Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials

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Abstract

Aims—To determine the benefits and toxicity of different corticosteroid regimes in preventing relapse in steroid responsive nephrotic syndrome.

Design—Meta-analysis of randomised controlled trials.

Subjects—Twelve trials involving 868 children aged 3 months to 18 years.

Main outcome measure—Frequency of relapse.

Results—A meta-analysis of five trials, which compared two months of prednisone with three months or more in the first episode, showed that the longer duration significantly reduced the risk of relapse at 12–24 months (relative risk 0.73; 95% confidence interval 0.60 to 0.89) without an increase in adverse events. There was an inverse linear relation (relative risk 1.382 (SE 0.215) − 0.133 (SE 0.048) duration; r² = 0.66; p = 0.05) between the duration of treatment and risk of relapse.

Conclusions—Children in their first episode of steroid responsive nephrotic syndrome should be treated with prednisone for at least three months, with an increase in benefit being shown for up to seven months of treatment.

Keywords: nephrotic syndrome; corticosteroid therapy; systematic review; meta-analysis

Corticosteroid therapy has been used in childhood nephrotic syndrome since the 1950s. Of children who present with their first episode, the majority of children have minimal change disease and 90–95% will respond to steroid therapy. 2 With steroid therapy, mortality has fallen from 35% to 3% because of a reduction in serious infections. Because of this dramatic before–after evidence that corticosteroids improve the outcome of nephrotic syndrome, oral corticosteroids are the first line treatment of any child presenting with idiopathic nephrotic syndrome. No properly controlled prospective trials of corticosteroids compared to placebo were carried out.

Nephrotic syndrome is a potentially chronic disease with about 70% of patients suffering a relapsing course and being at risk of the adverse effects of steroid treatment. A standard prednisone regimen developed by the International Study of Kidney Disease in Children (ISKDC) and the Arbeitsgemeinschaft für pädiatrische Nephrologie (APN) for the initial attack is widely used. This consists of daily prednisone (three consecutive days out of seven) or alternate day prednisone for four weeks.

Using data from several multicentre studies, it has been recommended 3 that the dose and duration of corticosteroid therapy should exceed that used in the standard regime. However, the optimal dose and duration of prednisone or other steroid agent that is most beneficial in maintaining remission and associated with least toxicity is not clear. The aim of this study is to assess the benefits and harms of corticosteroid therapy in the management of childhood nephrotic syndrome by conducting a systematic review and meta-analysis of randomised controlled trials. The information will assist clinicians in their decision making and identify to researchers questions that remain to be answered.

Methods

SEARCH STRATEGIES

Randomised and quasi-randomised trials of corticosteroid agents in steroid responsive nephrotic syndrome (SRNS) were identified from Medline (1966 to July 1998), Embase (1988 to July 1998), and the Cochrane Controlled Trials Register (Cochrane Library Issue 2, 1998). The databases were searched using optimally sensitive strategies for the identification of randomised controlled trials developed for the Cochrane Collaboration, 9 10 combined with text words and subject headings for nephrotic syndrome, lipoid nephrosis, child, and steroid. Reference lists of review articles, relevant trials, nephrology textbooks, and proceedings of scientific meetings were also searched. Investigators known to be active in the field were also contacted to seek information about any unpublished trials.

INCLUSION CRITERIA

Titles were screened by one reviewer (EH), who retained articles in which children with SRNS were treated with corticosteroid agents only. Abstracts were reviewed independently for study eligibility by two reviewers (EH, JK). Studies were selected if they were randomised or quasi-randomised trials, if they involved children aged 3 months to 18 years in their initial or subsequent episode of SRNS, 11 if they compared different durations, total doses, or other dose strategies of prednisone or other corticosteroid agent, and if follow up data for six months or more were available. Studies involving children with steroid resistant nephrotic syndrome, congenital nephrotic syndrome, or nephrotic syndrome associated with other glomerulonephritides were excluded.

