Oral Corticosteroid Use Is Effective for Cutaneous Hemangiomas

An Evidence-Based Evaluation

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**Objectives:** To determine the efficacy of systemic corticosteroid therapy in treating enlarging, problematic cutaneous hemangiomas and to assess the relationship of dose to response and adverse effects.

**Design:** A quantitative systematic literature review was performed and inclusion and exclusion criteria were applied.

**Setting:** Patients were treated in primary care, referral centers, and institutional practices. Most patients were ambulatory, although some required hospitalization.

**Patients:** Inclusion criteria were original case series with a minimum of 5 patients with enlarging, problematic cutaneous hemangiomas treated with systemic corticosteroids. Exclusion criteria were being older than 2 years, receiving simultaneous other treatments, being lost to follow-up, or having insufficient information. Twenty-four original case series met inclusion criteria; 10 case series remained (184 patients) after exclusion criteria were applied.

**Intervention:** Patients were given a mean prednisone equivalent daily dose of 2.9 mg/kg (95% confidence interval [CI], 2.7-3.1 mg/kg) for a mean of 1.8 months (95% CI, 1.5-2.2 months).

**Main Outcome Measures:** Response and rebound rates and dose-response and adverse effects–response relationships in responders vs nonresponders.

**Results:** Response was 84% (95% CI, 78%-89%; range, 60%-100%) and rebound was 36% (95% CI, 29%-44%; range, 0%-65%). A significant difference was found between the mean dose administered to responders vs nonresponders ($P < .001$). No significant difference was observed as to the occurrence of adverse effects ($P = .3$).

**Conclusion:** Systemic corticosteroid treatment seems to be effective for problematic cutaneous hemangiomas of infancy.

Arch Dermatol. 2001;137:1208-1213
MATERIALS AND METHODS

Two electronic databases, PubMed and MEDLINE, were used to search the medical literature for publications on the combined topics of “hemangiomas and corticosteroids.” A careful review all of the titles and abstracts was done to locate all case series meeting the inclusion criteria: (1) at least 5 patients with cutaneous hemangioma(s) treated with systemic corticosteroids and (2) original studies. Articles were obtained and read in detail. A review of the bibliographies of these articles (hand search) was also done to determine other case series that might have been inadvertently missed using the electronic search strategy. This hand search produced 4 articles not found by the electronic search. Case series in foreign languages whose abstracts revealed compliance with inclusion criteria were obtained, translated into English, and read in detail. Unpublished data and “gray literature” were not useful for the purposes of this analysis.

The following exclusion criteria were then rigidly applied to the patients in each case series to eliminate inappropriate patients and produce a homogeneous population amenable to systematic review:

- Age older than 2 years at initiation of treatment
- Lymphangiomas, cystic hygomas, and arteriovenous malformations
- Kasabach-Merritt syndrome
- Liver, subglottic, laryngeal, parotid, or gastrointestinal tract hemangiomas
- Stable or involuting hemangiomas
- Simultaneous treatment with other modalities (eg, laser, radiation, or surgery)

Quantitative systematic review (meta-analysis) is a relatively new tool to help physicians make evidence-based decisions. This technique involves the systematic examination of available evidence on a given clinical topic and the summary of that evidence using statistical techniques that pool data from multiple studies to yield a single result.

The purpose of this study was to use quantitative systematic review techniques to determine the efficacy of systemic corticosteroid therapy for enlarging, problematic, infantile cutaneous hemangiomas and to assess the relationship of dose to response and the adverse effect profile.

RESULTS

Review of the literature per the methods described in the previous section revealed 200 related references in 7 languages. Careful review of all titles and abstracts of these references revealed 24 original case series with a minimum of 5 patients having infantile hemangiomas treated with systemic corticosteroids that met inclusion criteria. After eliminating patients meeting the exclusion criteria (see the “Materials and Methods” section), a total of 10 case series representing 184 appropriate patients remained for systematic analysis (Table 1).

The largest case series was reported in the Chinese literature and included 411 patients with hemangiomas treated with systemic corticosteroids for 0.5 to 3 years. These patients had to be excluded because the major outcome measure for successful treatment in this study was not whether corticosteroid therapy induced stabilization or involution but rather whether the hemangiomia ultimately resolved. Also, the patients were treated significantly longer than those in other studies. The long duration of therapy makes it difficult to determine any effect the corticosteroid therapy had on the hemangiomas vs spontaneous involution.

Two other case series, with 10 otherwise appropriate patients, were excluded because of inability to determine the dose of corticosteroids used.

