

EARLY PREDNISONE THERAPY IN HENOCH-SCHÖNLEIN PURPURA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Objective To evaluate the efficacy of early prednisone therapy in preventing renal and treating extrarenal and renal symptoms in Henoch-Schönlein purpura (HSP) in a placebo-controlled trial.

Study design A total of 171 patients (84 treated with prednisone and 87 receiving placebo) were included and followed up for 6 months. The endpoints were renal involvement at 1, 3, and 6 months and healing of extrarenal symptoms. The analyses were performed on an intent-to-treat basis.

Results Prednisone (1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks) was effective in reducing the intensity of abdominal pain (pain score, 2.5 vs 4.8; $P = .029$) and joint pain (4.6 vs 7.3; $P = .030$). Prednisone did not prevent the development of renal symptoms but was effective in treating them; renal symptoms resolved in 61% of the prednisone patients after treatment, compared with 34% of the placebo patients (difference = 27%; 95% confidence interval = 3% to 47%; $P = .024$).

Conclusions The general use of prednisone in HSP is not supported, but patients with disturbing symptoms may benefit from early treatment, because prednisone reduces extrarenal symptoms and is effective in altering (but not preventing) the course of renal involvement. (*J Pediatr* 2006;149:241-7)

Henoch-Schönlein purpura (HSP) is the most common form of small vessel vasculitis in children.¹ Major manifestations include arthritis, abdominal pain, and renal disease. In most children, HSP is self-limiting within a few weeks, but severe abdominal pain, intestinal bleeding, and bowel intussusception may cause acute complications.² Renal symptoms in HSP vary from intermittent hematuria and proteinuria to severe nephritic-nephrotic syndrome.^{3,4} The severity and duration of urinary abnormalities have clear prognostic value in patients with HSP.^{5,6} Only patients without signs of renal involvement at onset have an excellent long-term prognosis; those diagnosed with HSP glomerulonephritis during childhood may develop renal disease years after apparent recovery.^{5,7} Prevention of renal disease, if possible, could improve the prognosis of HSP, the long-term outcome of which is highly dependent on renal symptoms.

Existing data on the efficacy of corticosteroid therapy in preventing and treating HSP, based on retrospective and uncontrolled trials, are controversial.⁸⁻¹² Only 1 placebo-controlled trial with 40 patients has been published, and this reported no effect of early steroid therapy on the risk of renal involvement at 1 year.¹³

METHODS

For this prospective, double-blinded, placebo-controlled trial of the effect of early prednisone on HSP, a total of 240 children with newly diagnosed HSP were screened at 4 university hospitals and 10 regional hospitals between 1999 and 2005. Criteria for entry into the study were age under 16 years and a clinical diagnosis of HSP (ie, typically distributed purpura or petechiae with or without gastrointestinal and/or joint pain). Exclusion criteria were thrombocytopenia, systemic vasculitis, and established nephritis (hematuria >10 erythrocytes/vision field or U-protein >300 mg/L) at onset. Any child with a disease in which prednisone therapy was contraindicated was excluded.

The local ethics committee for each study center and the National Agency for

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ARR	Absolute risk reduction	NNH	Number needed to harm
CI	Confidence interval	NNT	Number needed to treat
HSP	Henoch-Schönlein purpura	OR	Odds ratio
NNB	Number needed to benefit		