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Table 1  Characteristics of trials of corticosteroid therapy in children in their first episode of steroid responsive nephrotic syndrome

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Patients (controls)</th>
<th>Patients (expt)*</th>
<th>Experimental intervention dose</th>
<th>Duration</th>
<th>Control intervention dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleinknecht et al, 1982, France</td>
<td>29</td>
<td>29</td>
<td>Prednisone 2 mg/kg/day for 4 weeks and taper alternate days</td>
<td>1 year</td>
<td>Prednisone 2 mg/kg/day for 4 weeks and taper alternate days</td>
<td>5 months</td>
</tr>
<tr>
<td>APN, 1988, North Europe</td>
<td>29</td>
<td>32</td>
<td>Prednisone 60 mg/m²/day till urine protein free for 3 days and 40 mg/m² alternate days till albumin &gt;35 g/l</td>
<td>1 month (average)</td>
<td>Prednisone 60 mg/m²/day for 4 weeks and 40 mg/m² alternate days for 4 weeks</td>
<td>2 months</td>
</tr>
<tr>
<td>Ueda et al, 1988, Japan</td>
<td>29</td>
<td>17</td>
<td>Prednisolone 60 mg/m²/day for 4 weeks, 60 mg/m² alternate days for 4 weeks and taper by 10 mg/m²/mth to zero</td>
<td>7 months</td>
<td>Prednisolone 60 mg/m²/day for 4 weeks and 40 mg/m² on 3 of 7 days for 4 weeks</td>
<td>2 months</td>
</tr>
<tr>
<td>APN, 1993, North Europe</td>
<td>37</td>
<td>34</td>
<td>Prednisone—6 weeks each of 60 mg/m²/day and 40 mg/m² alternate days</td>
<td>3 months</td>
<td>Prednisone—4 weeks each of 60 mg/m²/day and 40 mg/m² alternate days</td>
<td>2 months</td>
</tr>
<tr>
<td>Ksiazek and Wyszynska, 1995, Poland</td>
<td>44</td>
<td>68‡</td>
<td>Prednisone 1-2 mg/kg/day for 4 weeks, 1 mg/kg alternate days for 4 weeks and taper by 25% per week for 4 weeks</td>
<td>3 months</td>
<td>Prednisone 4 weeks each of 1-2 mg/kg/day and 1 mg/kg on alternate days</td>
<td>2 months</td>
</tr>
<tr>
<td>Norero et al, 1996, Chile</td>
<td>27</td>
<td>29</td>
<td>Prednisolone—6 weeks each of 60 mg/m²/day and 40 mg/m² alternate days and taper by 25% each month</td>
<td>6 months</td>
<td>Prednisolone—4 weeks each of 60 mg/m²/day and 40 mg/m² alternate days</td>
<td>2 months</td>
</tr>
<tr>
<td>Bagga et al, 1999, India</td>
<td>23</td>
<td>22</td>
<td>Prednisone—4 weeks each of 2 mg/kg/day, 1.5 mg/kg/day, 1.5 mg/kg alternate days, 1 mg/kg alternate days</td>
<td>4 months</td>
<td>Prednisone—4 weeks each of 2 mg/kg/day and 1.5 mg/kg alternate days</td>
<td>2 months</td>
</tr>
</tbody>
</table>

*Experimental group. †Arbeitsgemeinschaft für Pädiatrische Nephrologie. ‡Experimental groups 1 and 2 in study by Ksiazek and Wyszynska.

