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Effects of Corticosteroid on Henoch-Schönlein Purpura: A Systematic Review

Pamela F. Weiss, MD, James A. Feinstein, MD, Xianqun Luan, MS, Jon M. Burnham, MD, MSCE, Chris Feudtner, MD, PhD, MPH

Division of Rheumatology, Pediatric Generalist Research Group, Division of General Pediatrics, and Division of Biostatistics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE. No consensus exists among general pediatricians or pediatric rheumatologists regarding whether corticosteroid therapy ameliorates the acute manifestations of Henoch-Schönlein purpura or mitigates renal injury. Therefore, we sought to synthesize the reported experimental and observational data regarding corticosteroid use.

METHODS. We performed a meta-analysis based on a comprehensive review of the literature in the Medline database (1956 to January 2007) and the Cochrane Controlled Trials Register. On the basis of reported outcomes among patients with Henoch-Schönlein purpura who were treated at diagnosis with corticosteroids compared with patients treated with supportive care only, we calculated odds ratios for the resolution of abdominal pain, the need for surgical intervention secondary to severe pain or intussusception, the likelihood of Henoch-Schönlein purpura recurrence, and the development of transient or persistent renal disease.

RESULTS. Of 201 articles retrieved from the initial literature search, 15 were eligible for inclusion. Corticosteroid treatment did not reduce the median time to resolution of abdominal pain but did significantly reduce the mean resolution time and increased the odds of resolution within 24 hours. Early corticosteroid treatment significantly reduced the odds of developing persistent renal disease. In addition, although the results were not statistically significant, the prospective data suggest reduced odds of both surgical intervention and recurrence.

CONCLUSIONS. Corticosteroids, given early in the course of illness, seem to produce consistent benefits for several major clinically relevant Henoch-Schönlein purpura outcomes.
Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood, affecting between 8 and 20 per 100 000 children annually and accounting for 49% of all childhood vasculitides in the United States. Although typically self-limited, HSP can cause gastrointestinal hemorrhage, intussusception, and end-stage renal disease (ESRD). Renal involvement, manifested by hematuria, proteinuria, nephrotic syndrome, or renal insufficiency, may occur in 60% of children. In 1 recent study, 54% of patients developed renal manifestations within 3 months of diagnosis, 11.6% had persistent abnormalities after 7 years, and none developed ESRD. However, previous studies have reported that as much as 21% of children with HSP-associated nephritis develop rapidly progressive glomerulonephritis: 15% of these children with HSP-associated rapidly progressive glomerulonephritis, which is to say 2% of all patients with HSP, may progress to have uremia or ESRD. Furthermore, even seemingly benign HSP may have long-lasting effects: 2 studies have reported that 40% and 70% of term pregnancies of women with a history of childhood-onset HSP were complicated by hypertension, proteinuria, or preeclampsia.

The goals of treating HSP are typically to (1) ameliorate acute symptoms, (2) mitigate short-term morbidity (such as abdominal complications that require surgery), and (3) prevent chronic renal insufficiency. Because HSP is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition (with resulting vascular injury and necrosis), and because corticosteroids inhibit inflammatory processes, early treatment with corticosteroids has been postulated to be effective for all 3 therapeutic goals, but much controversy remains. Although the literature is replete with retrospective studies that evaluated corticosteroid use for HSP, currently there are only 3 published prospective, placebo-controlled studies on the subject, and they vary in their conclusions regarding the utility of early corticosteroid administration.

Through a systematic review and meta-analysis, we sought to compare and contrast the experimental and observational data regarding corticosteroid use and, where appropriate, synthesize the data for 5 main clinical questions: (1) Do corticosteroids shorten the duration of abdominal symptoms in HSP? (2) Do corticosteroids decrease the odds of surgical intervention for HSP? (3) Do corticosteroids decrease the odds of disease recurrence? (4) Do corticosteroids decrease the odds of renal disease (transient plus persistent) in HSP? and (5) Do corticosteroids decrease the odds of developing persistent renal disease in HSP?

