Adverse Effects of Systemic Glucocorticosteroid Therapy in Infants With Hemangiomas

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Objective: To evaluate the short- and long-term adverse effects of systemic glucocorticosteroid (GS) therapy in infants with hemangiomas.

Design: Retrospective chart review of infants treated with GSs for hemangiomas during a 3-year period.

Setting: Tertiary care children’s hospital

Patients: Of 141 patients identified with hemangiomas, 22 were treated with GSs.

Interventions: Minimum of 1-month GS therapy at a minimum starting dose of 0.5 mg/kg per day.

Outcome Measures: Demographic and anthropometric measurements, starting dose and duration of GS therapy, subjective parental concerns, complications related to hemangioma, adjunctive treatment, and morning cortisol levels and/or results of corticotropin stimulation tests.

Results: The average starting dose was 2.23 mg/kg per day; average length of therapy was 28.1 weeks. Complaints of irritability, fussiness, or insomnia were identified in 16 patients (73%). Hypertension, defined as 3 or more episodes of systolic blood pressure higher than 105 mm Hg, was observed in 10 patients (45%). Morning cortisol levels were abnormal in 13 (87%) of the 15 patients evaluated. Low-dose corticotropin stimulation test results were abnormal in 2 of the 3 infants tested.

Conclusions: While GS therapy for infantile hemangiomas was tolerated well overall, changes in behavior, insomnia, and gastrointestinal symptoms were common parental concerns. Hypertension and hypothalamic-pituitary-adrenal axis suppression were observed frequently. Infants undergoing long-term GS treatment of hemangiomas should be monitored carefully for these potential adverse effects.

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Over the past 30 years, glucocorticosteroids (GSs) have been used for the treatment of hemangiomas in infants and children. Standard daily doses are 2 to 3 mg/kg of body weight. Recently, some investigators have advocated the use of up to 3 to 5 mg/kg with excellent results and mild reversible adverse effects. While current literature documents the adverse effects of GSs in the treatment of a wide spectrum of diseases, there are minimal data pertaining to GS therapy of infantile hemangiomas. Well-documented adverse effects of GSs include immunosuppression, osteoporosis, hypertension, cushingoid features, hypothalamic-pituitary-adrenal axis suppression, impaired glucose tolerance, and ocular complications. The use of GSs in children carries the additional risk of growth suppression, particularly during the growth spurts of infancy and adolescence.

Previous reports have indicated that systemic GS therapy is relatively safe for treatment of problematic hemangiomas with minimal short-term adverse effects and no serious long-term adverse effects. However, there is minimal literature that addresses the issue of adrenal suppression or hypertension in this group of patients. Our specific objective was to evaluate the short- and long-term adverse effects of GS therapy treating infantile hemangiomas with a goal of establishing guidelines for appropriate monitoring in this group of patients.

METHODS

EXPERIMENTAL DESIGN

Institutional review board approval was obtained prior to initiation of the study. Patients presenting to the pediatric dermatology clinic at an urban pediatric dermatology tertiary referral center between March 1998 and March 2001 with a diagnosis of hemangioma were identified in an electronic database. All infants who received systemic GS therapy were
identified and included in the study. Inclusion criteria included a minimum length of therapy of 1 month and a minimum starting dose of 0.5 mg/kg per day or 1 mg/kg every other day of prednisolone.

Demographic and clinical data were subsequently collected from a retrospective chart review. Data collection included the following: (1) biographic and/or demographic information including birthdate, age, sex, and location of lesion; (2) standard anthropometric measurements including length, weight, and blood pressure; (3) starting dose and duration of GS therapy; (4) visit data including subjective parental reports regarding fussiness, irritability, insomnia, and gastric complaints; (5) complications related to the hemangioma; (6) adjunct treatment including intralesional steroid injections, pulsed-dye laser therapy, or concurrent medications; (7) morning cortisol levels; and (8) results of low-dose corticotropin stimulation test if performed.

