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Original article

A randomized study on a 3-month versus a 7-month prednisolone regimen for the initial episode of childhood idiopathic nephrotic syndrome at a large Saudi center

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ABSTRACT

Background and objectives: The standard International Study of Kidney Disease in Children (ISKDC) regimen of prednisolone of 2 months duration for the treatment of the initial episode of Idiopathic Nephrotic Syndrome (INS) was associated with a high relapse rate. The long prednisolone protocols were introduced in order to reduce the relapse rate and steroid toxicities. The main objective of this study was to assess the efficacy and safety of a 3 months protocol of prednisolone versus a 7 months protocol for the first episode of idiopathic nephrotic syndrome.

Design and setting: The study took place in the Pediatric Nephrology Department of King Saud Medical City, Riyadh which is a large referral center all over Saudi Arabia. The study was a randomized control trial using 2 groups. Group A received the 3 months protocol and Group B received the 7 months protocol.

Patients and methods: All children with a confirmed diagnosis of Idiopathic Nephrotic Syndrome were included. The patients were randomized by simple randomization using sealed envelopes into two groups; group A comprised of 60 children using the daily regimen prednisolone 60 mg/m^2 OD X 1 ½ months then 40mg/m^2 on alternate day for 1 ½ months (total = 3 months) and group B also comprised of 60 children using the 7 months protocol, Prednisolone 60mg/m^2 OD x 1 month then 40mg/m^2 EOD x 2 months then 30mg/m^2 EOD for 2 months then 20mg/m^2 EOD for 2 months. The efficacy and safety of these two prednisolone regimens were recorded. The follow-up period was two years. Statistical analysis was done using the SPSS progress version 16 (Chicago, USA) $P < .05$ was taken as a significant result. Consort guidelines for randomized controlled trials (RCTs) were followed. The hospital ethical committee approved the study. The parents gave an informed consent.

Results: Group B protocol was found to be significantly better than the group A protocol in both years of follow-up. The mean time of first relapse was significantly better in group B than in group A ($P < .0001$). The relapse rate reduced significantly in group B vs group A in both the first year ($P = .0031$) as well as in the second year ($P = .00002$). The cumulative dose of steroids was significantly less in group B vs group A both in the first year of follow-up ($P = .0039$) as well as in the second year ($P = .0026$). The incidence of frequently relapsers was significantly less ($P = .049$) in group B as compared to group A. The risk of relapse was better in group B as compared to group A (RR 0.8039; 95% CI 0.6566 to 0.9843 significance ($P = .0346$). The side effects of corticosteroids were significantly less in group B protocol as compared to group A.

Conclusion: We concluded that the long 7 months protocol was significantly better than the 3 months prednisolone regimen in both efficacy and safety for the initial episode of childhood INS.

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1. Introduction

Idiopathic Nephrotic Syndrome (INS) is one of the most common glomerular disorder of childhood worldwide. The reported incidence is about 1.5 per 100,000 children per year [1]. It represents 90% of cases between 1 and 10 years of age with a male: female ratio of 2:1 [2].

Majority of patients show minimal change disease (MCD) on histopathology (almost 80%) [2]. 90% of MCD respond to daily corticosteroid therapy within 4 weeks [3]. Among these steroid responsive cases, 40–50% will have either frequent relapses or will be steroid dependent [3].

These multiple relapses predispose these children to complications of INS like infections, thrombotic episodes and acute renal insufficiency. Furthermore, these relapses require repeated courses of steroids which lead to several adverse effects of steroids such as Cushingoid appearance, obesity, striae, hypertension, hyperglycemia, cataracts, metabolic bone disease, osteoporosis, stunted growth, infections and psychological disturbances.

Henceforth, these patients may require certain second line drugs like Alkylating agents, calcineurin inhibitors, antiCD-20 monoclonal antibodies like Rituximab. These immunosuppressive drugs can result in serious side-effects like gonadal toxicity, cancer, bonemarrow suppression, nephrotoxicity and serious infections.