The mean age of patients at initiation of systemic corticosteroid administration was 4.5 months (95% confidence interval [CI], 3.8-5.2 months; range, 0.25-24.0 months). Statistical analysis revealed a mean prednisone equivalent daily dose of 2.9 mg/kg (95% CI, 2.7-3.1 mg/kg; range, 1.0-4.5 mg/kg) given over a mean of 1.8 months (95% CI, 1.5-2.2 months; range, 0.5-5.4 months) before tapering, if applicable, was begun. The mean response rate (stabilization or involution coincident with initiation of corticosteroid use) was 84% (95% CI, 78%-89%; range, 60%-100%). The mean rate of rebound was 36% (95% CI, 29%-44%; range, 0%-65%).

In univariate analysis, a t test showed a significant difference between the mean prednisone equivalent daily dose administered to responders (3.0 mg/kg; 95% CI, 2.8-
3.3 mg/kg) vs nonresponders (2.1 mg/kg; 95% CI, 1.7-2.6 mg/kg; \( P = .001 \)). There was no significant difference in duration of treatment (1.7 months [95% CI, 1.4-2.1 months] vs 2.3 months [95% CI, 1.4-3.3 months]; \( P = .3 \)) or the occurrence of adverse effects (34% [95% CI, 25%-43%] vs 47% [95% CI, 21%-74%]; \( P = .3 \)) in responders vs nonresponders, respectively. A t test confirmed a dose-response relationship (\( P = .001 \)). This relationship is also depicted in tabular format (Table 2).

### Table 1. Quantitative Systematic Review*

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Patients, No. †</th>
<th>Oral Corticosteroid Regimen</th>
<th>Prednisone Equivalent Dose, mg/kg per Day‡</th>
<th>Mean Initial Dose Duration, mo</th>
<th>Mean Time to Response, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarem and Edgerton,7 1967</td>
<td>7</td>
<td>Prednisolone, 20 mg/d</td>
<td>2.4</td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>Fost and Esterly,8 1968</td>
<td>5</td>
<td>Prednisone, 20 mg/d</td>
<td>2.7</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Brown et al,9 1972</td>
<td>7</td>
<td>Prednisone, 30-40 mg once daily</td>
<td>2.3</td>
<td>1.75</td>
<td>Unknown</td>
</tr>
<tr>
<td>Femenia and Sarinana,10 1976 (in Spanish)</td>
<td>6</td>
<td>Prednisone, 2 mg/kg once daily</td>
<td>1.0</td>
<td>2.1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bartoshesky et al,11 1978</td>
<td>21</td>
<td>Prednisone or equivalent, 3 mg/kg per day</td>
<td>3.0</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sasaki et al,12 1984</td>
<td>14</td>
<td>Methylprednisolone, 3 mg/kg per day for 3 d, then 1.5 mg/kg once daily; repeat every 6 wk if effective</td>
<td>1.0</td>
<td>2.5</td>
<td>Usually &lt;1</td>
</tr>
<tr>
<td>Enjolras et al,13 1990</td>
<td>11 (all severe)</td>
<td>Prednisone, 1-2 mg/kg per day</td>
<td>1.6</td>
<td>5.4</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pongprasit,14 1992</td>
<td>16</td>
<td>Prednisone, 3-4 mg/kg per day</td>
<td>3.4</td>
<td>4.8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sadan and Wolach,15 1996</td>
<td>53</td>
<td>Prednisone, 3 or 5 mg/kg per day in 4 doses (=40 mg/d); 40 got 1 cycle, 8 got 2 cycles, and 5 got 3 cycles</td>
<td>4.5</td>
<td>0.5</td>
<td>1-2 in 68% of patients</td>
</tr>
<tr>
<td>Akyüz et al,16 2001</td>
<td>44</td>
<td>Prednisolone, 2 mg/kg per day</td>
<td>2.0</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Weighted average (95% confidence interval) 184 NA 2.9 (2.7-3.1) 1.8 (1.5-2.2) NA

*NA indicates not applicable.
†Patients who met inclusion criteria and did not meet exclusion criteria.
‡Based on prednisone and prednisolone having equal potency and methylprednisolone being 1.25 times more potent.5
§Stabilization of previously growing hemangioma or decrease in size of hemangioma coincident with corticosteroid therapy.
‖Enlargement during tapering after response occurred. All reported rebounders responded again to corticosteroid therapy.

There was no significant difference in duration of treatment (1.7 months [95% CI, 1.4-2.1 months] vs 2.3 months [95% CI, 1.4-3.3 months]; \( P = .3 \)) or the occurrence of adverse effects (34% [95% CI, 25%-43%] vs 47% [95% CI, 21%-74%]; \( P = .3 \)) in responders vs nonresponders, respectively. A t test confirmed a dose-response relationship (\( P < .001 \)). This relationship is also depicted in tabular format (Table 2).