Clinical follow-up was performed in the pediatric dermatology clinic throughout systemic GS therapy. Length, weight, and blood pressure measurements were consistently performed by the same pediatric dermatology nurses. All blood pressure measurements were taken with the patient calm. Measurements were performed by pediatric nurses with a Dinamap blood pressure monitor (Critikon, London, England) and inflatable infant cuff. If multiple blood pressures were taken at an individual visit, the lowest blood pressure was recorded. A systolic blood pressure of greater than 105 mm Hg was considered elevated based on hypertension guidelines published by the American Academy of Pediatrics.\(^7\) According to these guidelines, in 12-month-old boys and girls measured at the 90th percentile for height, the 95th percentile for systolic blood pressure is 105 mm Hg.\(^9\)

All length and weight measurements available for each visit were recorded and plotted for age on the growth curve. Data were corrected for prematurity. A premature infant was defined as one born at less than 37 weeks estimated gestational age. Postconceptual age was greater than 40 weeks when GS therapy was started. Follow-up data for those patients not seen recently in the dermatology clinic were obtained from primary care physicians and clinics via telephone.

CORTICOTROPIN STIMULATION TEST

The low-dose corticotropin stimulation test is usually performed by initially drawing a baseline cortisol level followed by administration of 1 µg of corticotropin intravenously.\(^10\) Serum cortisol levels are then measured at 10 minutes, 20 minutes, and 30 minutes.\(^11\) In this study, serum cortisol levels were drawn at baseline and 15 and 30 minutes after corticotropin administration. After discussion with our pediatric endocrinologist, we determined that this would provide adequate results and simplify the procedure.

STATISTICS

Descriptive statistical analysis was performed on the data collected using SPSS for Windows version 9.0 (SPSS, Chicago, Ill) to calculate descriptive statistics, confidence intervals, and t tests. All data were tabulated and summarized. Analysis included z scores and percentiles on each length and weight measurement by using World Health Organization guidelines from Epi-Stat 2000. Calculations included average z scores and percentiles for both height and weight at the beginning and end of GS therapy.

A total of 141 patients with hemangiomas were identified. Of these, 22 patients were treated with GSs and included in the present study. A complete demographic profile of our patient population is provided in Table 1. The average starting dose of GS (prednisolone formulation) was 2.23 mg/kg per day (range, 0.9-3.75 mg/kg per day). Average age at initiation of therapy was 13.2 weeks (range, 4.6-24.9 weeks). The average length of therapy was 28.1 weeks (range, 10.7-48.7 weeks). The length of therapy varied according to the patient’s therapeutic response, severity of the hemangioma, and age on initiation of treatment. Six patients (27%) were started on alternate-day GS therapy. Complications associated with treated hemangiomas are summarized in Table 2.

Complaints of irritability, fussiness, insomnia, or behavior changes were identified in 16 patients (73%). Parents of 7 (32%) of our 22 patients reported symptoms of reflux, stomach upset, or intolerance of feeds, which were felt to indicate gastric irritation. However, 18 patients (82%) began ranitidine therapy with initiation of GS therapy. Two additional patients began ranitidine treatment during GS therapy.

A total of 250 blood pressure measurements from individual patient visits were recorded from the 22 infants during GS therapy. Most patients had 1 blood pressure measurement at each visit, but occasionally more
than 1 blood pressure measurement was taken if the first reading was thought to be inaccurate or the patient was not calm. Only the lowest blood pressure was recorded per visit. An average of 11 blood pressure values per patient were recorded (range, 4-22). Systolic blood pressure measurements ranged from 61 to 142 mm Hg. Eighteen (82%) of the 22 patients had at least 1 visit where the lowest obtainable systolic blood pressure was higher than 105 mm Hg. Analysis of these measurements revealed that 10 (45%) of 22 patients had systolic blood pressures higher than 105 mm Hg on at least 3 separate occasions.

