

ONLINE FIRST

Propranolol vs Corticosteroids for Infantile Hemangiomas

A Multicenter Retrospective Analysis

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Objective: To determine whether propranolol therapy is safe and effective and superior to oral corticosteroids for treating infantile hemangiomas (IHs).

Design: Multicenter retrospective chart review.

Setting: University of Miami and Miami Children's Hospital, Miami, Florida.

Patients: The study included 110 patients with IHs.

Main Outcome Measures: The percentage of clearance was quantified by documented serial global photography and clinical examinations (length, height, and width) to segregate patients into 2 groups: patients who had clearance of 75% or more and patients who had less than 75% clearance.

Results: The mean duration of treatment was 7.9 months for propranolol and 5.2 months for oral corticosteroids. Fifty-six of 68 patients (82%) who were receiving propranolol achieved clearance of 75% or more compared with 12 of 42 patients (29%) who were receiving oral corticosteroids ($P < .01$). Adverse effects were minimal in

the propranolol group: 1 patient had hypoglycemia and 2 patients had a nonspecific skin eruption that was not associated with propranolol therapy. All 42 patients in the corticosteroid group had 1 or more adverse effects ($P < .01$). Relapse after discontinuation of propranolol therapy occurred in 2 of the 68 patients; however, both patients responded to propranolol therapy on reinitiation of treatment. Surgical referrals after treatment were required in 8 patients (12%) in the propranolol group and 12 patients (29%) in the oral corticosteroid group ($P < .01$).

Conclusions: Propranolol therapy was more clinically effective and more cost-effective than oral corticosteroids in treating IHs. It also resulted in fewer surgical interventions and demonstrated better tolerance, with minimal adverse effects, compared with oral corticosteroids. Therefore, propranolol should be considered a first-line agent given its safety and efficacy in the treatment of IHs.

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INFANTILE HEMANGIOMAS (IHs) ARE common vascular tumors with a characteristic natural history of rapid growth during the first 3 to 12 months of age, followed by slow and spontaneous involution from 3 to 7 years of age.¹ However, spontaneous regression is no guarantee of a satisfactory cosmetic result. Also, ulceration, scarring, recurrent bleeding, and obstruction of vital structures with important functions such as vision, respiration, hearing, feeding, and defecation may complicate untreated IHs.¹ Larger and/or multiple cutaneous IHs may be associated with high-output cardiac failure, substantial structural abnormalities, cosmetic disfigurement, and psychosocial morbidity in both the child and the family. Therefore, IHs often require systemic, surgical, and/or laser treatment to avoid these adverse effects.

Until recently, the mainstay of treatment for IHs has been corticosteroids in various forms, including topical, intralesional, and oral formulations, with the most common being oral prednisolone.² Only in complicated or refractory IH cases have other treatment modalities, such as interferon alpha-2a, imiquimod, vincristine, cyclophosphamide, pulsed-dye laser, and, most recently, propranolol, been considered. Since 2008, several reports have demonstrated the effectiveness of propranolol (a nonselective β -blocker that is used to treat hypertension, supraventricular tachycardia, congestive heart failure, and thyrotoxicosis) for the treatment of IH.³⁻⁶ Propranolol's presumed mechanisms of action on IHs are attributable to vasoconstriction by decreasing the release of nitric oxide, inhibition of proangiogenic signals such as vascular endo-

thelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase 2/9, and induction of apoptosis in proliferating endothelial cells.⁷

Thus far, to our knowledge, no large retrospective study has been published to address several unanswered questions regarding propranolol's efficacy for treating IHs in a larger pediatric population without underlying cardiac abnormalities. Also, data are lacking on the specific therapeutic parameters of propranolol therapy for IHs, including the duration of treatment required to achieve clearance, the adverse effect profile, and the IH relapse rate after discontinuation of treatment. To date, the efficacy and adverse effect profile of propranolol therapy has yet to be compared with that of systemic corticosteroid therapy.

METHODS

STUDY DESIGN

Two major centers (the University of Miami and the Miami Children's Hospital, Miami, Florida) participated in the study. After receiving institutional review board approval, we conducted a retrospective chart review of 139 patients with IHs between February 2005 and October of 2010. The review comprised 2 parts.

