Treatment of nephrotic syndrome in children and controlled trials

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Abstract

Aim. To determine the sequential therapy of childhood nephrotic syndrome (NS) with presumed minimal change nephropathy using the evidence from clinical trials.

Methods. Meta-analysis of 22 randomized controlled trials was performed, using frequency of relapse and side effects of therapeutic regimes.

Results. A meta-analysis of seven trials comparing duration of therapy for initial onset showed that duration of at least 3 months significantly reduced the risk of relapse at 12–24 months (relative risk 0.73; 95% confidence interval 0.60–0.89) without an increase in adverse events. Five trials were performed for steroid treatment of relapse. Deflazacort reduced relapses during therapy, but is not generally available. No difference was observed when comparing single and divided dosing of prednisone. Frequency of relapses could not be influenced by duration of relapse therapy. Alternate day therapy was more effective than intermittent use of prednisone. Two studies out of five on cyclophosphamide or chlorambucil showed consistently that alkylating agents should be used before cyclosporine as alternative therapy to steroids.

Conclusions. Children with initial onset of NS should be treated with prednisone at a dose of 60 mg/m²/day for 6 weeks, followed by a dose of 40 mg/m²/48 h for at least another 6 weeks. If steroid toxicity for treatment of relapsing NS requires alternative treatment, cyclophosphamide (2 mg/kg/day for at least 8 weeks) remains the drug of choice with a curative potential. If children still relapse after alkylating agents, levamisole may serve as an alternative only for frequent relapsing NS, whereas steroid-dependent NS should be treated with cyclosporine.

Keywords: children; chlorambucil; controlled trials; corticosteroid therapy; cyclophosphamide; cyclosporine; meta-analysis; nephrotic syndrome; treatment

Introduction

The incidence of childhood nephrotic syndrome (NS) varies between two and seven new patients up to an age of 16 years per population of 10^5 [1]. Most patients will have minimal change nephropathy [2]. With the introduction of corticosteroid therapy for treatment of childhood NS, the mortality has dropped from 35% [3] to 3% [4], and today most children with initial onset of NS beyond the first year of life will be treated with corticosteroids without an initial biopsy. No properly controlled prospective trials of corticosteroids compared with placebo were carried out.

While standard prednisone regimen for the treatment of the initial manifestation of childhood NS have been developed by the International Study of Kidney Disease in Children (ISKDC) [5] and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) [6] there still is considerable debate about the optimal sequential therapy. In a recent survey among paediatric nephrologists in Canada, all responders had different opinions. The purpose of this paper is to propose a sequential therapeutic approach based on evidence from a systematic review and meta-analysis of randomized controlled trials. Objectives were a high proportion of patients with cumulative sustained remission for the duration of follow-up or the smallest proportion of frequent relapsing and steroid-dependent NS, while considering side effects.

Subjects and methods

Search strategies

Randomized and quasi-randomized trials of corticosteroid agents, alkylating agents and cyclosporine in steroid-responsive nephrotic syndrome (SRNS) were identified from Medline (1966 to July 2000) and Embase (1988 to July 1999). The databases were searched using sensitive strategies for the identification of randomized controlled trials combined with text words and subject headings for NS, lipoid nephrosis, child, cyclophosphamide, chlorambucil, alkylating agents, cyclosporine and steroid. Reference lists of review articles,
relevant trials, nephrology textbooks and proceedings of scientific meetings were also searched. Studies were selected if they were randomized or quasi-randomized trials, if they involved children aged 3 months to 18 years in their initial or subsequent episode of SRNS. Studies involving children with steroid-resistant NS, congenital NS or NS associated with other glomerulonephritides were excluded.

Results

Twenty-two trials were identified by full text review to be randomized controlled trials. Two articles [6,7] were duplicate publications, so the article containing the most information [7] was included. One trial [8], in abstract form only, was excluded as follow up data were only available to 3 months.