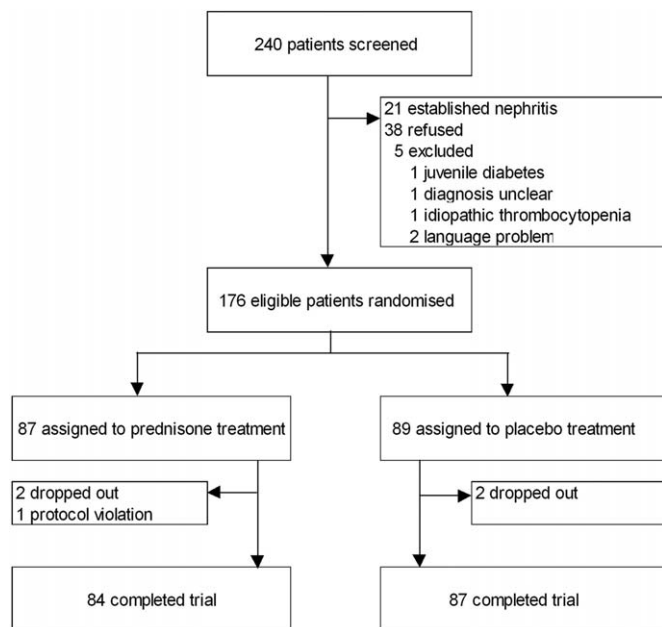


Figure 1. Trial profile.

Medicines in Finland all approved the study protocol. Once informed consent had been obtained from a parent, each patient received the medication and a symptom diary.

Oral prednisone was given twice a day at a dose of 1 mg/kg/day for the first 14 days, followed by a weaning dose of 0.5 mg/kg/day for 1 week and then 0.5 mg/kg/day once a day on alternate days for an additional week. The drug (prednisone as 5-mg tablets) and placebo tablets were similar in size and were supplied in lots of 200 tablets in similar containers marked with sequential numbers. The dosing of both drugs was the same—1 tablet per 5 kg of body weight, with a maximum dose of 10 tablets per day of placebo or prednisone (ie, 50 mg of prednisone was the maximum dose of corticosteroid). The daily drug intake was recorded in the diary, and the patient returned the remaining tablets after the study period for counting. Compliance with the medication was considered adequate if < 20% of the calculated dose relative to body weight was returned.

To ensure equal numbers of children in both groups in each center, a block randomization system was used, with a block size of 6. The observers and subjects in the trial were unaware of the randomization scheme. Pharmia Ltd (Espoo, Finland) packed the drugs, labelled the containers, and performed the randomization, retaining the key to the randomization until the end of the trial.

The protocol by which the 176 eligible patients were randomized to receive prednisone or a placebo is shown in Figure 1. Altogether, 171 patients (84 in the prednisone group and 87 in the placebo group) completed the trial. Six patients in the prednisone group and 4 in the placebo group withdrew from the treatment but completed the follow-up, and in 2 cases (1 in the prednisone group and 1 in the placebo group), the medication was stopped due to

Table 1. Clinical and laboratory features of participants at baseline

Characteristic	Prednisone (n = 84)	Placebo (n = 87)
Male/female	49/35	44/43
Mean age (years) at diagnosis	6.8 (2.0 to 15.2)	7.3 (1.7 to 15.6)
Mean time (days) to diagnosis*	4.7 (0 to 28)	6.4 (0 to 63)
Petechiae	84 (100%)	87 (100%)
Abdominal pain	28 (33%)	37 (43%)
Joint pain	59 (70%)	62 (71%)
Renal symptoms	16 (19%)	16 (18%)
Proteinuria†	4 (5%)	5 (6%)
Hematuria‡	10 (12%)	4 (5%)
Hematuria + proteinuria†‡	2 (2%)	7 (8%)

Data are number of patients (%) or mean (range).

*Time from first symptoms observed at home to diagnosis.

†U-protein 200 to 300 mg/L

‡U-erythrocytes 6 to 10 /vision field

varicella contact. All of these 12 patients were kept in the trial, followed up according to the protocol, and analyzed on the basis of intent-to-treat.

Symptom Diary and Clinical Examinations

Abdominal and joint symptoms were classified by parents in terms of severity as follows: 0 = no pain; 1 = mild pain, the child can move around and play; 2 = moderate pain, the child occasionally prefers to stay still; and 3 = severe pain, the child cannot move around or play or prefers to stay in bed. In both groups, paracetamol (15 mg/kg 1 to 3 times a day) was used as an analgesic for abdominal and/or joint pain when needed; its use was recorded in the diary. Hematuria and proteinuria were evaluated with a dipstick test daily for 1 month, with results recorded in the diary as follows: + = mild hematuria/proteinuria; ++ = moderate hematuria/proteinuria; and +++ = severe hematuria/proteinuria. Parents were advised to contact the researchers if severe proteinuria (+++) persisted for 3 consecutive days. Parents were also instructed to note any medication side effects in the diary.