Adverse effects were reported in 35% (95% CI, 27%-44%) of patients. This figure excludes the study by Pongprasit14 wherein some patients experienced cushingoid features, infections, or both but exact numbers were not given. No catastrophic adverse effects were seen in any reported patients, although Enjolras et al13 indicated serious temporary growth retardation in 4 patients. The most commonly reported adverse effects were behavior changes and irritability, cushingoid appearance, and transient growth delay. Other adverse effects reported included altered appetite and gastrointestinal tract upset, and 1 patient reportedly had osteoporosis, but no information was given as to degree of severity.

Multivariate analysis showed that the prednisone equivalent dose was the only significant factor associated with clinical response (\( P = .04 \)). Patient age and duration of treatment were not associated with response (\( P > .5 \)).

### COMMENT

Corticosteroids are the treatment of choice for hemangiomas of infancy that interfere with normal function, threaten permanent disfigurement, or are otherwise problematic.20 No consensus exists, however, as to the optimal treatment regimen or expected response rate. The initial dosing of prednisone at 1 to 3 mg/kg per day probably arose from existing treatment regimens for conditions such as nephrotic syndrome and asthma in infants and children.3 In more recent years, some clinicians have used higher doses14,15 with good efficacy, as illustrated by at least one study15 that demonstrated a greater response rate with 5 mg/kg per day than with 3 mg/kg per day. However, because no controlled trials exist, the optimal treatment regimen is unknown. We performed a
quantitative systematic review to provide an evidence-based answer to this question.

A key step in performing a meta-analysis is study selection using inclusion and exclusion criteria. There is a trade-off between generalizability and precision.21 We included originally reported patients with cutaneous hemangiomas treated with systemic corticosteroids. Exclusion criteria were chosen to provide generalizable data about cutaneous hemangiomas likely to respond to corticosteroid treatment. Patients with Kasabach-Merritt syndrome were excluded because the syndrome does not occur in true hemangiomas.22 Hepatic and parotid hemangiomas were excluded because of their poorer known response.13,23-27 Laryngeal and subglottic lesions were excluded because they are managed differently than cutaneous lesions, since minor growth might require tracheostomy, laser surgery, or intubation.28 The upper age limit of 2 years and the exclusion of stable or involuting hemangiomas were intended to eliminate lesions that were no longer proliferating.29 Patients simultaneously treated with other modalities, insufficiently documented, or lost to follow-up were also eliminated. Because of feasibility issues, we excluded individual case reports and used case series with at least 5 appropriate patients; only a single series (2 appropriate patients) was eliminated using this criterion.30 The large Chinese case series17 was eliminated because its end point was resolution, not stabilization or involution, of hemangiomas and patients were treated for much longer periods.

The results of this meta-analysis suggest that most infants with growing cutaneous hemangiomas will respond to systemic corticosteroid administration. A mean

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Rebound, %</th>
<th>Adverse Effects Reported (No.)</th>
<th>Description of Nonresponders</th>
<th>Description of Excluded Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>None</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>100</td>
<td>60</td>
<td>Mild growth decrease (1)</td>
<td>NA</td>
<td>16-month-old with stable, fibrotic hemangioma</td>
</tr>
<tr>
<td>100</td>
<td>43</td>
<td>None</td>
<td>NA</td>
<td>1 Liver hemangioma and 1 also given radiation</td>
</tr>
<tr>
<td>83</td>
<td>17</td>
<td>None</td>
<td>2-year-old with “cavernous” hemangioma</td>
<td>8 Cases &gt;2 y and 1 lost to follow-up</td>
</tr>
<tr>
<td>90</td>
<td>65</td>
<td>Temporary growth decrease (1), irritability, changed appetite, gastrointestinal tract upset</td>
<td>All deep lesions, all but 1 present at birth (may not all be hemangiomas)</td>
<td>1 Lymphangioma, 1 patient aged 4.5 y, 1 with macrocephaly and limb hypertrophy</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>None</td>
<td>NA</td>
<td>7 Patients aged 6-46 y, 10 stable lesions, and 1 midinvolution lesion</td>
</tr>
<tr>
<td>64</td>
<td>Unknown</td>
<td>Severe growth decrease (4)</td>
<td>Unknown</td>
<td>3 Hepatic, 12 laryngeal, and 1 gastrointestinal hemangiomatosis</td>
</tr>
<tr>
<td>100</td>
<td>Unknown</td>
<td>Cushingoid, infection</td>
<td>1 Giant “cavernous” hemangioma</td>
<td>2 Kasabach-Merritt, 1 Klippel-Trenaunay, 1 stable 5-year-old, 1 parotid, 1 laryngeal, 1 subglottic</td>
</tr>
<tr>
<td>93</td>
<td>20</td>
<td>Cushingoid (28), transient decreased growth (2), osteoporosis (1), behavior change (53)</td>
<td>4 Patients, all &lt;6 mo old at initiation, responded and then ceased involuting</td>
<td>1 Kasabach-Merritt, 6 subglottic</td>
</tr>
<tr>
<td>70</td>
<td>25</td>
<td>Moon face (19), increased appetite (nearly all), irritability (15)</td>
<td>Usually larger lesions, older patients</td>
<td>1 Kasabach-Merritt</td>
</tr>
<tr>
<td>84 (78-89)</td>
<td>36 (29-44)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2. Dose-Response Relationship*