Initial therapy

Eight trials [9–16] dealt with children in their initial episode of SPNS. Five trials [11–15] compared standard therapy (60 mg/m²/day prednisone for 4 weeks followed by 40 mg/m² on alternate days or on 3 consecutive days out of 7 for 2 months) with regimes of at least 3 months of therapy comprising 1–2 months of daily and 1.5–6 months of alternate day therapy. In one of these trials [13], standard therapy was compared with two experimental regimes. The outcomes from the experimental group treated for 6 months were included in the analyses. In a thorough meta-analysis, these five trials were analysed and also compared with two other clinical trials, which compared a shorter and a longer treatment protocol [17]. Figure 1 (adopted from [17]) clearly shows an overall reduction of the relative risk for relapse of NS for longer duration of therapy. While side effects were similar, meta-analysis of the five studies [11–15] involving 334 children, in which the experimental groups received a total calculated induction dose of prednisone of between 2922 and 4620 mg/m² administered over 3–7 months, showed that the longer durations and higher doses resulted in significant reductions in relapse rate, the number of relapses per patient per year, and the number of children who relapsed frequently, while serious adverse events and infectious were similar.

Corticosteroid therapy of relapse

Five studies [7,18–21] were identified for the treatment of relapse using different steroid regimens.

No difference was observed when comparing single morning and divided dosing of prednisone [19]. Delflazacort [20] reduced relapses during therapy, but is not generally available. Frequency of relapses could not be influenced by duration of relapse therapy [7]. Alternate day therapy was more effective than intermittent use of prednisone [21]. Table 1 summarizes three important trials [7,20,21]. Comparison of therapeutic interventions used in children with their first episode of NS with those used in children with relapsing NS was not possible as no studies compared the same interventions in these different patient groups.

Alternative therapy

A total of five studies dealt with cytotoxic therapy using alkylating agents [22–26]. There is only one comparative study for chlorambucil and cyclophosphamide [22], which may have had insufficient power. Therefore, the question about which alkylating agent remains open; however, most nephrologists favour cyclophosphamide. The first study comparing 8–12 weeks of cyclophosphamide [23] used a historic control and only included 18 patients per arm. This may be an explanation for the apparent disagreement with the study of Ueda et al. [26], which consisted of 32 patients in the control arm of 8 weeks and 41 patients in the experimental group of 12 weeks. Ueda et al. [26] came to the conclusion that there was no significant gain from 8 to 12 weeks. There was no further similar study to resolve the question about optimal duration of treatment with cyclophosphamide. There was agreement between two studies comparing alkylating agents and cyclosporine [24,25]. Both studies concluded that a course of cytotoxic drugs leads to a higher rate of cumulative sustained remission when compared with cyclosporine. Two studies [27,28] evaluated the use of azathioprine in steroid-responsive frequent-relapsing NS of childhood and both failed to show a therapeutic effect on the stability of remission after withdrawal of corticosteroid treatment. There was only one randomized trial on levamisole, which demonstrated an effect [29]. However, the effect was more pronounced in patients with frequent relapsing NS when compared with patients with steroid-dependent NS.
Discussion

As shown elegantly by Hodson et al. [17], treatment of children in their first episode of SRNS with prednisone for between 3 and 7 months compared with 2 months results in fewer children experiencing relapses within 12–24 months without a notable increase in adverse effects. There appeared to be a linear dose–response relationship between the risk of relapse and the duration and total induction dose of prednisone [17]. It is surprising that only very few countries have proceeded to the administration of 12 weeks of prednisone despite the evidence.

Even with the latter primary therapy, there will be a proportion of patients who relapse. They should be treated with steroids in order to classify them as infrequent relapers, frequent relapers or steroid-dependent patients using ISKDC guidelines [30]. Unlike with the initial onset of the disease, the duration of therapy does not predict the long-term outcome, and therefore high doses of prednisone only seem justified until remission is achieved [6].

If alternative therapy is indicated (the reasons remain poorly defined but are predominantly because of steroid toxicity) then alkylating agents should be used as a first line therapy of choice. Cyclosporine serves a steroid-sparing agent but is inferior to the alkylating agents in inducing long-term remission [24,25]. Azathioprine is not effective [27,28]. Alternative drugs, which have been proposed such as enalapril, mycophenolate mofetil or tacrolimus have not been tested in randomized trials.

References