Hydrochlorothiazide treatment was started in 8 (36%) of the 22 patients for persistent hypertension. Six of the 8 patients started on hydrochlorothiazide therapy had 5 or more separate episodes of systolic blood pressure higher than 105 mm Hg. Seven of the 8 patients responded well to hydrochlorothiazide treatment alone; however, 1 patient required the addition of captopril to the regimen.

Patients in the hypertensive group were noted to have a higher mean starting GS dose (2.41 mg/kg per day) than the nonhypertensive group (1.98 mg/kg per day) \( (P = .27; 95\% \) confidence interval \([CI]\), −1.23 to 0.37). Patients with hypertension were also younger at the start of GS treatment (11.0 weeks) than those in the nonhypertensive group (13.5 weeks) \( (P = .39; 95\% \) CI, −3.27 to 8.05). However, these results did not reach statistical significance. There was a positive correlation between the highest dose of GS received and hypertension. Patients who received the highest dose of GS initially developed hypertension more quickly \( (r = .486; P = .04) \). Hypertension was noted an average of 7 weeks and a median of 3 weeks after initiation of GS therapy.

Concomitant therapy included intralesional steroid injections in 4 patients (Table 3). Intralesional steroid injections were performed by an oculoplastic surgeon in 3 patients and by a pediatric otolaryngologist in 1 patient. Pulsed-dye laser therapy was performed in 10 patients (45%) for treatment of ulcerations or diffuse superficial lesions.

Hypothalamic-pituitary-adrenal axis function was measured by obtaining morning cortisol levels in 15 patients. Morning cortisol levels were measured after the GS dose had been tapered to physiologic levels. In our group of patients, morning cortisol levels were measured an average of 29 weeks (median, 24 weeks) after initiation of GS therapy. The average morning cortisol level was 8.4 µg/dL. A value above 18 µg/dL indicates adrenal suppression, low-dose corticotropin stimulation, or other disease states. Low cortisol levels less than 1 µg/dL, the only undetectable values in the entire group. Neither the length of GS therapy nor the maximum dose of GS showed a significant correlation with morning cortisol levels.

For 3 patients who needed further evaluation of adrenal suppression, low-dose corticotropin stimulation tests were performed. Only 1 of the 3 showed normal findings 30 minutes after corticotropin administration. Normal responsiveness is determined by a cortisol level rise of 10 µg/dL above baseline or a peak level above 18 µg/dL. 

Baseline length and weights were obtained on all individuals. Six patients continued GS therapy during the compilation of the data. Therefore, lengths were obtained for 16 patients before and after GS therapy. The baseline average length for age percentile for the entire group was determined to be 38.5. The average change in length percentile was approximately –7.9. This change was not statistically significant \( (P = .37; 95\% \) CI, –26.2 to 10.3). The baseline average weight for age percentile was 62.3. The average change for weight percentile was –7.8. Again, this change was not statistically significant \( (P = .33; 95\% \) CI, –25.4 to 9.0).

Hemangiomas are the most common soft tissue tumor of infancy with a female-to-male ratio of 2:1 to 5:1. The incidence of hemangiomas in full-term infants is approximately 10% to 12% but increases to more than 20% in premature infants. Our patients exhibited a similar demographic profile in that our group consisted of 17 girls (77%) and 5 boys (23%). Seven (32%) of our infants were premature.

Most hemangiomas occur on the head or neck. Because infants with cutaneous hemangiomas involving the chin, lips, or mandibular regions, particularly in the “beard” distribution, are at greatest risk for airway involvement, these hemangiomas may warrant more aggressive treatment. Similarly, hemangiomas with ocular proximity may pose a risk of ophthalmologic complications and often require therapy. Twenty-one (95%) of the infants treated with GS in the present study had hemangiomas involving the head and neck.