PART 1

Data were collected from 139 IH patient charts, which included race, sex, mother's pregnancy history, age at initiation of therapy, location, presence of PHACES syndrome and other comorbidities, presence or absence of ulceration during treatment, dosage of propranolol or corticosteroid therapy, age at discontinuation of therapy, age at last follow-up visit, status of IH at last follow-up visit, presence or absence of rebound growth after discontinuation of therapy, imaging data, adverse effect profile, and approximate cost of therapy per patient.

PART 2

Twenty-nine of 139 charts were excluded: 22 patients had other treatments (eg, topical or intralesional corticosteroids, topical imiquimod, pulsed-dye laser), and 7 patients were unavailable for follow-up. A total of 110 patients remained for treatment analysis. As a measure of clinical outcome, the percentage of clearance was quantified by serial global photography and documented by clinical examinations (using length, height, and width to calculate volume). The patients were placed into 2 groups: those who had clearance of 75% or more (defined by a correlating percentage of decrease in volume, a cosmetically acceptable result by physician and/or parent, and a lack of need for further treatment) and those who did not (ie, <75% clearance).

For the propranolol group, the treatment protocol used in the 2 centers participating in the study included an outpatient pretherapeutic pediatric cardiology consultation as well as blood glucose and blood pressure monitoring during the first 48 hours of treatment. Hospital admission was necessary in 2 of the premature patients in the neonatal period for close monitoring. In patients with facial segmental IHs who were at risk for PHACES syndrome, magnetic resonance images of the brain were obtained to assess the vasculature before the initiation of propranolol therapy and to avoid any potential consequence of medication-induced hypotension, which could potentially precipitate a vaso-occlusive event given the risk of malformed vasculature.

The propranolol treatment regimen started at 0.5 mg/kg/d divided into 2 doses for 3 days, increased to 1.0 mg/kg/d divided

into 2 doses for 3 days, and finally reached the target dose of 2.0 mg/kg/d divided into 2 doses. Vitals were checked after the first dose was administered and after each additional increased dose thereafter. At the end of the treatment period, the propranolol therapy was tapered over a 2-week period to minimize the risk of a hyperadrenergic withdrawal response.⁸ For the oral corticosteroid group, the dosage of therapy ranged from 2 to 4 mg/kg/d. However, most patients were treated at the dose of 4 mg/kg/d.

STATISTICAL ANALYSIS

The data were analyzed using SPSS version 18.0 software (SPSS Inc, Chicago, Illinois). Mann-Whitney tests were used to compare the nonparametrically distributed outcomes of clearance between the propranolol and the oral corticosteroid groups, adverse effects, ulcerations during treatment, clearance between patients with periocular involvement in the propranolol and corticosteroid groups, and clearance between patients who were previously treated with corticosteroids followed by propranolol and those who received only propranolol. $P < .05$ was considered statistically significant.

RESULTS

PART 1

A total of 139 charts were reviewed. We captured patient demographics and the characteristics of their IHs (**Table**). Our patients were predominantly female (male:female ratio, 107:32). Seventy-five patients (54%) were white, 62 (45%) were Hispanic, and 2 (1%) were African American. These demographics are similar to the national IH data.⁹ However, there is a greater representation of Hispanics living in Miami, Florida, where our research was conducted. Hispanic ethnicity was not categorized by race in our retrospective study, so we may have missed a subcategory of white Hispanics.

While most of the IHs (78%) were located on the head and neck (59% on the face and 19% on the scalp), the rest were distributed on the trunk (7%), extremities (10%), and genitalia (5%). Twenty-four patients (17%) had a history of prematurity (defined as <37 weeks' gestational age), and 11 (8%) were products of multiple gestations. Fourteen of the patients' mothers (10%) had pregnancy complications: 2 placental abnormalities (1 placenta previa, 1 placental insufficiency) and 2 gestational diabetes resulting in macrosomia. Nine patients required neonatal intensive care unit hospitalizations, and 1 patient had evidence of a subarachnoid bleed. The mean age at treatment initiation was 4.5 months.