The standard therapy developed by the International Study of Kidney Disease in Children (ISKDC) and later modified by the Arbetsgemein Schaft for Pediatrische Nephrologie (APN) consisted of 4 weeks daily and 4 weeks of alternate day prednisolone (total 8 weeks). However, this protocol was associated with a high relapse rate (65%) and approximately 40% of these children developed frequent relapses [3].

Surveys in both North America and the United Kingdom found considerable diversity in the approach of pediatric nephrologists to the initial therapy of children with INS. Another APN trial, showed that a 12-weeks course of prednisolone significantly reduced the relapse rate from 61% to 36% [4].

In a meta-analysis [5], 6 RCTs compared a 2-months protocol of prednisolone to a 3-months or more protocol in the initial episode of INS. The relative risk of relapse was significantly reduced by the longer duration at 1–2 years (RR 0.70, 95% CI 0.58–0.84). Furthermore, in 4 trials, it was shown that the risk of relapse reduced significantly with 6 months of prednisolone therapy as compared to a 3-month protocol (RR 0.5, 95% of CI 0.45–0.71).

Subsequently, several studies were done on prolonging the prednisolone therapy from 3 months upto 6 or 7 months [5–11]. It was shown that prolonging the duration upto 6 or 7 months showed better results in reducing the relapse rate, risk of relapse and the incidence of frequent relapses.

The long protocols were classified as 3 months or 6,7 months protocols. Several studies have reported significantly better efficacy and safety of the prolonged 6,7 months protocol [5–11].

We undertook this RCT in order to statistically compare the efficacy and safety of a 3 months versus a long prednisolone (7 months) protocol for the initial episode of INS at a large Saudi center.

2. Subjects and methods

2.1. Subjects and randomization

This was a randomized trial comparing the efficacy and safety of a 3 months versus a 7 months prednisolone protocol for the first attack of childhood INS. Children who presented with the first episode of INS between January 1, 2011 to December 31, 2014 were assessed for study enrollment at the Pediatric Nephrology Unit of the King Saud Medical City (KSMC) Riyadh, Saudi Arabia. The follow-up period was 2 years from the point where therapy was stopped. The hospital ethical committee approved the study and the parents gave an informed consent. The patients were randomized into two groups (group A and group B) based on simple randomization using sealed envelopes. Consort guidelines for RCTs were followed.

2.1.1. Randomization method: concealment

The clinicians participating in the study were randomly given sealed envelopes containing treatment allotments. When a patient agreed for the treatment, the envelope was opened and the allotted treatment given [12].

2.2. Treatments

(a)Children in group A (3 months protocol) were administered prednisolone in a single once daily dose of 60 mg/m^2 for 1 ½ months taken soon after breakfast, then 40 mg/m^2 on alternate days for another 1 ½ months then tapered as follows: 20 mg/m^2/EOD x 1 week then 10 mg/m^2/EOD for another week then stopped [13].

(b)Children in group B (7 months protocol) were treated as follows: 60 mg/m^2/OD for 1 month then 40 mg/m^2/EOD for 2 months then 30 mg/m^2/EOD for 2 months then 20 mg/m^2/EOD for 2 months then stopped [8].

(c)Relapses were treated as follows: Prednisolone 60 mg/m^2 daily once till urine protein is negative for 5 days, then 40 mg/m^2 on alternate days for 1 month then stop. In case of frequent relapsers and steroid dependent cases, relapses were treated as follows; prednisolone 60 mg/m^2/OD till urine protein was negative for 5 days then 40 mg/m^2/EOD x 1 month then 30 mg/m^2/EOD for 1 month then 20 mg/m^2/EOD x another 1 month and then stop [13].

2.3. Patients and their parents

We informed the parents about the side effects of corticosteroids. Patients were advised to take low salt, high protein and low-fat diet during the relapse but otherwise high biological value protein diet. Subjects were followed regularly for up to 2 years after completion of the initial prednisolone regimen.

