrepancies of the final results. In this regard, it is

ostensible that sample size showed substantial variations in relation to the present experience.

Regarding gender and age as influencing variables over the evolution of SSNS^{23,24}, gender was not significantly related to relapse incidence unlike the study of Takeda et al.²⁵ In contrast, a relationship with average age was observed. In both groups, patients > 7 years had an increased frequency of relapses.

Steroid toxicity is known to be related to the accumulated dose^{26,27}. However, no significant differences were found between both groups regarding ophthalmologic damage^{28,29}, central obesity and insulin resistance³⁰; and although several patients developed cushingoid facies, this event was transitory and reversible³¹.

Steroid toxicity over mineral metabolism (osteopenia) was not found either³², and although it is known that the increase of both the bone content and density is linear in the pre-pubertal population, this bias was lessened in the included pre-pubertal females and males by separately studying bone density and mineral content and adjusting the results to anthropometric and gender variables. Moreover, to attenuate the eventual bone mass reduction, the studied population received calcium carbonate and vitamin D supplements according to established guidelines¹⁴.

Finally, registries on arterial hypertension, which were probably associated to the corticosteroid effect on endogenous angiotensin II (patients in group A had a percentage increase of up to 30% for stage I), were transitory and responded to nifedipine administration³³.

Behavioral changes in patients receiving steroid therapy were not evaluated (mild euphoria, insomnia, increased appetite) despite these symptoms can have a frequency up to 25% according to some references³⁴.

This work had several limitations. Firstly, although sample size was the result of pre-established statistical guidelines, it is evident that the number of patients with relapse was relatively small in each group, which limited the observation of differences.

Similarly, the lack of histopathological diagnosis in every patient may have covered up different etiologies of the primary nephrotic syndrome^{35,36}. However, established international guidelines concerning indications for

initial renal biopsy in pediatric patients with SSNS were followed^{37,38}.

In conclusion, although prolonged steroid treatments have been documented,^{2,3} the increase in the number of observed relapses in children > 7 years allows considering whether this group would require the implementation of prolonged therapeutic regimes, according to the experience obtained from this study.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors declare no conflict of interests.