Radiological abnormalities were observed in 19 of the 139 patients (14%). Two of the 19 patients had multifocal hemangiomas with diffuse liver involvement on ultrasonography. Nine patients had abnormal findings on magnetic resonance imaging of the brain, with aberrant external carotid artery connections feeding the IH that was located in the head and neck area. Two patients had an IH that was located in the brain (posterior pons, left frontal lobe), and 1 patient had an IH that was located in the right anterior chamber of the eye. One patient had dilation of the superior ophthalmic vein with frontal bone remodeling. Another patient had a hypoplastic posterior cerebral artery (PCA); 1 patient had a prominent left PCA;

Table. Characteristics of Study Patients

Characteristic	Propranolol (n=75)	Oral Corticosteroids (n=42)	Other Treatments (n=22)	Total No. (%) of Patients (N=139)
Mean age at initiation of treatment, mo	4.9	4.5	7.6	139 (100)
Prior treatment, ^a %	53	16	0	69 (50)
Male	20	8	4	32 (23)
Female	56	34	17	107 (77)
History of prematurity	15	6	3	24 (17)
Placental abnormalities	2	0	0	2 (1)
Products of multiple gestations, twin gestation	9	1	1	11 (8)
PHACES syndrome	0	1	0	1 (1)
Radiological abnormalities ^b	9	7	2	18 (14)
Ophthalmologic abnormalities	8	5	0	13 (9)

^aTopical and intralesional corticosteroids, topical imiquimod, and pulsed-dye laser.

^bTwo patients had multifocal hemangiomatosis with diffuse liver involvement on ultrasonograms; 9 patients had abnormal findings on magnetic resonance images of the brain, with aberrant external carotid artery connections; 2 patients had an infantile hemangioma that was located in the brain (posterior pons, left frontal lobe); 1 patient had an infantile hemangioma that was located in the right anterior chamber of the eye; 1 patient had dilation of the superior ophthalmic vein with frontal bone remodeling; 1 patient had a hypoplastic posterior cerebral artery (PCA); 1 patient had a prominent left PCA, and 1 patient had absence of the right PCA.

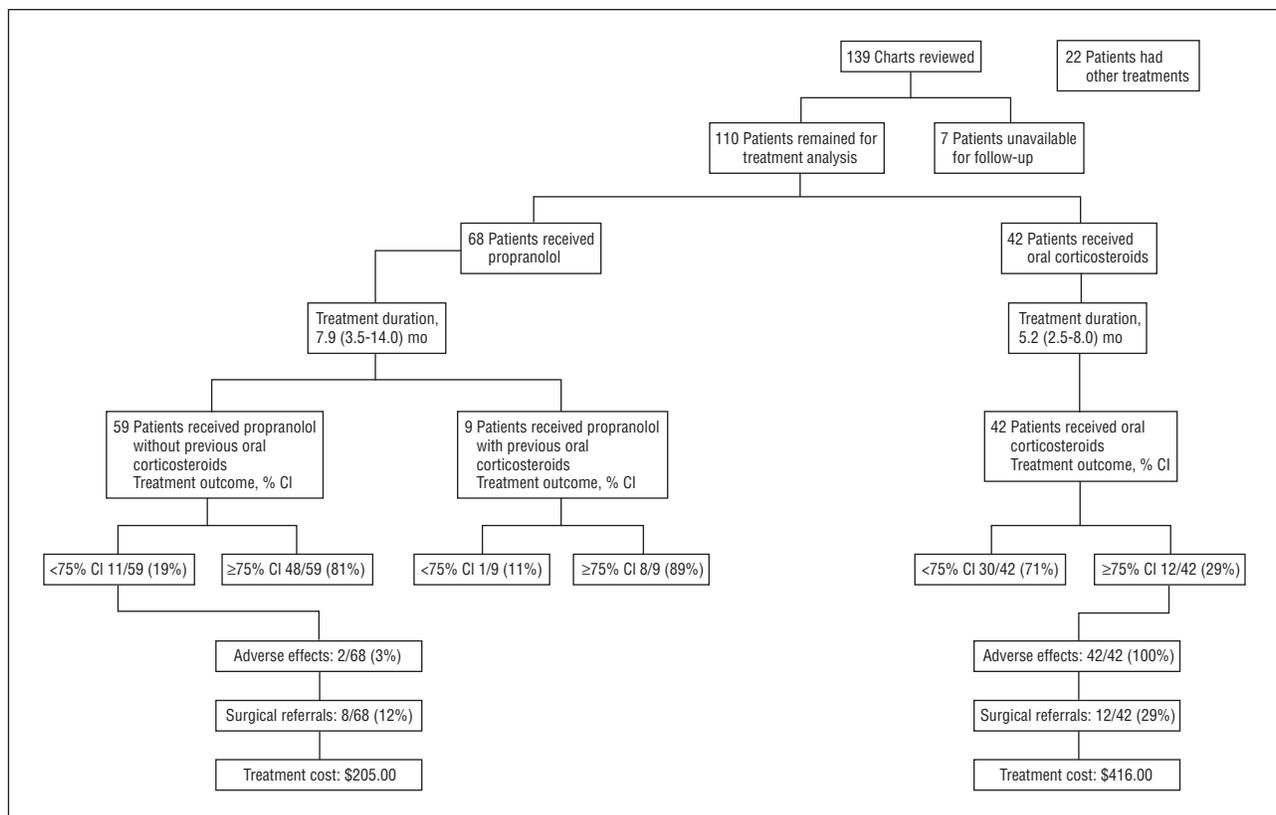


Figure 1. Study flowchart. CI indicates clearance.