2.4. Outcome measures

The primary study end point was the time to initial relapse. The secondary end point/outcome measures were: rate of relapse, relative risk of relapse, incidence of frequently relapsing steroid sensitive nephrotic syndrome, incidence of steroid dependent nephrotic syndrome, incidence of use of second line drugs, rate of adverse events, rate of serious adverse events and the incidence of psychological changes. Monitoring of prednisolone related adverse effects was done by doing the following: clinical data including BP, cushingoid features, acne, striae, hirsutism, psychological changes, poor vision, backache. Investigations included half yearly eye checkup for cataracts, bone mineral density at the end of each year and psychological evaluation at the end of each year, calcium, phosphate, alkaline phosphate and vitamin D level, X-ray spine, AP lateral in case of suspected fractures or osteoporosis, fasting and if necessary, random and postprandial blood glucose, checkup of vaccination card and screening for infections. All side effects were assessed by the same observer. Upper GIT Endoscopy was done when gastritis was suspected.

Metabolic bone disease was assessed by serum Ca, PO4, ALP, X-Ray bone and bone mineral density. DSM criteria were applied for psychological changes. Those patients who had no relapse at all

were said to be cured.

2.5. Definitions

The definitions of relapse, remission, frequent relapse, steroid dependent resistant were as per the ISKDC (Table 1) [2].

2.6. Inclusion criteria

- Children with the initial episode of INS (secondary causes excluded).
- Age range: 1–12 years.
- No prior therapy with steroids or immunosuppressive therapy.
- Informed consent.

2.7. Exclusion criteria

- Congenital nephrotic syndrome.
- Infantile nephrotic syndrome.
- Children with a prior history of poor compliance with medical therapy.
- Children with known allergy to prednisolone.
- Children below 1 year and above 12 years.
- Children with persistent hypertension or gross hematuria.
- Children with family history of known genetic causes of nephrotic syndrome.

2.8. Statistical analysis

The following statistical tests were performed:

- Student's t-test was used for comparison of means.
- Chi-square test was used for comparison of percentages.
- Relative risk calculation was done using MedCalc
- *P* value < .05 was taken as a significant result.
- Statistical power for the study was 80% (Value: 0.8416)
- Calculation of sample size [14].
- Intention to treat analysis was applied.
- Help of an experienced statistician was taken when necessary
- SPSS version 16.0 (SPSS Chicago, USA) was used when necessary.

3. Results

124 patients were assigned for eligibility for the study. Four patients were excluded: 2 for not meeting inclusion criteria and 2 declined to participate. The 2 patients who did not meet exclusion criteria were steroid resistant. Sixty patients were allotted to both group A and group B, but only 58 from each group completed the study. Two patients from each group were lost to follow-up (Table 2). No significant difference was observed in the baseline characteristics of the two groups (Table 3).

The group B protocol was found to be significantly better than group A protocol in both efficacy (Table 4) and safety (Table 5). The relative risk of relapse was significantly less in group B (RR 0.839,95% CI 0.6566 to 0.9843 significance *P* = *.0346*).

The mean relapse rate was significantly better in group B as compared to group A *(P* = *.031)* in the first year as well in the second year *(P* < *.00002)*.

The percentage of frequent relapsers (FRNS) was significantly less *(P* = *.0139)* in group B. Second line drugs were used both in the first year and second year of followup.

The metabolic bone disease observed was osteomalacia. No serious psychological changes were seen. The two most commonly observed psychological changes were euphoria and hyperactivity.

4. Discussion

Our study comprised of 2 groups: Group A and Group B. Group A received the 3 months prednisolone protocol and Group B received the 7 months protocol. All the patients had new onset childhood idiopathic nephrotic syndrome. There were no significant differences in the baseline characteristics of the two groups. Group B regimen was found to be significantly better as regards to the relapse rate, time of first relapse, relative risk of relapse, cumulative steroid dose, percentage of frequent relapsers and steroid dependent cases. Furthermore, the adverse effects of corticosteroids were significantly better in group B regimen than group A. Thus, our study showed that the 7 months prednisolone regimen was significantly better than the 3 months in both efficacy and safety.