Table 2  Characteristics and aims of trials of corticosteroid therapy in children with relapsing steroid responsive nephrotic syndrome

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Study aim</th>
<th>Participants</th>
<th>Experimental intervention</th>
<th>Control intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISKDC*†, 1979, USA, Canada, Europe</td>
<td>Comparison of daily with intermittent therapy to maintain remission</td>
<td>64 children with frequently relapsing nephrotic syndrome; 32 experimental, 32 control</td>
<td>Prednisone 60 mg/m²/day for 4 weeks, then tapered daily dose for 4 weeks</td>
<td>Prednisone 60 mg/m²/day till remission, 35 mg/m² on alternate days. Total 6 months</td>
</tr>
<tr>
<td>APN*†, 1981, North Europe</td>
<td>Comparison of alternate day with intermittent therapy to maintain remission</td>
<td>64 children with frequently relapsing nephrotic syndrome; 30 experimental, 34 control</td>
<td>Prednisone 60 mg/m²/day till remission, 35 mg/m² on alternate days. Total 6 months</td>
<td>Prednisone 60 mg/m²/day till remission, 40 mg/m² on 3 days of 7 for 4 weeks</td>
</tr>
<tr>
<td>Imbascialli et al, 1985, Italy</td>
<td>Comparison of IV and oral steroid to induce and maintain remission</td>
<td>67 children with either initial episode or no relapse in previous year; 33 experimental, 34 control</td>
<td>Methylprednisone 20 mg/kg IV for 3 days, prednisone 20 mg/m²/day for 4 weeks, 20 mg/m² and 10 mg/m² alternate days for 4 weeks, 20 mg/m² alternate days for 4 months</td>
<td>Prednisone 60 mg/m²/day for 4 weeks, 40 mg/m² on alternate days for 4 weeks, 20 mg/m² alternate days for 4 months</td>
</tr>
<tr>
<td>Ekka et al, 1997, India</td>
<td>Comparison of daily with divided dose to induce and maintain remission</td>
<td>106 children in relapse; 52 experimental, 54 control</td>
<td>Prednisolone 2 mg/kg/day for 2 or 4 weeks as single morning dose, 1.5 mg/kg alternate days for 4 weeks</td>
<td>Prednisolone 2 mg/kg/day for 2 or 4 weeks in 3 divided doses, 1.5 mg/kg alternate days for 4 weeks</td>
</tr>
<tr>
<td>Broyer et al, 1997, France</td>
<td>Comparison of deflazacort and prednisone to induce and maintain remission</td>
<td>40 children with steroid dependent nephrotic syndrome; 20 experimental, 20 control</td>
<td>Deflazacort equal to prednisone 60 mg/m²/day to remission, 60 mg/m² alternate days for 6 weeks, 15-20 mg/m² alternate days. Total 1 year</td>
<td>Prednisone 60 mg/m²/day to remission, 60 mg/m² alternate days for 6 weeks, 15-20 mg/m² alternate days. Total 1 year</td>
</tr>
</tbody>
</table>

*International Study of Kidney Disease in Children. †Arbeitsgemeinschaft für Pädiatrische Nephrologie.
null
from Ksiazek and Wyszynski

therapy in children with their first episode of nephrotic syndrome. Results are ordered by trial weights. Only the experimental arm of six months duration

Figure 1 Meta-analysis of the relative risk (95% CI) for relapse of nephrotic syndrome by 12–24 months in five trials (334 patients) of corticosteroid

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with their first episode of nephrotic syndrome. Duration of 1 month compared with standard duration of 2 months

APN 1988

Duration of 3 months or more compared with standard duration

Ueda et al 1988

Norera et al 1996

APN 1993

Ksiazek and Wyszynska 1995

Bagga et al 1999

Subtotal (95% CI) chi squared 4.63

Duration of 12 months compared with 5 months

Kleinknecht et al 1982

Table 3 shows the assessment of study quality. Randomisation was adequately concealed in five studies. In two studies20 22 the numbers of children in the treatment and control groups differed considerably, and in the Polish study22 it was stated that the parents could influence which treatment group their child was assigned to. In the Japanese study20 the calculated total protocol dose (4620 mg/m²) exceeded the dose administered (3132 (SD 417) mg/m²) suggesting that the protocol was not adhered to in all patients. Only three studies were analysed on an intention to treat basis.22 24 26 Fewer than 10% of participants were excluded in seven studies.10–24 26 Only one study28 reported that outcome assessment was blinded. However, most studies reported the primary outcome measure using the ISKDC’s definition of relapse.5