and 1 patient had an absence of the right PCA. Also, 1 patient met the criteria for PHACES syndrome (Dandy-Walker malformation and a segmental facial IH).

PART 2

We compared the outcomes of IHs treated with propranolol vs oral corticosteroids. We matched both groups based on patient age and location, size, and type of lesion. This comparison was possible because it has been shown that IHs occur in a nonrandom distribution, along the embry-

onic lines of cleavage.¹⁰ Finally, we compared the overall clinical outcomes of these 2 groups using the percentage of clearance (**Figure 1**). Overall, 56 of 68 patients (82%) achieved clearance of 75% or more in the propranolol group compared with 12 of 42 patients (29%) in the corticosteroid group ($P < .01$). The number of adverse effects observed in the propranolol group was 1 of 68 (1%). This number was significantly less than that observed in the corticosteroid group (42 of 42 [100%]) ($P < .01$). The number of surgical referrals in the propranolol group (8 of 68 [12%]) was significantly less than the number of surgical

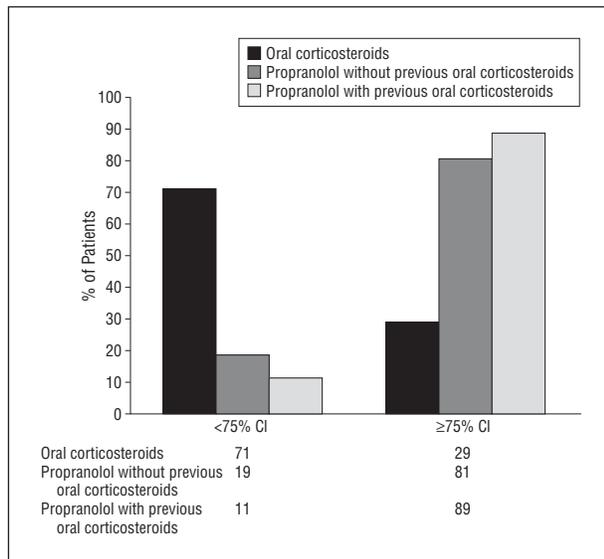


Figure 2. Treatment outcome graph. CI indicates clearance.

referrals in the corticosteroid group (12 of 42 [29%]) ($P=.03$). Furthermore, the number of ulcerations was significantly lower in the propranolol group (4 of 68 [6%]) than in the corticosteroid group, in which 11 of the 42 IHS (26%) ulcerated ($P<.01$).

PROPRANOLOL GROUP

The propranolol group was further divided into 2 groups. The first group comprised patients who had been treated only with propranolol without previous oral corticosteroids. In this group, 48 of 59 patients (81%) had clearance of 75% or more and 11 of 59 patients (19%) had clearance of less than 75%. The second group consisted of those patients who were receiving propranolol and who also had undergone previous treatment with oral corticosteroids. In this group, 8 of 9 patients (89%) had clearance of 75% or more and 1 of 9 patients (11%) had clearance of less than 75%. The difference in clearance between these 2 groups was not statistically significant ($P=.52$).

One of 68 patients (1%) had hypoglycemia, and 2 (3%) had a nonspecific skin eruption. Propranolol therapy was discontinued in the latter 2 patients and then restarted at a later date, without recurrence. Therefore, their adverse effects were determined unlikely to be related to propranolol therapy. Eight of 68 patients (12%) were referred for surgery after propranolol treatment. The average duration of treatment was 7.9 months, and the total average treatment cost for propranolol therapy alone was \$205.32 per patient.