The patients were examined by a doctor at study inclusion and then at 7 to 10 days and 1, 3, and 6 months after the start of medication. Body weight, height, blood pressure, and any skin, abdominal, joint, and respiratory signs and symptoms were recorded. Laboratory tests for urine microscopy and U-protein/U-albumin were performed. All results of the clinical examinations and laboratory findings were recorded on a structured data sheet.

Renal affects were recorded if U-erythrocyte/U-protein readings of + to ++ for 3 or more consecutive days or U-erythrocyte/U-protein readings of +++ for 2 or more consecutive days were obtained by dipstick during drug treatment. Renal involvement as an endpoint was defined as U-protein > 200 mg/L, U-albumin > 30 mg/L, or U-erythrocytes > 5/vision field.

Table II. Influence of prednisone and placebo treatment on body weight, blood pressure, and the need for analgesics on abdominal and joint pain

Characteristic	Prednisone (n = 84)	Placebo (n = 87)	Mean difference	95% CI	P value
Increase in weight (kg)	1.4 (−1.8 to 4.7)	0.4 (−5.4 to 6.2)	1.1	0.5 to 1.6	<.001
Systolic blood pressure (mm Hg)*	109 (85 to 129)	106 (84 to 144)	3.2	−0.7 to 7.1	.113
Diastolic blood pressure (mm Hg)*	64 (44 to 90)	61 (48 to 78)	3.6	0.9 to 6.2	.009
Need for analgesic (days)†	2.2 (0 to 12)	2.7 (0 to 16)	0.6	−0.7 to 1.9	.369
Abdominal pain score					
Severity‡	2.5 (0 to 22)	4.8 (0 to 39)	2.4	0.3 to 4.5	.029
Duration#	1.5 (0 to 11)	2.7 (0 to 13)	1.2	0.1 to 2.3	.028
Joint pain score					
Severity‡	4.6 (0 to 17)	7.3 (0 to 29)	2.7	0.3 to 5.2	.030
Duration#	3.1 (0 to 12)	4.4 (0 to 13)	1.3	−0.1 to 2.6	.076

Data are mean (range).

*Measured by taking the mean blood pressure of the control visits at 7 to 10 days and 1 month.

†Days when taking analgesic at home.

‡Mean sum of scores for pain in symptom diary within the first 2 weeks.

#Mean sum of days with pain in symptom diary within the first 2 weeks.

Sample Size and Statistical Analysis

The sample size calculations were based on the assumption that approximately 40% of untreated HSP patients develop renal involvement.^{2,6} A 50% reduction in the incidence of renal involvement to 20% was considered a clinically relevant response to the treatment. Based on 2-tailed testing with $\alpha = 0.05$ and $\beta = 0.20$, a sample size of 81 children in both groups was determined. All analyses were performed on an intent-to-treat basis. SPSS (version 12.0 for Windows) and StatsDirect (version 2.4.1) were used for the statistical analysis.

The primary endpoint was renal involvement diagnosed on the basis of urinary findings (U-protein, U-erythrocytes) at the 1-, 3-, and 6-month control visits. The secondary endpoints were the severity and duration of abdominal and joint symptoms during treatment, according to the symptom diary. The Kaplan-Meier method was used to compare the effect of treatment on renal symptoms from the 1-month visit onward and to compare the disappearance of extrarenal symptoms between treatment groups, with the differences evaluated using the log-rank test. Sum scores for the severity of abdominal and joint pain and the duration of abdominal and joint pain (in days) were calculated for each patient in both groups according to the symptom diary, and the differences were evaluated using the *t* test. The differences in skin symptoms between the 2 groups at the first control visit and 1-month visit were evaluated using the χ^2 test. Forward stepwise logistic regression analysis was used to determine the most predictive risk factors for renal involvement. Sex, age at diagnoses of HSP, mild renal symptoms at onset (+/−), severe abdominal pain (+/−), and purpura persisting for more than 1 month (+/−) were included in the base model. Differences and their 95% confidence intervals (CIs) were calculated for the proportions of renal involvement between the treatment groups. The number needed to treat (NNT) was calculated from the formula $NNT = 100/\text{absolute risk reduction}$