While current literature documents the adverse effects of GS therapy in the treatment of a wide spectrum of diseases, there are few data pertaining to GS therapy in the treatment of infantile hemangiomas. The average GS starting dose in our patients was 2.23 mg/kg per day, which is consistent with the average recommended starting daily dose. Our average duration of therapy was 28.1 weeks, which included an average of 4 to 8 weeks at the higher starting dose followed by a very gradual steroid taper. The rate of tapering was dependent on many factors, includ-
ing rebound hemangioma growth, age of the infant, and development of GS adverse effects.

Review of the literature reveals great variation in GS therapy for hemangiomas. Bennett and colleagues conducted a meta-analysis of 10 studies of problematic hemangiomas treated with systemic GSs. Patients were given a mean prednisone dose of 2.9 mg/kg per day and were treated for a mean of 1.8 months. The authors comment that most of the studies did not mention if or how tapering was accomplished; therefore the actual treatment period may have been longer. In a study by Boon and colleagues, the mean duration of GS treatment for hemangiomas was 7.9 months. Currently, there are no standardized GS dosing regimens, and practices vary significantly between clinicians. The optimal dose and duration of GS therapy and rate of GS taper remain undetermined.

**SUBJECTIVE COMPLAINTS**

The parents of 73% of our patients (n=16) reported behavior changes of fussiness and insomniania consistent with previously reported personality changes, irritability, and crying (Table 4). Perceived gastric irritation was reported by the parents in 32% of the patients (n=7), which is higher than the 21% reported in a previous study. Additionally, because ranitidine therapy was initiated for 20 (91%) of the 22 infants at some point during GS therapy, our results may be an underestimate of the true incidence of gastrointestinal adverse effects, or there may have been reporter bias in the subjective response. The issue of prophylactic treatment with antacids and ranitidine remains controversial. Therapy with these agents is considered appropriate for symptoms of gastritis or esophagitis.

**HYPERTENSION**

Although hypertension is a known adverse effect of GS therapy, there are no large studies reporting hypertension in the treatment of infantile hemangiomas. In a report by Sadan and Wolach, 60 infants were treated with high doses of prednisone (3-5 mg/kg per day), and the issue of hypertension was not addressed. In a recent study published by Boon et al., only 1 infant of 62 was found to be hypertensive. However, blood pressure was not routinely measured in this study group. In a literature review by Bennett and colleagues, the 10 studies reviewed did not specifically monitor for hypertension. A study by Blei and Chianese evaluating corticosteroid toxic effects in infants with hemangiomas mentions blood pressure monitoring, but these data were not included in the results or discussion section of the article.

In contrast to these reports, 10 patients in our study group (45%) had systolic blood pressures higher than 105 mm Hg on 3 separate occasions. Hypertension was found to develop more quickly in patients who received a higher initial GS dose. The high incidence of hypertension cannot be attributed to mineralocorticoid effects because the same formulation of prednisolone was used as in previous studies. Hypertension was persistent in 8 patients and was managed with hydrochlorothiazide. These 8 patients did not demonstrate overt evidence of any end-organ damage of the kidney, brain, heart, or any other target organ. Interestingly, most parents reported improvement in irritability with treatment of hypertension.

The clinical relevance and long-term effects of these episodes of hypertension are unclear. To our knowledge, there are no studies reporting the long-term sequelae in infants with GS-induced, short-term hypertension. Interestingly, Pokorny and colleagues reported the case of a 3-month-old infant who received high-dose corticosteroids for treatment of a hemangioma of the nasal sidewall. The infant was found to have hypertrophic cardiomyopathy after presenting with weight loss, tachypnea, and poor feeding. In this case report, it is unclear whether the cardiomyopathy was steroid induced or if the child was genetically predisposed to this condition. Also, the authors do not report whether the affected infant was hypertensive at any time.

Of our 22 patients, none has developed clinical signs of heart failure. Additional studies are needed to further investigate the clinical significance of hypertension lasting several weeks to months in this patient population.