METHODS

Data Sources

The published medical literature was searched by using the Cochrane Controlled Trials Register (CCTR) and Medline database. Articles written in all languages were included in the search, and translation was obtained when needed.

CCTR and Medline were searched by using the Medical Subject Headings (MeSH) terms “steroids,” “methylprednisolone,” and “dexamethasone” and the key words “Henoch” and “corticosteroids.” “Henoch” and “purpura, Schönlein-Henoch” were grouped together and joined by “or.” “Steroids,” “methylprednisolone,” “dexamethasone,” and “corticosteroids” were grouped together and joined by “or.” Both groups of terms were joined together by “and.” The only limit applied to the search was “all children: 0–18 years.”

Given the large number of studies obtained from the literature search (N = 201), we cite in this report only the studies that were chosen for inclusion. A full list of publications is available at www.pediatric-generalists.org/weiss.htm.

Study Eligibility

Eligible studies were limited to those that examined the use of corticosteroids for the treatment of HSP; observational and randomized, controlled trials were included. An article was excluded if it (1) was a review, (2) examined therapy with a drug other than corticosteroids, (3) was a case report with fewer than 5 subjects with HSP, (4) focused on individuals older than 18 years, (5) did not discuss therapy with corticosteroids, (6) included only patients with nephritis at study onset, (7) did not assess definite outcomes, or (8) did not discuss HSP.

Study Selection

The initial literature search of the CCTR and Medline databases yielded 201 articles in 14 languages. Titles were reviewed to screen for eligibility. If the title yielded insufficient data to determine if a study was eligible, the abstract was obtained and reviewed. Articles without sufficient information in the abstract or those without an accessible abstract were examined in full text. Interpreters who were familiar with medical language and study designs evaluated all articles written in languages other than English.

Two of the authors (Drs Weiss and Feinstein) independently screened each of the potential titles, abstracts, and articles to determine inclusion. Disagreements were resolved by discussion and consensus mediated by a third author (Dr Feudtner). Reasons for article exclusion are presented in Table 1. After all the exclusions were applied, 15 articles remained for further analysis (Table 2).

In an attempt to find all relevant articles, the reference lists of included articles were searched and yielded 2 additional articles for potential inclusion. However, neither article was included because the outcomes could not be abstracted. In addition, the authors of the in-
Although there is no consensus regarding the indication of corticosteroids in HSP, symptoms in HSP? Do Corticosteroids Shorten the Duration of Abdominal Pain?

RESULTS

Data Extraction

Two authors (Drs Weiss and Feinstein) independently abstracted data from the remaining articles. Disagreements were resolved by discussion and consensus mediated by a third author (Dr Feudtner). Abstracted data from the remaining articles included information regarding the study population, existence of a control group, study limitations, and information relating to the resolution of abdominal pain, surgical intervention, recurrence, and the incidence of renal sequelae.

Statistical Analyses

Pooled odds ratios (ORs) were obtained by using the “metan” command for Stata 9.2 (Stata Corp, College Station, TX) for each of 5 clinical outcomes: (1) resolution of abdominal pain; (2) surgical intervention for severe abdominal pain or intussusception; (3) recurrence; (4) cumulative renal abnormalities; and (5) persistent renal abnormalities. The odds of having each outcome in patients who were treated with corticosteroids was compared with patients treated with routine supportive care for both prospective and retrospective studies. Results from fixed-effects models are reported. Tests for heterogeneity were performed for each analysis as a way to evaluate to what extent the results were consistent and suitable for fixed-effect modeling. If the test for heterogeneity was significant, we did not calculate a pooled OR. The Egger test for bias was performed and funnel plots were performed for each of the clinical outcomes to evaluate for publication bias. Each of the funnel plots was symmetrical, which suggests the absence of publication bias. The Egger test for bias could only be applied to analyses with 2 or more studies.

Do Corticosteroids Decrease the Incidence of Surgical Intervention for HSP?