(ARR). (ARR = effect of prednisone treatment [%] − effect of placebo treatment [%].) The 95% CIs were calculated for NNT and described in terms of the number needed to harm (NNH) and number needed to benefit (NNB).¹⁴

RESULTS

The 2 groups had similar age and sex distributions at the time of enrollment, as well as similar baseline characteristics in terms of symptoms (Table I).

Efficacy of Prednisone in Treating Abdominal and Joint Pain and Purpura

Prednisone was effective in reducing extrarenal symptoms, in that the mean sum of scores for abdominal pain (severity) within 2 weeks of diagnosis, according to symptom diary, was significantly lower in the prednisone group than in the placebo group ($P = .029$), and the mean sum of total days with pain (duration) was 1.2 days less in the prednisone group ($P = .028$). The incidence of severe abdominal pain necessitating hospital admission was greater in the placebo group (9 out of 87 patients) than in the prednisone group (5 out of 84 patients). Two of the 5 patients in the prednisone treatment group were unable to take the tablets due to severe abdominal symptoms.

The prednisone group also had a lower mean sum of scores for joint pain (severity) within 2 weeks after diagnosis, according to the symptom diary ($P = .030$), and their mean sum of total days with joint pain was 1.3 days less ($P = .076$), although this result was not statistically significant. The mean scores for abdominal and joint pain are given in Table II, and the disappearance of abdominal and joint symptoms is depicted in Figure 2.

A total of 27 of the 75 patients (36%) in the prednisone group and 41 of the 73 patients (56%) in the placebo group ($P = .021$) exhibited purpura at the first control visit (7 to 10 days after study inclusion). There was no significant differ-