A meta-analysis of 5 RCTs was done comparing an 8 weeks prednisolone protocol to a 12 weeks protocol [6]. The risk of relapse at 2 years was significantly reduced (RR 0.73;95% CI 0.6 to 0.89). There was no increase in side effects. They concluded that the initial prednisolone regimen should be of 12 weeks duration. They also observed that increasing the prednisolone duration to 7 months was associated with an excellent outcome.

In a 2015 update [7], the addition of three well-designed studies has changed the conclusion of the previous Cochrane database. It was found that high risk of bias studies overestimated the effect of longer course therapy compared with recent low risk bias studies.

These low risk bias studies showed no significant difference in the risk of FRNS between prednisolone for 2–3 months and longer durations prednisolone indicating no benefit in prolonging the duration beyond 2–3 months.

In a study by O.P Mishra et al. [8] significantly better results were seen in the 5 months prednisolone protocol as compared to a 3 months protocol. The mean relapse rate was significantly lower (0.63 vs 1.54 *P* = *.011*), the mean cumulative dose of prednisolone was significantly less (*P* = *.033),* the total relapses up to 1 year were significantly less (21.6% vs 70.2% *P* = *.001),* the percentage of patients with no relapse at 1 year were (76% vs 29%) and the cumulative risk of relapse was significantly lower (0.05 vs 1.31). The side

Table 1
The international study of kidney disease in children (definitions).

Nephrotic syndrome: proteinuria>40 mg/h/m^2 or >50 mg/kg/day or protein/creatinine ratio >0.2 g/mmol (>2 g/g) and hypoalbuminemia <25 g/l with or without edema
Remission: proteinuria <4 mg/h/m^2 or 0-trace on Albustix for 3 consecutive days
Steroid responsive: complete remission achieved with steroid therapy
Steroid resistant: failure to achieve remission following 4 week' prednisolone 60 mg/m^2 followed by 3 methylprednisolone pulses
Relapse: proteinuria>>40 mg/h/m^2 or >50 mg/kg/day or Albustix +++ for 3 consecutive days after having been in remission
Frequent relapse: 2 or more relapses within 6 months of initial response or 4 or more relapses within a period of 1 year
Steroid dependence: 2 consecutive relapses during corticosteroid therapy or within 14 days after cessation of therapy
Early nonresponder: steroid resistance during the first episode
Late nonresponder: steroid resistance in a patience who had previously responded to corticosteroid therapy

Table 2
Consort 2010 flow diagram.