Only 3 studies (1 randomized, controlled trial and 2 observational trials) reported intussusception, a rare and potentially life-threatening abdominal complication during the acute phase of HSP.11,18,19 Huber et al11 provided the only prospective study that reported incidence of intussusception; the risk of intussusception was reduced, but not to a significant degree, in the group that received corticosteroids (OR: 0.16; 95% CI: 0.01–3.62). The 2 retrospective studies together suggest a protective effect of corticosteroid exposure (OR: 0.75; 95% CI: 0.13–4.46) (Fig 2). There was no evidence of heterogeneity between the studies (P = .39).
Does Early Treatment With Corticosteroids Decrease the Odds of HSP Recurrence?

Recurrences affect up to one third of children with HSP.13,21 Many of these children require additional hospital admissions and pharmacotherapy. The 2 prospective studies with recurrence data suggest a protective effect of corticosteroids (OR: 0.32; 95% CI: 0.07–1.49), and there was no significant heterogeneity ($P = .70$) (Fig 3).11,14 The 5 retrospective observational studies that examined HSP recurrence exhibited heterogeneity ($P < .01$), so a pooled OR is not reported.11,13,14,20–23 The ORs and 95% CIs are reported for each study (Fig 3). No evidence of publication bias was found (Egger test: $P = .55$).

Do Corticosteroids Decrease the Likelihood of Developing Cumulative Renal Abnormalities With HSP?

Eight studies have reported data on cumulative (transient or persistent) renal abnormalities during the year

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**TABLE 2** Summary of Included Articles and Corticosteroid Use

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Corticosteroid Dose</th>
<th>Initiation of Treatment From Time of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronkainen et al9 (2006)</td>
<td>171</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>1</td>
<td>2 wk, weaning over 2 wk</td>
</tr>
<tr>
<td>Huber et al11 (2004)</td>
<td>40</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>2</td>
<td>1 wk, weaning over 1 wk</td>
</tr>
<tr>
<td>Mollica et al14 (1992)</td>
<td>168</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>1</td>
<td>2 wk</td>
</tr>
<tr>
<td>Trapani et al12 (2005)</td>
<td>150</td>
<td>Retrospective</td>
<td>1–2</td>
<td>Mean of 13.7 d (range: 7–32)</td>
</tr>
<tr>
<td>Gonzalez-Gay and Llorca13 (2005)</td>
<td>78</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Reinehr et al16 (2000)</td>
<td>101</td>
<td>Retrospective</td>
<td>2*</td>
<td>1 wk</td>
</tr>
<tr>
<td>Reinehr et al17 (2000)</td>
<td>171</td>
<td>Retrospective</td>
<td>2*</td>
<td>1 wk</td>
</tr>
<tr>
<td>Chao et al18 (2000)</td>
<td>20</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>Range: 3–7 d</td>
</tr>
<tr>
<td>Saulsbury15 (1999)</td>
<td>100</td>
<td>Retrospective</td>
<td>1.6</td>
<td>Mean: 8.9 d (range: 5–28 d)</td>
</tr>
<tr>
<td>Tempel et al16 (1993)</td>
<td>86</td>
<td>Retrospective</td>
<td>2</td>
<td>1 wk, weaning over 1 wk</td>
</tr>
<tr>
<td>Saulsbury17 (1993)</td>
<td>69</td>
<td>Retrospective</td>
<td>1.7</td>
<td>Mean: 8 d (range: 5–10 d)</td>
</tr>
<tr>
<td>Dawod and Aki18 (1990)</td>
<td>40</td>
<td>Retrospective</td>
<td>1–2</td>
<td>Mean: 7 d (range: 3–30 d)</td>
</tr>
<tr>
<td>Buchanec et al19 (1988)</td>
<td>39</td>
<td>Retrospective</td>
<td>1–2.5</td>
<td>10 d, weaning over 1–2 wk</td>
</tr>
<tr>
<td>Buchanec et al20 (1987)</td>
<td>33</td>
<td>Retrospective</td>
<td>1–2.5</td>
<td>10 d, weaning over 1–2 wk</td>
</tr>
<tr>
<td>Rosenblum and Winter21 (1987)</td>
<td>43</td>
<td>Retrospective</td>
<td>1–2</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

$^a$ Dose was increased to 3 to 5 mg/kg per day if abdominal pain was present for >24 hours.