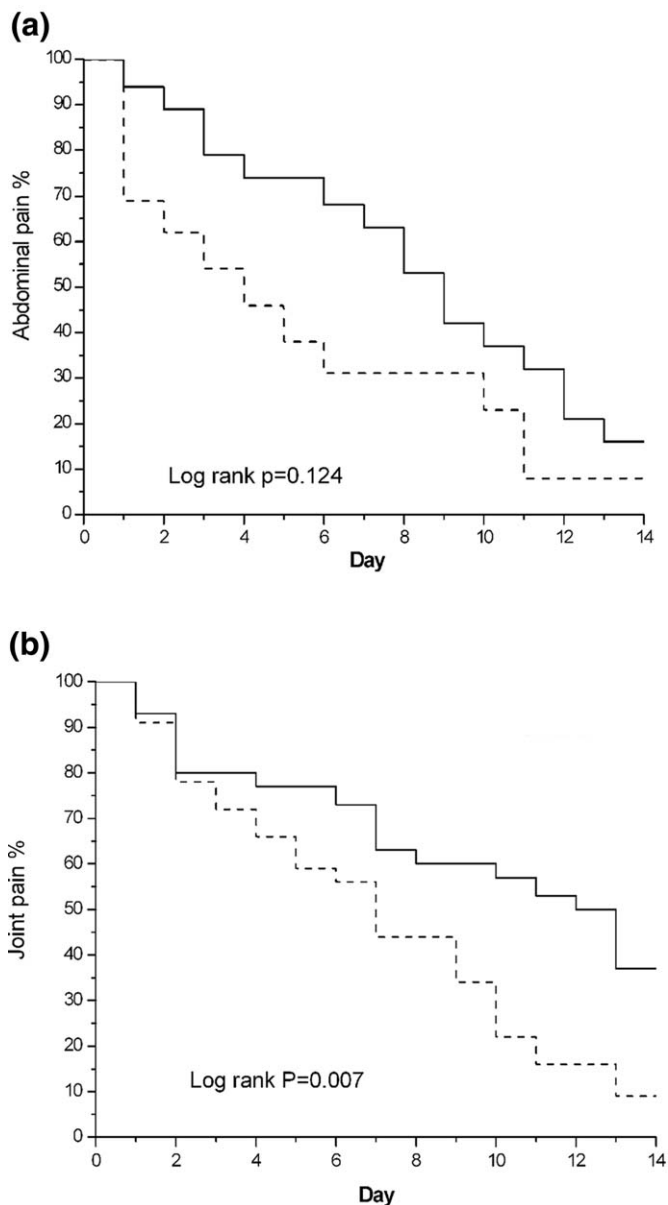


Figure 2. Disappearance of abdominal and joint symptoms, by treatment group. (a) Disappearance of abdominal symptoms; solid line, placebo (n = 19); dashed line, prednisone (n = 13). (b) Disappearance of joint symptoms; solid line, placebo (n = 30); dashed line, prednisone (n = 32).

ence in skin symptoms between the 2 groups at the 1-month control visit or in the recurrence of purpura after 1 month. The need to take analgesics (paracetamol) at home for stomach or joint pain was a mean of 2.2 days in the prednisone group and 2.7 days in the placebo group ($P = .369$; Table II).

Efficacy of Prednisone in Treating Renal Symptoms

Prednisone did not prevent the development of renal symptoms. Altogether, 74 patients (43%) had renal symptoms (38 in the prednisone group and 36 in the placebo group) during the 6 months of follow-up; 71 of these patients (96%; 36 in the prednisone group and 35 in the placebo group) had these symptoms or developed them during the 1-month treat-

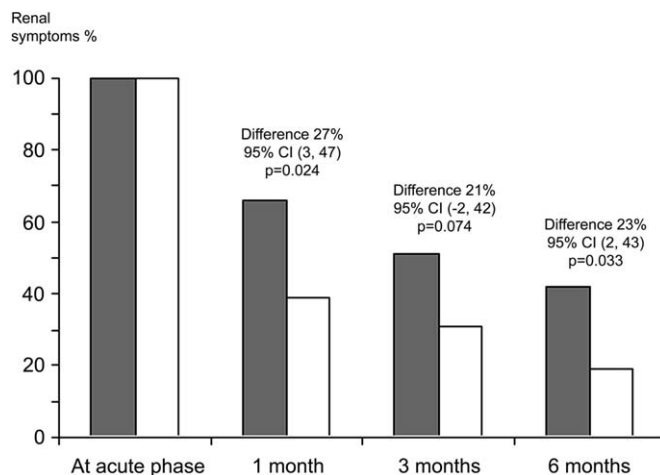


Figure 3. Renal involvement after treatment in HSP patients with mild renal symptoms in the acute phase, by treatment group (36 in the prednisone group and 35 in the placebo group). *P* values, differences for proportions, and their 95% CIs in the resolution of renal symptoms are given above the columns for each control visit (1, 3, and 6 months). Grey bar, placebo; white bar, prednisone.

ment period. Seven patients (4 in the prednisone group and 3 in the placebo group) developed severe nephritis and underwent biopsy.

To analyze the effect of prednisone in altering the course of renal disease, we analyzed the rate of resolution of renal symptoms in these 71 patients by treatment group. Renal symptoms resolved significantly more rapidly in the patients in the prednisone group than in those in the placebo group, although resolution of renal symptoms did also occur in the placebo group (Figure 3).

Prednisone treatment was most effective in treating renal disease in patients over age 6 years who had or developed renal symptoms during the first month after the diagnosis of HSP. A total of 15 of the 24 patients (63%) in this category in the prednisone group were free of renal symptoms after treatment, compared with 3 of 20 (15%) in the placebo group (difference = 48%; 95% CI = 19% to 68%; $P = .001$).