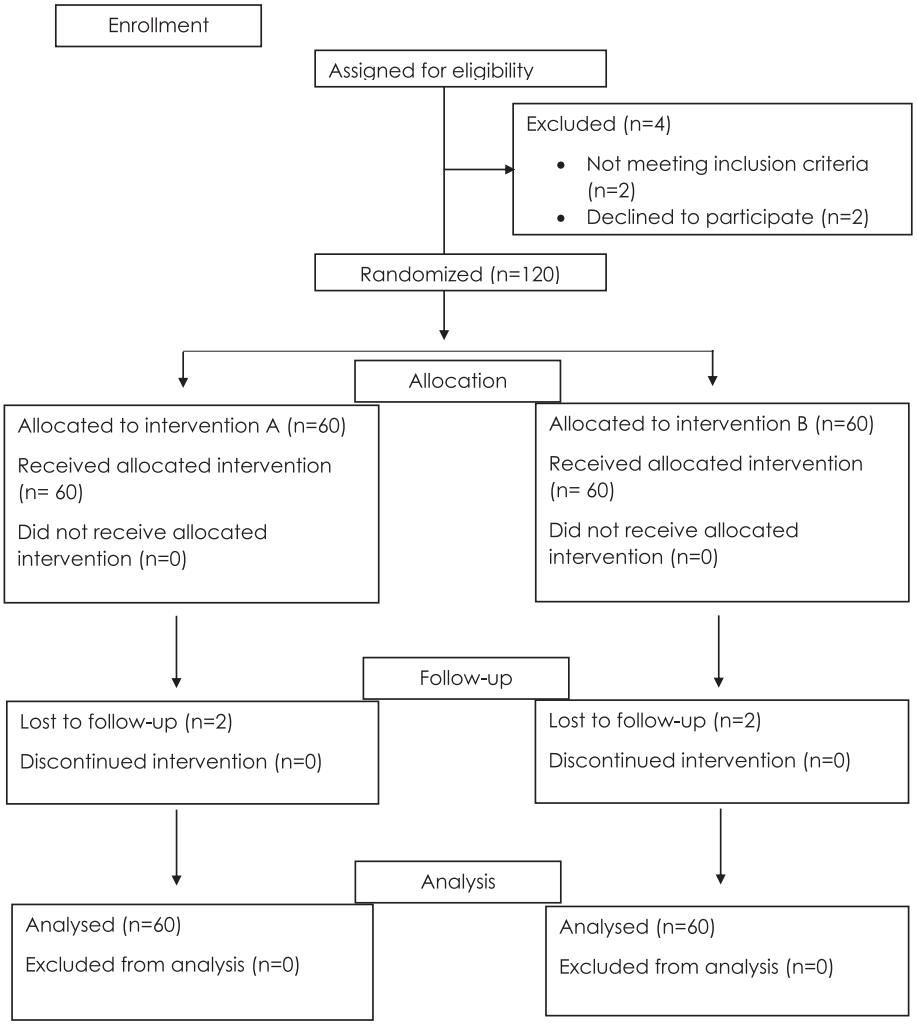

Table 3
The baseline characteristics of the patients in the 2 study groups at the beginning of the study.

Parameters	Group A	Group B	*P* value
Mean age (SD) (years)	5(2)	5.2(1.8)	*.5659 (NS)*
Mean weight (SD) (kg)	15.1(3)	15.6(2.5)	*.3233 (NS)*
Mean Height (SD) (cms)	105(2)	105(2)	*1.0000 (NS)*
Sex (M: F) Ratio	1.9: 1	2:1	-
Mean BP (SD)mmofHg	100/70(5/3) mmofHg	101/68 (4.6/2.9) mmofHg	*.5367 (NS)* *.3552 (NS)*
Mean Hb g/dl + Platelet count (SD)	Hb = 13(2) PLT = 300(58)	12.8(1.5) 310(6)	*.5367 (NS)* *.3552 (NS)*
Mean Serum (SD) Creatinine μmol/L	24(4.1)	25(4)	*.1789 (NS)*
Mean Serum protein (SD) mmol/L	30(3)	29(4)	*.1240 (NS)*
Mean Serum Albumin (SD) mmol/L	12(2)	11.8(2)	*.5849 (NS)*
Mean Serum cholesterol (SD) mmol/L	12(2.2)	11.8(2.3)	*.6273 (NS)*
Mean LDL cholesterol (SD) mmol/L	3.6(1.0)	3.5(0.8)	*.5464 (NS)*
Mean Serum Triglyceride (SD) mmol/L	2.0(0.5)	2.2(0.7)	*1.000 (NS)*
Fasting Blood glucose mmol/L (SD)	4.1(0.8)	4.0(0.6)	*.04401 (NS)*
Urine Protein/Creatinine Ratio (mg of protein/mmol of creatinine) (SD)	1000(150)	1005(146)	*.8535 (NS)*

effects were similar in both groups.

There was another study by Hiroka M et al. [9], This study comprised of 2 groups: 3 months versus a 6 months prednisolone regimen. In children less than 4 years of age, the 6 months protocol showed less steroid toxicities, had significant persistent remission *(P = .01)* and there were less children with frequent relapses *(P = .05)*. In children older than 4 years, no significant difference was found in the persistent remission in the 2 groups.

Table 4
Comparing the efficacy of the two prednisolone regimens.