$^b$ Mean dose: 1.6 mg/kg per day (range: 1.2–2.0 mg/kg per day).

$^c$ Mean dose: 1.7 mg/kg per day (range: 1.3–2.1 mg/kg per day).

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A

B

FIGURE 1

Corticosteroid (CS) treatment of HSP and resolution of abdominal pain. A, Prospective: time to resolution of abdominal pain (days) reported in means and medians. B, Retrospective: ORs (95% CIs) of abdominal pain resolution within 24 hours of corticosteroid administration. The box size is proportional to the inverse of the magnitude of the variance.
after diagnosis. Heterogeneity was present among both the prospective and retrospective studies (P = .03 and P < .01, respectively), so pooled ORs are not reported. Instead, the individual ORs and 95% CIs of each study, prospective and retrospective, are shown (Fig 4). No evidence of publication bias was found (Egger test: P = .99).

**Do Corticosteroids Decrease the Likelihood of Developing Persistent Renal Abnormalities?**

In the 3 prospective studies, early corticosteroid treatment significantly reduced the odds of developing persistent renal disease (OR: 0.43; 95% CI: 0.19–0.96) (Fig 5A). There was no evidence of marked heterogeneity among the studies (P = .341). In addition, no evidence of publication bias was found (Egger test: P = .99). The retrospective study by Saulsbury did not show a statistically significant difference in renal outcome between the exposed and unexposed patients (OR: 1.25; 95% CI: 0.29–5.37) (Fig 5B).

**Sensitivity Analyses**

**Does the Dose of Corticosteroid Matter?**

We investigated if the corticosteroid dose affects the likelihood of developing persistent renal disease by using unrestricted and restricted regression models and the
likelihood-ratio test. The doses and duration of treatment for each study are listed in Table 2. Two studies were excluded from this analysis because corticosteroid dose was not reported.20,23 The result of the likelihood-ratio test was statistically insignificant (P = .07), which suggests but fails to identify a significant dose-response effect.

What Future Study Would Reverse the Findings of This Meta-analysis?

Sensitivity analyses were performed to determine what sample size and magnitude of effect of a future hypothetical study would be required to reverse the findings, from the prospective studies, regarding the benefit of corticosteroid to decrease persistent renal disease presented in this meta-analysis. We conducted sensitivity analyses with hypothetical sample sizes of 200 and 400 patients and assuming an incidence of 5% and 20% persistent renal involvement in the control group (Fig 6). If the baseline risk of renal involvement in controls is 5%, a new study with 200 patients would need an effect size greater than an OR of 3.0 for the pooled OR to reach...
1.0. A study with 400 patients would need an effect size greater than an OR of 2.25 for the new pooled OR to reach 1.0; for the new pooled OR to be statistically significant, the effect size would need to be larger than 3 (Fig 6A). If the baseline risk of renal involvement in controls is 20%, the OR of a new study with 200 patients would need to be >1.75 to raise the pooled OR to 1.0 and >3.0 to achieve significance. A new study with 400 patients would need an OR of >1.4 to raise the pooled OR to 1.0 and >2.25 to achieve statistical significance (Fig 6B).

DISCUSSION
This systematic review and data summary of 15 eligible articles suggests that early treatment of corticosteroids for children with HSP is associated with statistically significant increased odds of abdominal pain resolution within 24 hours and reduced odds of persistent renal disease. In addition, although the analyses lacked sufficient statistical precision, the likelihood of surgical intervention and of HSP recurrence may also be reduced. Overall, across all analyses, the pattern of effect is in the direction favoring the use of corticosteroids; none of the analyses indicated harm.

This review emphasizes the necessity for a more complete understanding of the ways in which corticosteroids impact the course of HSP, in both the acute and chronic settings. Corticosteroids were first postulated to benefit children with HSP in the 1950s and are effective in the treatment of other vasculitides in children and adults. Corticosteroids are the cornerstone of treatment for the majority of juvenile vasculitides including systemic lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa, and Takayasu arteritis. By contrast, corticosteroid treatment is controversial for use for Kawasaki disease, another acute childhood vasculitis with potential morbidity and mortality: 1 recent report found no effect of corticosteroid, whereas others have heralded the beneficial effects of corticosteroids. Given this information should corticosteroid be given to children who present to the hospital with new-onset HSP? A rigorous answer to this question would have substantial clinical implications. Despite the widespread use of corticosteroids for vasculitides, there is no consensus yet among physicians as to whether corticosteroids should be given for HSP and, if so, for what indications.