OUTCOME OF CHILDREN IN THEIR FIRST EPISODE OF SRNS

Meta-analysis of the five studies20–24 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 three to seven 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 (table 4, fig 1). There was no increase in serious adverse events, infections, or cumulative steroid dose reported. No significant heterogeneity was shown (fig 1). Only one of the five studies showed adequate allocation concealment, so subgroup analysis based on study quality was not possible. A single study20 showed that a total dose and duration less than the standard regime resulted in a significantly higher relapse rate at 12 months (RR 1.46; 95% confidence interval (CI) 1.01 to 2.12) and a shorter time to first relapse (WMD −3.00; 95% CI −4.94 to −1.06). A further single trial21 showed no evidence that the relapse rate was significantly reduced by giving prednisone for one year compared with five months (RR 0.76; 95% CI 0.51 to 1.13).

In the six studies19–24 comparing standard therapy with other doses and durations of therapy, there was no significant association between the rate of relapse in the control groups treated for only two months (control event rate) and the relative risk for relapse at 12–24 months (r² = 0.18, p = 0.4). Combining these six studies (fig 2) showed that the risk of relapse was significantly reduced with increased duration (RR = 1.382 (SE 0.215) − 0.133 duration (SE 0.048); r² = 0.66; p = 0.05) and dose (RR 1.701 (SE 0.292) − 0.000264 dose (SE 8.630×10⁻⁶); r² = 0.70; p = 0.04) of prednisone. To explore whether duration or dose of prednisone determined the treatment response, we plotted the ratio of total dose to duration against relative risk (RR) to determine the average monthly dose (fig 3). This suggested that a reduction in risk of relapse was primarily associated with an increase in duration not dose, as an increase in
dose per month appeared to be associated with increased rather than decreased relative risk for relapse.

CHILDREN WITH RELAPSING SRNS

Tables 2 and 5 show the characteristics and results of the studies in children with relapsing SRNS. Alternate day therapy was significantly more effective than intermittent therapy in maintaining remission in frequently relapsing children during six months of therapy but there was no difference by 12 months. Single daily dosing was as effective as multiple daily dosing in achieving and maintaining remission in children who relapsed frequently. Deflazacort significantly reduced the number of children who relapsed during therapy and reduced the relapse rate among those who relapsed without significant differences in side effects. Comparison of therapeutic interventions used in children with their first episode of nephrotic syndrome with those used in children with relapsing nephrotic syndrome was not possible as no studies compared the same interventions in these different patient groups.

Discussion

Treatment of children in their first episode of SRNS with prednisone for between three and seven months compared with two months results in fewer children experiencing relapses within 12–24 months without a notable increase in adverse effects. In addition there is a linear dose–response relation between the risk of relapse and the duration and total induction dose of prednisone.

Examination of the relation between the risk for relapse and the ratio of dose to duration suggests that longer duration of treatment is more important than total dose in reducing the risk. The relative risk of relapse at 12–24 months falls by 0.133 (13%) for every month increase in therapy to seven months (fig 2). Table 6 illustrates the relation between the duration of prednisone therapy and the relapse rate when treated for two months. The higher the relapse rate with two months of therapy (control event rate), the greater the magnitude of the treatment effect expected with increased durations of prednisone therapy. The control event rate in six studies ranged from 48% to 91% with a mean of 66%. With relapse rate of 66% in children treated for two months, the event rate would fall by 9% for every increase by one month in the duration of therapy so that treatment for six months would reduce the risk of relapse by 36% (4 × 9%) to 30% compared with two months. Ideally clinicians should know the control event rate in their local population so that they can determine how much increasing the duration of therapy will improve the outcome among their patients.

