Propranolol for Treatment of Genital Infantile Hemangioma

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Purpose: Genital infantile hemangiomas are vascular anomalies that often require complex management and interdisciplinary care. Propranolol was first used to treat patients with infantile hemangiomas in 2008 and has since gained acceptance as first-line therapy.

Materials and Methods: We review the presentation, course, management and outcomes of all cases of genital infantile hemangiomas managed by propranolol administration at a single institution from April 2010 to July 2014.

Results: During the study period 9 patients with genital infantile hemangiomas were referred to our hemangioma treatment clinic. Propranolol was initially administered under careful outpatient monitoring at a dose of 1 mg/kg daily in 8 patients. One patient, a 700 gm premature infant, was started on therapy in the inpatient setting at 0.5 mg/kg daily, given the history of prematurity. All patients underwent successful increase of dose to at least 2 mg/kg for the observation phase after tolerating the starting doses. One patient discontinued propranolol prematurely per parental request due to concern regarding peripheral vasoconstriction. Otherwise, no patient demonstrated significant hypotension, symptomatic bradycardia, hypoglycemia or other major side effect requiring treatment discontinuation. All patients who continued the treatment protocol had excellent response to therapy.

Conclusions: Propranolol therapy for genital infantile hemangiomas was successfully initiated and the dosage increased in 9 young children without significant side effects and with marked improvement in all patients who continued on treatment. Propranolol is the only Food and Drug Administration approved therapy for treatment of patients with this vascular anomaly and should be considered first-line therapy for genital infantile hemangiomas.

Key Words: genitalia, hemangioma, propranolol

Abbreviations and Acronyms

ECG = electrocardiogram

IH = infantile hemangioma

MRI = magnetic resonance imaging

SCAMP = Standardized Clinical Assessment and Management Plan

VAC = Vascular Anomalies Committee

Accepted for publication September 12, 2015.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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INFANTILE hemangiomas represent the most common type of benign vascular tumor of infancy, with an incidence of 1 in 200 live births.[1,2] Although these tumors usually manifest in the skin and subcutaneous tissue of the head and neck, trunk and extremities, 1% of all infantile hemangiomas involve the genitalia.[3,4] Genital infantile hemangiomas may be associated with other urogenital, anorectal and spinal malformations, such as Klippel-Trenaunay-Weber syndrome, external genital malformations, lipomyelomenigocele, tethered cord, vesicorenal abnormalities and imperforate anus.[1,5]

The natural history of IH typically involves 3 phases.[2] IHs emerge within a few weeks of birth and then undergo rapid proliferation for 6 to 12 months.[6] Growth plateaus by age

0022-5347/16/1953-0731/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.09.069
Vol. 195, 731-737, March 2016
Printed in U.S.A.

1 year, after which most IHs slowly regress during the involution phase. Complete regression occurs by age 7 years in 75% to 90% of patients. Nonetheless, some patients suffer permanent damage from scarring or from deposition of fibrofatty residual tissue. While IHs are often asymptomatic, some common presenting symptoms include functional impairment, rapid growth, tissue deformity, ulceration and bleeding, pain, infection and effect on cosmesis.[7] Diagnosis of IH is made by clinical history and physical examination. Radiographic studies including MRI and ultrasound can be useful for diagnostic clarification.

IHs requiring intervention have traditionally been managed by pharmacotherapy, including systemic corticosteroids and surgery. However, these conventional treatment strategies may be associated with significant morbidity. Since the discovery in 2008 that IH could be treated with oral propranolol, this treatment has emerged as a first-line therapy. Propranolol has been used in the pediatric population for many years to treat cardiac and noncardiac diseases. However, its effectiveness in treating IH was only recently identified in 2008, after it was administered to a patient with IH for a different indication.[8] Since that time, propranolol has gained Food and Drug Administration approval for this indication and is now considered first-line therapy for IH.

Propranolol causes occasional adverse effects, most commonly bradycardia, hypotension and hypoglycemia.[9] Nonetheless, its safety has been well established even in high risk populations, such as preterm neonates and patients with complex congenital heart disease.[10,11]

The Cleveland Clinic VAC is an institution wide multidisciplinary committee that has been involved in developing a clinical treatment protocol since 2009. This protocol has subsequently been used in approximately 150 pediatric patients. A subset of the patients treated for IH using this protocol has presented with lesions in the genital region, and with adverse effects on voiding and cosmesis. Our study represents the first known retrospective review to date regarding the use of propranolol for the treatment of patients with genital IH. In this study we assess, characterize, and present the safety and efficacy of the VAC protocol in treating genital IH.

METHODS

Given the diversity of the presentation of IH, the range of subspecialties involved and the need for assessment of cardiac risk, a systematized approach to assessing outcomes and adverse events was crucial to optimizing patient outcomes. Thus, the SCAMP paradigm was adopted to achieve these goals.[12] We developed a standardized protocol for initiating treatment with propranolol in patients with IH (supplementary Appendix, http://jurology.com/). The protocol was established with 3 goals, consisting of 1) patient safety, with a comprehensive cardiovascular evaluation performed before treatment and initiation of treatment under the supervision of an experienced pediatric cardiologist, 2) facilitation of multidisciplinary involvement in patient care and 3) careful documentation of methods and results to facilitate quality improvement.

An infantile hemangioma database was subsequently created, which included all patients with a diagnosis of IH who had been treated with propranolol according to the VAC SCAMP. This database was then culled for patients with a diagnosis of genital IH. Patients were included if they had a lesion involving the penis, scrotum, labia, clitoral hood or clitoris, vagina, pubis or perineum. We then reviewed the presentation, course, management and outcomes of all cases of genital IH managed at our institution from 2009 to 2014.

Nine infants with a diagnosis of genital IH were identified. All patients were evaluated by a pediatric cardiologist before initiation of treatment with propranolol. Referrals were made from dermatology, pediatric urology, plastic surgery and general pediatrics. Diagnosis was based on history and physical examination, with ultrasound and MRI used as adjunctive methods in 3 cases to assess for the presence of internal extension. Cardiovascular screening included a complete medical and family history, physical examination, 12-lead ECG and echocardiography.

Treatment with propranolol was initiated by the pediatric cardiologist in an outpatient setting in 8 patients and in the neonatal intensive care unit in 1 patient according to the VAC protocol. Propranolol was initially administered under careful outpatient monitoring at a dose of 1 mg/kg daily in the 8 outpatients. Treatment in the inpatient, an infant with a weight of 700 gm who was born prematurely at 25 weeks of gestation, was initiated at a lower dose of 0.5 mg/kg daily, given the status as a low birthweight premature infant. All patients underwent careful monitoring of vital signs, including pretreatment and posttreatment blood pressure, heart rate and blood glucose. Doses were then increased to at least 2 mg/kg for the observation and adjustment phases.

Patients were seen by the pediatric cardiologist at the hemangioma treatment clinic every 2 to 3 months to assess progress and side effects, and to adjust treatment dosage based on weight gain and response. At completion of the treatment protocol patients were weaned off of propranolol during a 1-month period. Photographs were taken by a professional medical photographer at every visit to document progress during the treatment course.

RESULTS

Patient Characteristics

Seven females and 2 males with genital IH were referred to a pediatric cardiologist at our institution for treatment with oral propranolol between