References

1. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. *Kidney Int.* 1981;20:765–71.
2. Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. *J Pediatr.* 1979;95:239–43.
3. Brodel J, Ehrich JH, Coord. Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. *Arbeitsgemeinschaft für Pädiatrische Nephrologie. Lancet.* 1988;331:380–3.
4. Fakhouri F, Bocquet N, Taupin P, Presne C, Gagnadoux MF, Landais P, et al. Steroid-sensitive nephrotic syndrome: from childhood to adulthood. *Am J Kidney Dis.* 2003;41:550–7.
5. Koskimies O, Vilska J, Rapola J, Hallman N. Long-term outcome of primary nephrotic syndrome. *Arch Dis Child.* 1982;57:544–8.
6. Serra HA, Roganovich JM, Rizzo LF. Glucocorticoides: paradigma de medicina trasnacional. De lo molecular al uso clínico. *Medicina (Buenos Aires).* 2012;72:158–70.
7. Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. *N Engl J Med.* 2004;351:868–75.
8. Pecoraro C, Caropreso MR, Malgieri G, Ferretti AVS, Raddi G, Piscitelli A, et al. Therapy of first episode of steroid responsive nephrotic syndrome: a randomized controlled trial [abstract]. *Pediatr Nephrol.* 2004;19:C72.
9. Alt MA, Etl S, PC T, Lai WM, Tse KC, Chiu MC. Long versus standard course corticosteroid therapy for nephrotic syndrome in children. *HK J Paediatr. (New series).* 2009;14:103–7.
10. Jayantha UK. Prolonged versus standard steroid therapy for children with a relapsing course of nephrotic syndrome. *Pediatr Nephrol.* 2004;19:C99.
11. van der Sluis IM, de Ridder MA, Boot AM, Krenning EP, de Muinck Keizer-Schrama SM. Reference data for bone density and body composition measured with dual-energy x-ray absorptiometry in white children and young adults. *Arch Dis Child.* 2002;87:341–7.
12. Crown A, Lightman S. Why is the management of glucocorticoid deficiency still controversial: a review of the literature. *Clin Endocrinol (Oxf).* 2005;63:483–92.
13. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev.* 2005;CD001533.
14. Comité de Nefrología, Sociedad Argentina de Pediatría. Consenso de tratamiento del síndrome nefrótico en la infancia. *Arch Argent Pediatr.* 2014;112:277–84.
15. KDIGO Clinical Practice Guideline for Glomerulonephritis. Steroid-sensitive nephrotic syndrome in children. *Kidney Int Suppl.* 2012;2:163–71.
16. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. *Pediatr Nephrol.* 1999;13:824–7.
17. Hiraoka M, Tsukahara H, Matsubara K, Tsurusawa M, Takeda N, Haruki S, et al. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. *Am J Kidney Dis.* 2003;41:1155–62.
18. Ueda N, Chihara M, Kawaguchi M, Niinomi Y, Nonoda T, Matsumoto J, et al. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr.* 1988;112:122–6.
19. Ksiazek J, Wyszynska T. Short versus long initial prednisolone treatment in steroid-sensitive nephrotic syndrome in children. *Acta Paediatr.* 1995;84:889–93.
20. Sinha A, Saha A, Kumar M, Sharma S, Afzal K, Mehta A, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int.* 2015;87:217–24.
21. Yoshikawa N, Nakanishi K, Sako M, Oba MS, Mori R, Ota E, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int.* 2015;87:225–32.
22. Hoyer PF. New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear evidence against long steroid therapy. *Kidney Int.* 2015;87:17–9.
23. McKinney PA, Feltbower RG, Brocklebank JT, Fitzpatrick MM. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol.* 2001;16:1040–4.
24. Andersen RF, Thrane N, Noergaard K, Rytter L, Jespersen B, Rittig S. Early age at debut is a predictor of steroid-dependent and frequent relapsing nephritic syndrome. *Pediatr Nephrol.* 2010;25:1299–304.
25. Takeda A, Matsutani H, Niimura F, Ohgushi H. Risk factors for relapse in childhood nephrotic syndrome. *Pediatr Nephrol.* 1996;10:740–1.
26. Moghadam-Kia S, Werth VP. Prevention and treatment of systemic glucocorticoid side effects. *Int J Dermatol.* 2010;49:239–48.
27. Lukert BP. Editorial: Glucocorticoid replacement—How much is enough? *J Clin Endocrinol Metab.* 2006;91:793–4.
28. Bobrow J. American Academy of Ophthalmology. *Cristalino y catarata.* Barcelona: Elsevier; 2009. p. 47–52.
29. Tham CC, Ng JS, Li RT, Chik KW, Lam DS. Intraocular pressure profile of a child on a systemic corticosteroid. *Am J Ophthalmol.* 2004;137:198–201.
30. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, et al. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. *Nephron Clin Pract.* 2007;105:c54–7.
31. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an

- Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008;93:1526–40.
32. Tsampalieros A, Gupta P, Denburg MR, Shults J, Zemel BS, Mostoufi-Moab S, et al. Glucocorticoid effects on changes in bone mineral density and cortical structure in childhood nephrotic syndrome. *J Bone Mineral Res.* 2013;28:480–8.
 33. Goodwin JE, Zhang J, Gonzalez D, Albinsson S, Geller DS. Knockout of the vascular endothelial glucocorticoid receptor abrogates dexamethasone-induced hypertension. *J Hypertens.* 2011;29:1347–56.
 34. Sharfstein SS, Sack DS, Fauci AS. Relationship between alternate-day corticosteroid therapy and behavioral abnormalities. *JAMA.* 1982;248:2987–9.
 35. Kumar J, Gulati S, Sharma AP, Sharma RK, Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. *Pediatr Nephrol.* 2003;18:657–60.
 36. Nammalwar BR, Vijayakumar M, Prahlad N. Experience of renal biopsy in children with nephrotic syndrome. *Pediatr Nephrol.* 2006;21:286–8.
 37. Caletti MG, Gallo G, Zumino D, Díaz MA, Vitacco M. [Primary nephrotic syndrome. Follow-up of 202 pediatric patients]. *Bol Med Hosp Infant Mex.* 1981;38:457–72.
 38. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. *Pediatrics.* 2009;124:747–57.