The treatment regime for the initial episode of SRNS was originally determined by the ISKDC. Subsequently the APN showed that alternate day therapy was more effective than intermittent administration in maintaining remission and that three months of therapy was more effective than two in preventing relapse. These data led to the recommendation that
Table 5  Outcome of five trials of corticosteroid therapy in children with relapsing steroid responsive nephrotic syndrome

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Relapse on therapy, RR (95% CI)</th>
<th>Relapse by 9 months, RR (95% CI)</th>
<th>Relapse by 12 months, RR (95% CI)</th>
<th>Mean relapse rate during study, WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISKDC, 1979b</td>
<td>0.20 (0.09, 0.82)</td>
<td>1.00 (0.89, 1.12)</td>
<td>1.20 (0.93, 1.55)</td>
<td>0.54 (−0.50, 1.58)</td>
</tr>
<tr>
<td>APN, 1981a</td>
<td>0.60 (0.36, 1.02)</td>
<td>1.20 (0.75, 1.52)</td>
<td>1.06 (0.77, 1.50)</td>
<td>−0.20 (−0.65, 0.25)</td>
</tr>
<tr>
<td>Imbasciani et al, 1985c</td>
<td>1.07 (0.77, 1.50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ektak et al, 1997c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broyer et al, 1997a</td>
<td>0.44 (0.25, 0.78)</td>
<td></td>
<td>−1.90 (−2.77, −1.03)</td>
<td></td>
</tr>
</tbody>
</table>

RR, relative risk; WMD, weighted mean difference.

ISKDC, International Study of Kidney Disease in Children.
APN, Arbeitsgemeinschaft für Pädiatrische Nephrologie.

Table 6  Expected relapse rates of nephrotic syndrome in different groups of children at different risk of relapse after two months of prednisone

<table>
<thead>
<tr>
<th>Relapse rate when treated for 2 months (%)</th>
<th>Reduction in relapse rate for each additional month of therapy above 2 months (%)</th>
<th>Relapse rate if treated for an additional 5 months (total 7 months) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>60</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

*Regression equation for duration of prednisone treatment: RR = 1.38 − 0.133 duration.

Publication bias resulting from the exclusion of some unpublished trials cannot be totally excluded. Publication bias may result in an overestimate of treatment efficacy if the unpublished trials show no treatment effect. Formal testing using funnel plots or regression analysis was not possible because of the small number of studies. Responses from four senior investigators active in the field did not reveal any unpublished studies.

From the data, it was not possible to determine whether durations of treatment exceeding seven months would result in further reductions in the risk for relapse. No evidence of benefit through prolonging treatment to 12 months was shown in one study. Similarly the efficacy of total induction doses outside the range of doses used in the trials cannot be determined. No increase in toxicity was shown in the trials. However, individual trials were not designed specifically to study toxicity and so were underpowered for the detection of side effects of corticosteroids. Thus the low reported incidence of side effects with prolonged duration of corticosteroids could be explained by a type 2 statistical error and may not be generalisable to larger groups of children.

From this meta-analysis of randomised controlled trials it can be concluded that children in their first episode of nephrotic syndrome should be treated for at least three months, with an increase in benefit being shown for up to seven months of treatment. In a population with a baseline risk for relapse of 60% with two months of prednisone, daily prednisone for four weeks followed by alternate day therapy for six months would be expected to reduce the number of children experiencing a relapse by about 40%.

This work was supported by the Australian Kidney Foundation. The authors wish to thank Professors Barratt, Brodél, Broyer, and Ponticelli for responding to our requests for information about unpublished trials. This work has been presented in part at the 35th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology (Brisbane, 1999), the Annual Scientific Meeting of the Royal Australasian College of Physicians (Melbourne, 1999), and the 33rd Annual Meeting of the European Society for Paediatric Nephrology (Prague, 1999).

Corticosteroid therapy in nephrotic syndrome