Relapses	Group A	Group B	*P* value
Duration of Follow-up	2 years	2 years	–
Mean Time of First Relapse (SD)	6months (2)	10months(3)	*<.0001* (significant)
Mean Relapse rate (1st yr) (SD) (Relapses/year)	1.5(1)	1.0(0.8)	*.0031* (significant)
Mean Relapse rate (2nd yr) (SD) (Relapses/year)	1.8(0.9)	1.2(0.7)	*.0002* (significant)
Cumulative Steroid dose (1st yr) mg/m^2/month	620(150)	550(107)	*.0039* (significant)
Cumulative Steroid dose (2nd yr) mg/m^2/month	580(140)	510(106)	*.0026* (significant)
Percentage Frequent Relapsers	50	28	*.0139* (significant)
Percentage steroid dependent case	20	6	*<.0232* (significant)
Percentage Cured	15	31	*.00381* (significant)
Infrequent relapsers percentage	15	35	*.0118* (significant)
Percentage using second line drugs	40	20	*.00173* (significant)

Table 5
Comparing steroid side effects (Follow up 2 years).

S.no	Side effects of steroids	Group A	Group B	*P* value
1	Cushingoid	25(47%)	15(15%)	*.0002*
2	Gastritis	21(35%)	10(17%)	*.0252*
3	Hirsutism acne	12(20%)	3(5%)	*.0134*
4	Hypertension	12(20%)	4(6.7%)	*.0329*
5	Infections	12(20%)	4(6.7%)	*.0329*
6	Stunted growth	14(23.33%)	5(8.3%)	*.0250*
7	Metabolic bone disease	10(16.6%)	2(3.33%)	*.0157*
8	Hyperglycemia	0	0	-
9	Psychological disturbances	4(6.66%)	0	*.0429*
10	Striae	5(8.33%)	0	*.0230*
11	Posteriorsubcapsular cataracts	0	0	-

Yet another study by ALT Ma et al. [10] compared the standard 8 weeks ISKDC protocol to the 6 months prednisolone protocol. It was a retrospective study. The results were significantly better in the long prednisolone protocol: higher sustained remission *(P=.0046),* lower relapse rate (33% versus 75% *P=.026)* and less side effects (no growth retardation or hypertension seen).

In a randomized study by Ksiazek, J et al. [11], patients were divided into 3 groups: 2 months, 3 months and 6 months prednisolone regimens. Best results were seen with the 6 months protocol. Percentage of relapse free patients at 2 m, 3 m and 6 months were: 36.4%, 32.4% and 65.3%. Percentage of relapses free at 2 years were 27.3%, 20.6% and 50%. The number of relapses per patient per year at 2 m,3 m and 6 months were as follows: 0.79, 0.77 and 0.49.

However, contrary results were obtained in a multicenter randomized trial from Netherlands [15]. The patients were randomized into 2 broad groups: a 3 months prednisolone and a 6 months prednisolone. The cumulative dose of steroids was similar in both groups. The results were as follows: 3 m versus 6 months protocol: relapse rate (77%,80%), frequent relapses (45%,50%), the use of maintenance prednisolone and other second line drugs used (50%,59%). Their conclusion was that prolongation of the prednisolone regimen alone to 6 months without increasing the cumulative dose of steroids did not show any additional benefit.

We observed that except for a few studies, most of the previous studies showed significantly better efficacy and safety with the long course prednisolone regimen for the first episode of INS in children.

Their findings were similar to our observations.

5. Conclusion

Thereby, we conclude that the prolonged prednisolone protocol of 7 months duration is significantly better than standard prednisolone regimen of 3 months duration in both efficacy and safety. We recommend, however, that more multicenter trials should be conducted worldwide in order to finalize the best and optimum prednisolone regimen for the first episode of new onset idiopathic nephrotic syndrome.

Conflict of interest

There was no conflict of interest in this randomized trial.

Ethical statement

The hospital ethical committee was approached and the RCT has been approved by them.

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