Patient survival after the course of medication without renal involvement in all patients, in patients over age 6 years at study inclusion, and in patients with mild renal symptoms at inclusion is illustrated in Figure 4.

Risk Factors for Renal Involvement

Renal signs at onset (odds ratio [OR] = 10.7; 95% CI = 4.2 to 27.4; $P < .001$), severe abdominal pain (OR = 8.2, 95% CI = 1.8 to 37.8; $P = .007$), and persistent purpura (OR = 3.7; 95% CI = 1.4 to 9.6; $P = .008$) turned out to be the most important predictive factors for developing nephritis in logistic regression analysis.

Number Needed to Treat

NNT figures with 95% confidence intervals calculated for early prednisone treatment for HSP are depicted in Figure 5. Twelve patients with HSP at any age and with any symp-

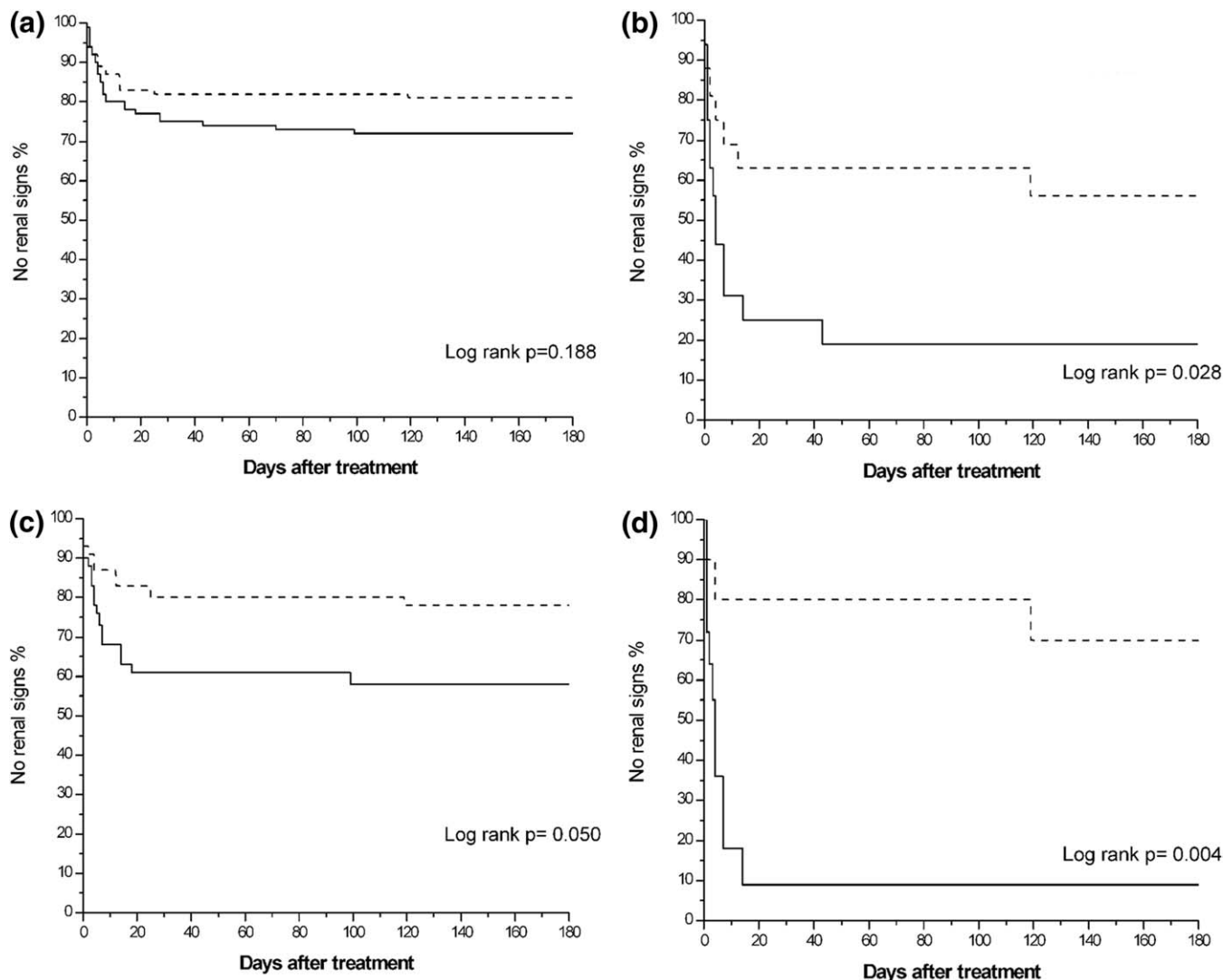


Figure 4. Renal signs after treatment, by treatment group. Treatment was provided for the first 28 days. (a) All patients; solid line, placebo (n = 87); dashed line, prednisone (n = 84). (b) Patients with mild renal symptoms at inclusion; solid line (n = 16); dashed line, prednisone (n = 16). (c) Patients >6 years; solid line, placebo (n = 41); dashed line, prednisone (n = 46). (d) Patients >6 years with mild renal symptoms at inclusion; solid line, placebo (n = 11); dashed line, prednisone (n = 10).

toms at onset need be treated to prevent renal involvement in 1 case, whereas 1 more patient would benefit from placebo treatment when treating 24 (95% CI = 2 NNB to ∞ to 24 NNH). Early prednisone treatment seemed most useful for patients over age 6 years with mild renal symptoms at onset (NNT = 2; 95% CI = 2 NNB to 6 NNB).

Safety of Treatment