ORAL CORTICOSTEROID GROUP

In the oral corticosteroid group, 12 of 42 patients (29%) had clearance of 75% or more, and 30 patients (71%) had clearance of less than 75%. Forty-two patients (100%) patients had adverse effects. All patients exhibited Cushingoid features. Four patients had gastroesophageal reflux, 2 had hypertension, and 1 experienced a life-threatening arterial bleed as a result of an ulceration that

eroded through the external carotid artery and required emergency surgery to achieve hemostasis. Also, 1 patient developed hirsutism, 1 had failure to thrive and poor weight gain, 1 had hypercholesterolemia, 1 had scarring and lip contraction leading to functional impairment, 1 received trimethoprim-sulfamethoxazole (Bactrim) for *Pneumocystis carinii* pneumonia prophylaxis, and 2 received respiratory syncytial vaccination series with palivizumab (Synagis).

Twelve patients (29%) were referred for surgery after oral corticosteroid treatment. The average duration of treatment was 5.2 months, and the total average treatment cost for oral prednisolone was \$416.00 per patient.

COMMENT

TREATMENT OUTCOMES

This retrospective study of 110 patients confirmed that a daily cumulative dose of 2 mg/kg of propranolol is highly effective in the treatment of IHS. Furthermore, it demonstrated that propranolol therapy is superior to oral corticosteroid treatment, the former criterion standard therapy for IHS (Figure 2).

Our study revealed that of the patients who received systemic corticosteroids before propranolol, 89% achieved lesion clearance of 75% or more compared with the 81% who achieved lesion clearance of 75% or more with propranolol alone. The difference in the treatment outcome may indicate that a combination treatment of a short course of systemic corticosteroids in conjunction with propranolol may be more effective than treatment with propranolol alone; however, these results were not statistically significant. Nevertheless, they indicate that the outcome in the propranolol group did not seem to be greatly affected by previous oral corticosteroid treatment.

It has been believed that therapy must be administered during the proliferative phase of IHS to arrest the progressive growth of the vascular lesion.¹¹ However, in this study, we found similar outcomes in patients treated with propranolol before and after 1 year of age (7 of 68 patients were started on propranolol therapy after the age of 12 months, and all had $\geq 75\%$ clearance). This finding indicates that propranolol's long-term effect is not solely related to its antiproliferative effect on the vasculature but is also due to its apoptosis and vasoconstriction.

Seven of the 68 patients in the propranolol group had periocular involvement of their IHS. One of the 7 was unavailable for follow-up, 3 had clearance of 75% or more, and 3 had clearance of less than 75%. In the oral corticosteroid group, 10 of the 42 patients had periocular involvement of their IHS. Six of the 10 had clearance of less than 75%, and 4 had clearance of 75% or more. This number of patients was not sufficient to draw a definitive conclusion as to whether propranolol therapy is superior to oral corticosteroid treatment for IHS with periocular involvement. Also, the difference between the 2 groups that achieved clearance of 75% or more was not statistically significant ($P=.71$). Unfortunately, we could not obtain any follow-up data regarding the improvement of amblyopia or astigmatism.

Eleven of the 42 IHs (26%) ulcerated during oral corticosteroid treatment; however, only 4 of 68 (6%) ulcerated during propranolol treatment ($P < .01$). These results indicate that IHs treated with oral corticosteroids ulcerate at a greater rate than those treated with propranolol, which could be related to their presumed mechanism of action.

ADVERSE EFFECTS OF PROPRANOLOL THERAPY

The known adverse effects of propranolol therapy include bradycardia, hypotension, hypoglycemia, bronchospasm, congestive heart failure, nausea, vomiting, abdominal cramping, sleep disturbance, night terrors, and depression. Several recent reports have also associated hyperkalemia with early initiation of propranolol therapy, requiring treatment with furosemide, fluids, and nebulized albuterol.¹²

In our study, only 1 of 68 patients had hypoglycemia. Although 2 of the 68 patients experienced nonspecific skin eruptions, neither of the eruptions had a clear correlation to propranolol therapy, and neither recurred on re-treatment. The low incidence of adverse effects in our study patients may be partially related to our detailed pretherapeutic protocol and to the protective measures taken during intercurrent illnesses. For example, the treatment was interrupted in 6 of the 68 patients: 2 developed fever, 2 developed rash, 1 developed tachycardia, and 1 developed viral upper respiratory infection with reactive airway disease. It should be mentioned that several cases of hypoglycemia have been reported in the literature among patients with IHs who were treated with propranolol.^{13,14} However, these cases have mainly been associated with concurrent illnesses or poor oral intake for various reasons. Therefore, propranolol should not be administered on days with diminished oral intake, and parents should be educated about the warning signs of hypoglycemia, such as fussiness, poor feeding, apnea, loss of consciousness, seizures, and hypothermia.

