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Dramatic Shift in the Infantile Hemangioma Treatment Paradigm at a Single Institution

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Abstract

Historically, the first line of treatment for infantile hemangioma (IHs) has been oral corticosteroids, but because of recent discoveries recognizing the effectiveness of oral and topical beta-blockers, IH management is dynamically changing. With these new treatment options, some physicians are altering the way they manage IHs despite having little evidence based data on the treatment methods. Highlighting treatment changes at a single large tertiary pediatric referral center, we conclude that despite the numerous studies already published on this topic, more reliable prospective studies are needed to determine the safety, efficacy, and best treatment algorithms for the use of topical and oral beta-blockers for the treatment of IHs.

Keywords

Hemangioma; Propranolol; Timolol; Corticosteroids; Beta-Blockers

Introduction

For the last 40 years, corticosteroids have been the first-line therapy for complicated infantile hemangioma (IHs),¹ but numerous recent reports describing the effectiveness of oral and topical beta-blockers² have now led to a change in IH management. Some physicians have rapidly adopted novel protocols to manage IH despite having little evidence based data on which to rely. This report highlights the dramatic shift in the IH treatment paradigm observed at a large tertiary pediatric referral center.

Materials and Methods

All patients with a diagnosis of IH presenting to the dermatology clinic between 2007 and 2011 were eligible for enrollment in an IRB approved study. We queried our database for information on management of IH and confirmed clinical data by reviewing medical records. If a patient's IH management was merely observational for a given year, that year was counted as an "untreated" year. Pharmacologic interventions included oral

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corticosteroids, topical corticosteroids, oral propranolol, topical timolol, and intralesional steroids. Interventions used infrequently such as interferon and vincristine were not included. If a patient received more than one medication within one year, the following tiered system was applied: oral medications > intralesional injections > topical medications. A separate category was created for patients who were treated with both oral steroids and oral propranolol in the same year. Patients receiving both topical timolol and topical steroid were excluded (n=4).

Results

Of the 565 patients who consented, 229 (40%) were treated with pharmacologic intervention and 109 (19%) were treated with systemic medications over the study period (Fig. 1). The number of patients treated with oral steroids dropped from 57% to 10% ($p<0.001$). Figure 1A shows the rapid transition in treatment methods over time, with oral corticosteroids most common in 2007 (57%) and topical timolol as the most prescribed in 2011 (53%). In 2011, the number of IH cases treated with timolol was nearly double that in 2010 and double the number of cases treated with propranolol in the same year ($p<0.001$).

Discussion

Oral corticosteroids have been the cornerstone of IH treatment since 1968. Treatments began to change when Labreze's sentinel report of propranolol use for the treatment of IH was published.² Numerous publications describing propranolol's efficacy soon followed, but they were not subjected to the stringency of clinical trials, and most were not prospective, randomized, or controlled. Many of these publications were case reports.³ In clinical use, propranolol has been found to be rapidly effective for IHs. These observations, coupled with the immediate availability of the medication, have led to a rapid adoption of off-label propranolol for treatment of IHs. It is estimated that at least 30,000 off-label prescriptions were written for propranolol to treat IHs in 2011.⁴ A similar trend is reflected in our data. Consensus guidelines were recently published to begin to develop evidence-based practices.⁵

In 2010, topical timolol solution was reported as an off-label treatment for IHs. Given the commercial availability of this drug and the perceived safety with the use of topical application, we predict that there will be widespread adoption of this drug for treatment of IHs, analogous to our experience. Infants who were previously untreated may now receive topical beta-blockers. Consequently, the bar for treatment may be lowered exposing more infants to this drug.

After the initial adoption of propranolol as an IH treatment, most of our patients were untreated. An increasing number of patients were referred to our clinic during the study years. Although propranolol use was identified in 2008, we were not offering it as first-line treatment and reserved its use for the most severe cases. Once our comfort level with propranolol increased, more patients received the therapy, and patients with less severe cases who did not qualify for systemic treatment were given topical timolol when it became available, further decreasing the number of patients left untreated.

The rapid shift from oral corticosteroids to oral and topical beta-blockers demonstrates the dramatic transformation occurring in IH management. These treatment trends highlight the broader matter of adoption of off-label prescribing practices in children, where no U.S. Food and Drug Administration indications exist and where there are no adequate clinical trials or safety data.⁶ After evaluating trends at our institution, we conclude that despite the numerous studies already published on this topic, more reliable prospective studies are still

needed to ensure the safety, efficacy, and best treatment algorithms for the use of topical and oral beta-blockers for the treatment of IHs.

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Figure 1.

(A) Significant increase in use of propranolol and timolol and significant decrease in oral steroids between 2007 and 2011. (B) The percentage of treated patients increased over the study period. (C) Dramatic increase in topical treatment from 2008 to 2011.