There are several important potential limitations of the evidence we present. First, the definition of renal involvement differed among the studies, which means that different dimensions or degrees of HSP severity were potentially captured. For example, among the 3 prospective studies, the definition of proteinuria ranged from 200 to 400 mg/L, and the definition of hematuria ranged from 5 to 10 red blood cells per high-powered field. Second, the dosing regimens and mode of delivery for corticosteroids were not the same in each study (Table 2). When corticosteroid therapy was stratified by high- versus low-dose steroids for each of the clinical
outcomes, there were no statistical differences between the 2 groups (data not shown). Although various doses of corticosteroids or the method of delivery (oral versus intravenous) may affect the size of the risk reduction, these changes in dose or route are unlikely to reverse the direction of effects. Third, the studies did not uniformly classify HSP cases as incident or recurrent. Therefore, the potential exists to inappropriately group severe recurrence with milder recurrence such as rash alone. Likewise, given uncertainty about loss to follow-up, particularly in the corticosteroid-treated group, the protective effect of corticosteroids is likely to be an underestimate.

Two other limitations should be kept in mind when interpreting these data. First, our ability to draw robust conclusions was hampered by the limited number of prospective studies and small numbers of patients within the studies, which often resulted in imprecise measures of treatment effects. Although the effect of corticosteroid on several of the outcomes did achieve statistically significant evidence of benefit, the failure to demonstrate benefit regarding other outcomes and the failure to show a significant dose-response effect may reflect either the still relatively underpowered nature of the combined existing studies or a true absence of impact. Second, the effects noted in the retrospective observational studies probably include some degree of confounding by indication, whereby patients with greater disease severity were more likely to receive corticosteroids. Given that most of the retrospective studies nevertheless continued to show a benefit, the results across all studies are more reassuring.

These caveats notwithstanding, our findings suggest that the potential benefit of corticosteroid administration early in the course of HSP may be more prominent than previously suggested for both acute (pain, surgical intervention) and chronic (recurrence, renal disease) complications of disease. If corticosteroid therapy is truly as effective as this meta-analysis suggests, then broader use of corticosteroids or the method of delivery (oral versus intravenous) may affect the size of the risk reduction, of HSP and improving patient outcomes for both children and adults.

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REFERENCES

**DEBATE ON ENDING SAT GAINS GROUND**

“The social scientist Charles Murray has a knack for noisily tapping into cultural preoccupations. In his 1984 book, ‘Losing Ground,’ he argued that welfare perpetuated dependency and should be eliminated. In *The Bell Curve* (1994), which he wrote with Richard J. Herrnstein, he argued that those who get ahead in America (mostly whites) are genetically endowed with more intelligence than those who do not (disproportionately African-Americans). Now Mr. Murray is at it again, proposing in a recent article to abolish the SAT. This position cannot help but provoke a double-take. After all, while making his arguments about genes, race and intelligence, Mr. Murray promoted the IQ test as a reliable measure of aptitude. Yet he is suggesting that one of the most widely used assessment tests be eliminated. Unlike other critics of the SAT, Mr. Murray’s other theories are misguided or offensive could find themselves agreeing with him on this issue. Unlike other critics of the SAT, Mr. Murray does not see the test as flawed, nor does he think that the wealthy have an unfair advantage because they can buy expensive coaching. But he recognizes that most people do not agree with him and believe the test is rigged to favor the rich. ‘It is a corrosive symbol of privilege,’ he said. And so, he concludes that college admissions offices should reject the SAT and substitute other standardized tests: subject or so-called achievement tests that gauge knowledge in specific disciplines like history or chemistry. ‘This is really a hot topic,’ said William R. Fitzsimmons, the dean of admissions and financial aid at Harvard University.”


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