<table>
<thead>
<tr>
<th>Prednisone Equivalent Daily Dose, mg/kg</th>
<th>Patients, No.</th>
<th>Mean Response, % (95% CI)</th>
<th>Rebound Reported, % (95% CI)</th>
<th>Adverse Effects Reported, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>26</td>
<td>69 (50-88)</td>
<td>70 (50-88)</td>
<td>4 (0-12)</td>
</tr>
<tr>
<td>&gt;2-3</td>
<td>63</td>
<td>75 (64-86)</td>
<td>25 (14-37)</td>
<td>16 (0-34)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>94</td>
<td>94 (89-99)</td>
<td>34 (23-45)</td>
<td>51 (39-62)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
Adrenal axis suppression and hypertension.31 Without specific monitoring, these would usually go unnoticed.

This review demonstrates the need for prospective studies (preferably randomized and controlled) to determine optimal dosing, response, toxic effects, and alternative means of giving corticosteroids (eg, alternate-day therapy, short bursts with rapid taper, and use of dexamethasone). This analysis and our own experience indicate that administration of oral prednisone or prednisolone (2-3 mg/kg per day) is effective in stabilizing or shrinking most growing cutaneous hemangiomas. Treatment should be maintained until cessation of growth or shrinkage of the hemangioma is accomplished. Then the dose can be reduced, but the pace of tapering depends on several factors (ie, the age of the infant, the indication for treatment, any toxic effects, and any rebound growth). The initial corticosteroid dose was maintained a mean duration of 1.8 months in this analysis. Because nearly 40% of patients reported rebound with tapering, brief courses of 2 to 3 weeks' duration are probably inadequate.

Several limitations of this review are evident. Strict exclusion criteria reduced the number of included patients. This decreased the power of the study but improved the generalizability of results. Extracutaneous hemangiomas were excluded; therefore, our results would not be a good predictor of their response rate. Because controlled studies are not available on this topic, studies included were retrospective case series; data were not always complete; treatment regimens varied within series; and studies were not randomized, masked, or controlled. Also, there was no way to eliminate the possibility of spontaneous stabilization or involution (although lesions were not stable at initiation of therapy).

A review of this type is never able to overcome the limitations of the primary studies. Biases such as selection bias are impossible to eliminate. This occurs when patients are not consecutively selected or entry criteria or criteria to assess treatment effect are not clear, rigorously applied, or uniform among studies. Other such problems include failure to address reliability of outcome criteria or to provide full information on dropouts. Publication bias is also impossible to eliminate (includes a tendency to report studies with positive results).

Some assumptions were used to calculate prednisone equivalent daily dose. Weight, for example, was a calculated value based on patient age (50th percentile weight was determined by normogram) when not provided, and the alternate-day dose divided by 2 was used to determine the equivalent daily dose. These assumptions could have resulted in slightly erroneous results. Finally, we recognize the limitations of quantitative systematic reviews: such analyses are not devoid of subjectivity and cannot eliminate all sources of variability among studies or the need for sound reasoning and individualizing care on a case-by-case basis.

In conclusion, corticosteroid treatment is effective for problematic hemangiomas of infancy. The benefit-risk ratio is acceptable, and at least 3 of every 4 appropriately selected and treated patients respond. This meta-
analysis provides evidence-based justification for the use of corticosteroids for hemangiomas of infancy.

Accepted for publication May 22, 2001.

We acknowledge and thank Jean Hu, MD, Jose Catacora, MD, and Dong Fang, MD, for their excellent assistance in translating foreign-language articles.

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REFERENCES