Neither prednisone nor placebo caused any serious side effects. The medication was stopped in 1 patient in each group due to a varicella contact during treatment; in neither case did fulminant varicella disease develop. Parents reported improved appetite in 26 (31%) and increased liveliness in 7 (8%) of the 84 patients in the prednisone group. The patients in the prednisone group gained more weight after 1 month and had a slightly higher mean diastolic blood pressure compared with those in the placebo group (Table II).

DISCUSSION

Although reports on the use of corticosteroids to treat HSP first appeared around 1950,¹⁵ no prospective placebo-controlled studies with sample size and power calculations have been published to date. Because the incidence of HSP is 20.4/100,000 children per year,¹ compiling a patient series of adequate size for a placebo-controlled trial is not easy; this is likely why evidence-based data on the efficacy of steroid treatment for HSP are lacking. Here we report a prospective, randomized, placebo-controlled trial demonstrating that early prednisone treatment is effective in reducing abdominal and joint symptoms in HSP and also in altering the course of renal involvement caused by the disease.

We performed our trial over a 6-year period. Patient loss during follow-up was very small; 98% of the patients completed all 3 control visits. Adequately completed symptom diaries were returned by 127 of the 171 patients (74%).

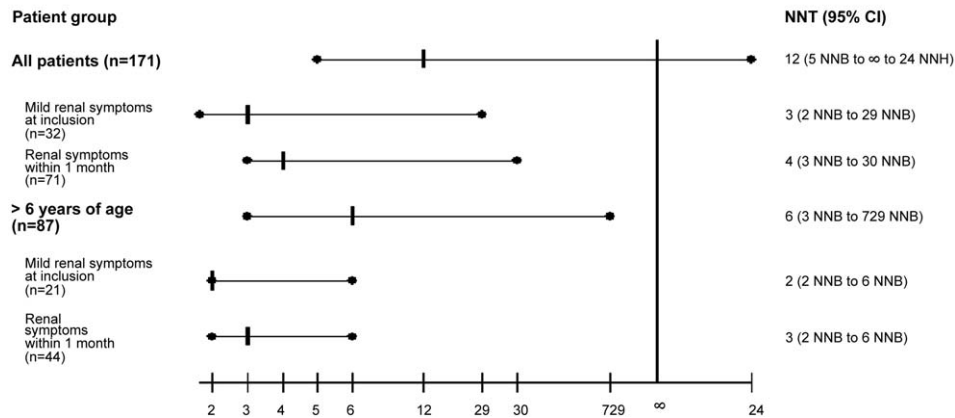


Figure 5. NNT figures for early prednisone treatment for HSP with 95% confidence intervals for NNT and described as NNH and NNB. See the text for details.