**HPA SUPPRESSION**

Hypothalamic-pituitary-adrenal axis suppression is one of the most important long-term adverse effects of GS therapy. Laboratory detectable HPA suppression can be seen in patients after as few as 2 to 4 weeks of supraphysiologic doses of GSs. The risk of HPA axis suppression is increased with (1) the use of GS having intermediate to long halflife, (2) the administration of divided-dose therapy, or (3) when systemic GS therapy is administered at any time of day other than early morning.

An early morning plasma cortisol level is a simple test to screen basal HPA axis function. In the present study, 13 (89%) of 15 patients exhibited cortisol levels lower than the normal pituitary reserve (18 µg/dL) for stress situations. Three of these 15 patients had received intralesional steroid injections in addition to oral GS therapy. Intralesional and intramuscular GS injections are known to have a prolonged effect on HPA axis suppression. Interestingly, 2 of the 4 patients in the present study who received intralesional steroid injections had morning cortisol values lower than 1 µg/dL. These were the only undetectable values in the entire study.
A single morning cortisol level may not be a very accurate assessment of HPA axis suppression because of episodic secretion of GS. A new low-dose corticotropin stimulation test for evaluating HPA axis suppression seems to correlate best with adrenocortical response to clinical stress. This test is believed to be 95% sensitive and at least 95% specific in the evaluation of adrenal insufficiency. Abnormal values suggest a subnormal response of the adrenal gland to physical stress and the need for stress doses of GS until recovery of the HPA axis.

Two of our 3 patients who underwent a low-dose corticotropin stimulation test had abnormal results (Figure). Of the 2 abnormal responses, one was measured 6 months after GS therapy, and the other was measured while a steroid taper dose of 0.15 mg/kg every other day (physiologic doses) was being administered in preparation for surgery. A study from Thailand using the standard-dose (250 µg) corticotropin stimulation test revealed that 64% of children taking GSs for nephrotic syndrome had normal results within 29 days of discontinuation of GS therapy, and 90% tested normal 9 months after discontinuation of GS therapy. Studies indicate a delay in the recovery of the HPA axis after discontinuation of supraphysiologic GS therapy.

Based on a review of the literature, as well as our own findings, we advise that stress doses of GSs be considered in all patients undergoing long-term GS therapy until adrenal sufficiency has been reestablished. Stress situations include high fever, traumatic accidents, or surgery, as defined by Lucky. If morning cortisol or corticotropin stimulation testing is not performed, one should recognize that the patient may be adrenally suppressed. While in general a longer duration of therapy may necessitate a longer need for stress doses of steroids, adrenal suppression varies from patient to patient. Although 2 of our patients had abnormal corticotropin stimulation test results, there were no overt signs of adrenal crisis. The clinical significance of an abnormal corticotropin stimulation test result remains unknown.

GROWTH SUPPRESSION

Glucocorticosteroids are known to slow growth of the long bones and to retard bone aging. The degree of growth suppression is influenced by the dose of the GS and duration of GS therapy. It has been shown that prednisone doses of only 3 to 5 mg/kg per day can impair growth, particularly in prepubertal children. A meta-analysis of long-term treatment of asthma with supraphysiologic doses of prednisone showed a high correlation with a statistically significant reduction in height. Sixteen patients had completed GS therapy at the time of data analysis. Growth parameters were obtained at the beginning and on completion of GS therapy as well as at regular visits during GS treatment. Multiple length and weight points were recorded and plotted on standard growth curves. At least 9 of the infants experienced decreases from their previous growth curves during GS therapy, although this did not reach statistical significance.

Our group of patients was treated for an average of 28 weeks without a statistically significant decline in growth parameters during therapy. Fortunately, in studies where there has been significant growth delay, many patients have exhibited catch-up growth. Blei and Chianese reported that in 30 infants treated with GS doses of 2 to 4 mg/kg per day for a period of 1 to 12 months, 47% of infants had a decreased rate of statural growth, and 30% had a decreased rate of weight gain. It is important to note that in this study, minimum and maximum percentiles were recorded at any point during treatment, and the value at the end of GS treatment was not recorded. It is possible that patients demonstrated catch-up growth by the end of GS therapy after GS doses were tapered and/or reduced to alternate day therapy. Blei and Chianese also reported that patients observed after termination of GS therapy demonstrated catch-up growth. Our study examined growth parameters from the initiation of GS therapy until completion of therapy. We did not observe a statistically significant difference in growth curve percentiles, although an overall decline was noted in length and weight.