Although further prospective studies are needed to determine the precise incidence of the adverse effects of propranolol therapy in patients with IHs, we encountered only 1 serious adverse effect in our retrospective study. Taken together, propranolol therapy had a much safer adverse effect profile when compared with oral corticosteroid therapy.

RELAPSE AND RESISTANCE

Relapse of individual IHs was observed in 2 of the 68 patients (3%) who were receiving propranolol: one with diffuse neonatal hemangiomas, and the other with periorcular involvement. Both patients started the treatment at 3 months of age and discontinued therapy at 10 months of age. These 2 patients may have ended therapy prematurely, because when propranolol was reintroduced, both IHs again regressed. A similar observation was made in the 6 patients whose propranolol therapy had to be temporarily discontinued owing to intercurrent illnesses (fever, rash, tachycardia, and viral upper respiratory illness or reactive airway disease). Likewise, our results agree with those of a previous study in which 2 of 32 patients

had rebound growth in their IHs after cessation of treatment before 12 months of age.¹⁵ In both of these patients, re-treatment with propranolol was effective as well. Moreover, relapse after discontinuation of propranolol therapy in patients older than 12 to 14 months has also been described.⁶ Because of these experiences, most of our patients who received propranolol underwent extended treatment for up to 1 year of age to prevent relapses of their IHs. On the other hand, in the oral corticosteroid group, the treatment duration was limited owing to the adverse effects associated with prolonged treatment. Therefore, it is possible that longer treatment with propranolol may have influenced the final clinical outcome that was observed in our patients. However, as has been described previously, improvement with propranolol therapy is seen relatively quickly and not solely as a result of prolonged treatment.³⁻⁶

SURGICAL REFERRALS

Propranolol reduced the need for surgery, with overall better cosmetic outcomes. In our study, 8 of 68 IHs (12%) treated with propranolol required surgery after treatment, whereas 12 of 42 IHs (29%) treated with oral corticosteroids required surgery. All of these lesions were considered refractory to treatment or were deemed cosmetically unacceptable owing to critical locations such as the nasal tip or the periorbital region.

TREATMENT COST

The average cost of oral corticosteroids per IH treated was \$416.00, which was calculated based on an average treatment duration of 5.2 months. This amount does not include the additional costs incurred for the prophylactic treatment of oral corticosteroid-related adverse effects, such as increased rates of infection owing to immunosuppression and gastroesophageal reflux. On the other hand, the average cost of propranolol per IH treated was \$205.32, which was based on an average treatment duration of 7.9 months. However, this amount does not include a pediatric cardiology consultation for cardiac clearance to initiate therapy.

In conclusion, our study showed that propranolol therapy was more effective in lesion clearance, required fewer surgical referrals after treatment, and demonstrated superior tolerance, with minimal adverse effects. Propranolol proved to be safe in treating IH in our patients as no major adverse effects occurred. Also, propranolol therapy was more cost-effective, with a cost reduction of more than 50% per patient. Therefore, based on the results of this study, we believe that propranolol therapy is superior to traditional first-line oral corticosteroids in the treatment of IH, and we propose that propranolol be considered a first-line agent given its safety and efficacy for the treatment of IH.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Price and Alvarez Connelly. *Acquisition of data:* Price, Lattouf, and Baum. *Analysis and interpretation of data:* Price, Lattouf, Baum, McLeod, Schachner, Duarte, and Alvarez Connelly. *Drafting of the manuscript:* Price, Lattouf, Baum, and McLeod. *Critical revision of the manuscript for important intellectual content:* Price, Schachner, Duarte, and Alvarez Connelly. *Statistical analysis:* McLeod. *Administrative, technical, and material support:* Lattouf and Duarte. *Study supervision:* Price, Schachner, and Alvarez Connelly.

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Additional Contributions: Whitney Valins, BS, organized the data for this study.

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Archives Web Quiz Winner

Congratulations to the winner of our September quiz, Vijay Zawar, MD, DNB, DVD, Skin Diseases Center, Nashik, India. The correct answer to our September challenge was *trichodysplasia spinulosa*. For a complete discussion of this case, see the Off-Center Fold section in the October *Archives* (Burns A, Arnason T, Fraser R, Murray S, Walsh N. Keratotic “spiny” papules in an immunosuppressed child. *Arch Dermatol*. 2011; 147[10]:1215-1220).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the *Archives*. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.