Our primary endpoint was renal involvement at the 1-, 3-, and 6-month control visits. Endpoint criteria were selected based on earlier work of Koskimies et al,⁶ who demonstrated that the occurrence and duration of urinary abnormalities have clear prognostic value in HSP patients. Those authors found poor outcome after 2 years of follow-up in 7 of their 19 patients (37%) with persistent urinary abnormalities after 4 weeks, compared with none of their 18 patients whose urine cleared in < 4 weeks.⁶

We used prednisone at a dose of 1 mg/kg/day because the main aim was to prevent nephritis, and because patients with established nephritis had been excluded. This was the dose used by Mollica et al⁸ in an earlier preventive study. The renal symptoms in this series were generally mild; only 7 patients (4 in the prednisone group and 3 in the placebo group) underwent biopsy, 2 received medication for hypertension, and none developed renal insufficiency during follow-up.

Early prednisone treatment was more effective in reducing the severity and duration of abdominal and joint pain compared with placebo. Earlier clinical experience, as well as uncontrolled studies, suggested an improvement in abdominal symptoms,^{2,10} but the level of evidence has remained low because of the retrospective and uncontrolled nature of the findings. Earlier authors were careful in making recommendations for the use of steroids to treat symptoms, however, which in most cases heal spontaneously within 3 days.¹⁰ It has been suggested that steroid therapy may reduce invagination and intestinal bleeding,^{2,13} but because these complications are very rare, the use of steroids has not been considered necessary for all patients.² In our study, the incidence of severe abdominal pain was almost twice as high in the placebo group (9 of 87 patients) than in the prednisone group (5 of 84 patients). Moreover, 2 patients out of the 5 with severe abdominal symptoms in the prednisone group could not take the tablets because of their severe symptoms. Abdominal pain is usually the most disturbing symptom in the acute phase of HSP and can lead to hospitalization. Based on these results, steroids can be effective in treating disturbing extrarenal symptoms of HSP, and their use seems to be indicated in cases with severe symptoms.

The effect of steroids on the prevention or treatment of nephritis has been controversial, and it is difficult to compare the results obtained in various studies because of differences in study design.^{8,9,11} In the prospective but nonrandomized study of 168 patients, Mollica et al⁸ concluded that early corticosteroid treatment prevented the development of nephropathy. In our trial, early prednisone treatment did not prevent the development of renal symptoms, but prednisone was definitely effective in altering the course of renal disease in patients with signs of mild renal symptoms at inclusion or within the first month after the diagnosis, although the spontaneous resolution of renal symptoms was also noticed (Figure 3). The efficacy of prednisone is demonstrated by the fact that only 3 patients with mild renal symptoms at inclusion need to be treated to save 1 patient from renal involvement after treatment; this figure is reduced to 2 if only those over age 6 years at onset are included.

In the sole previously published placebo-controlled study, Huber et al¹³ found no effect of prednisone treatment in reducing renal involvement during 1 year of follow-up. Taking into account our sample size calculation and the approximate 40% incidence of renal involvement in HSP patients, their sample size (n = 40) was evidently too small to allow for any definite conclusions.

It is evident that not all HSP patients need early steroid treatment, and treatment should be targeted at patients who have a high risk of renal involvement or severe extrarenal symptoms. Earlier multivariate studies have suggested age at onset, persistent purpura, and severe abdominal pain as risk factors for renal involvement.^{9,16} In our series, persistent purpura, severe abdominal pain, and even mild renal symptoms at onset were predictive factors for renal involvement in logistic regression analysis. In clinical use, risk factors that are visible or easily measurable at the first physician visit due to HSP could be the most useful in terms of determining whether or not to prescribe early steroid treatment; based on our findings, these risk factors are age over 6 years and renal symptoms at onset.

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