OTHER GS THERAPY COMPLICATIONS

Corticosteroid-induced glaucoma is considered one of the most severe adverse effects of GS therapy because the loss of the visual field is irreversible. The 8 patients in the present study with periorbital hemangiomas or midface hemangiomas with ocular proximity were observed closely by ophthalmologists and showed no evidence of glaucoma or cataracts.

Glucocorticosteroid-induced osteoporosis may be due to inhibition of osteoblast function, stimulation of osteoclast activity, and/or reduced calcium absorption in the intestines and kidneys. Osteoporosis is difficult to measure in infants, since no bone mineral density standards exist for this age group. Unfortunately, this is a complication that is not reduced in frequency with alternate-day therapy. Although 1 of our 22 patients experienced...
a radial fracture during GS therapy, and this was the patient taking the highest starting GS dose, there was no radiographic evidence of osteoporosis. However, since demineralization of bone on conventional radiographs is not detectable until at least 30% of bone mineral density is lost, this is not a sensitive method for routine monitoring. Careful attention to any bone symptoms and evidence of calcium loss is important in these patients. Prospective studies of bone mineral density measurements and the development of standards for the infant age group are needed to further study the issue of steroid-induced osteoporosis in this patient population.

Recent pediatric literature has raised concerns regarding potential adverse neurodevelopmental effects in premature infants treated postnatally with steroids. An excellent systematic review by Barrington illustrates that postnatal steroids are associated with an increase in cerebral palsy and neurodevelopmental impairment. This study demonstrates a real and direct toxic effect of steroids on the developing nervous system.

Several other studies have also reported concerns of neurodevelopment in premature infants receiving steroids postnatally. To our knowledge, these neurodevelopmental adverse effects have not been reported in term infants treated with GSs for several months. In our patient population, parents did not observe any adverse neurodevelopmental effects, but this was not systematically evaluated. Further long-term studies are needed to clarify this issue, but these reports suggest that clinicians should exercise caution in prescribing GS therapy in the immediate postnatal period, particularly for the premature infant.

Immunosuppression is an additional concern with GS therapy, especially in infants. None of our patients developed any serious infections while being treated with GSs. However, patients receiving high-dose GS therapy should be warned that, owing to the immunosuppressive effects of such GS treatment, live or live-attenuated vaccines are contraindicated. In contrast, only killed or inactivated vaccines should be administered to infants who are undergoing GS therapy.

Glucocorticosteroid treatment remains the first-line drug therapy for problematic hemangiomas of infancy. In our study, most patients experienced improvement or stabilization of their hemangiomas in response to GS therapy. However, adverse effects were commonly observed. Parents frequently reported subjective complaints of mood changes, insomnia, and gastrointestinal symptoms. Objective changes including hypertension and HPA axis suppression were also frequently observed. Additional studies are necessary to further elucidate the clinical significance of these observed adverse effects and to investigate the risk of other adverse effects such as osteoporosis and neurodevelopmental complications.

Until those studies are done, based on our results, we recommend that blood pressure be closely monitored during GS treatment and that drug therapy be considered for steroid-induced hypertension. Evaluation of the HPA axis should be considered in infants who have received prolonged GS therapy, and parents should be counseled on the potential need for stress doses of GS when appropriate. Length and weight should be documented regularly on growth charts during and after GS therapy to screen for growth suppression, although changes in these parameters were not statistically significant in our study. To minimize GS adverse effects, we suggest that daily to alternate-day therapy be given as a single morning dose and that GSs with a longer half-life be avoided.

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REFERENCES


CONCLUSIONS