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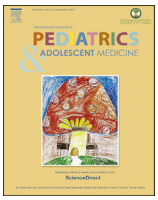

Original article

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

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