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● *Original Contribution*

ULTRASOUND IN ASSESSING THE EFFICACY OF PROPRANOLOL THERAPY FOR INFANTILE HEMANGIOMAS

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Abstract—This study was aimed at assessing the efficacy of propranolol treatment in infantile hemangiomas (IHs) by ultrasound. Thirty-one patients with IHs were administered propranolol and were assessed by ultrasound before treatment, 3 mo after treatment and at the end of treatment. Longitudinal and transverse diameters, as well as thickness of hemangiomas measured by clinical observation differed significantly ($p < 0.05$) from measurements obtained by ultrasound. Ultrasound also revealed that longitudinal and transverse diameters, thickness, vascular density, blood flow velocity (arterial and venous) and arterial peak systolic blood flow velocity of hemangiomas were significantly decreased ($p < 0.05$) after treatment compared with before treatment. The resistive index and systolic/diastolic blood flow velocity in IHs were significantly higher ($p < 0.05$) after treatment than before treatment. In conclusion, ultrasound can evaluate the efficacy of propranolol at the termination of therapy. (E-mail: shjyjm@163.com) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Propranolol, Infantile hemangiomas.**

INTRODUCTION

Infantile hemangiomas (IHs) are the most common vascular tumors in infancy, with an estimated worldwide prevalence of 1%–10% in newborns and infants (Haggstrom et al. 2007). Although most IHs are innocuous and undergo complete regression spontaneously in 60% of 4-y-old patients and 76% of 7-y-old patients (Margileth and Museles 1965), some patients require immediate treatment because of life-threatening complications (Storch and Hoeger 2010). In 2008, Léauté-Labrèze et al. (2008) reported, for the first time, the use of propranolol in the treatment of a severe infantile hemangioma with beneficial effects. Since then, propranolol has become an effective and highly promising therapy for IHs (Georgountzou et al. 2012; Mazereeuw-Hautier et al. 2010; Mousa et al. 2010). Currently, propranolol is recommended as the first-line treatment for complex IHs (Schiestl et al. 2011). The effect of propranolol is mostly easily assessed in terms of a reduction in the area or volume of the IH. However, an objective way to assess the efficacy of propranolol therapy in the treatment of IHs is to use ultrasound, which has yet to be described.

In 1989, Lieb et al. (1990) described the use of color Doppler ultrasound to simultaneously assess organ structure and blood flow using 2-D imaging and Doppler evaluation, respectively, in a patient with an orbital varix that was previously diagnosed on the basis of clinical findings and computed tomography. This study also reported that color Doppler ultrasound is a useful adjunct to computed tomography evaluation of suspected vascular lesions in the orbit (Lieb et al. 1990). In this context, we aimed to assess the efficacy of ultrasound in identifying changes in IH size, morphology and blood flow in patients before, during and at the end of propranolol treatment. We also aimed to determine whether ultrasound helps in the decision to discontinue propranolol therapy.

METHODS

Patients

Infants with hemangiomas were recruited from the outpatient department of our hospital between January 2009 and December 2013 and prospectively enrolled

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into this study. A definite diagnosis of proliferative hemangioma was based on standard guidelines proposed by Enjolras and Mulliken (1997). Parents of study infants were informed of the purpose of the study and signed a detailed informed consent describing the study design and potential adverse effects of propranolol treatment. The study was approved by the medical ethics committee affiliated with the hospital of Ningxia Medical University.

Patients <2 y of age who exhibited normal development and no organ or systemic diseases and who had not received other treatment for hemangiomas (*e.g.,* surgical treatment, laser therapy and drugs) were included in this study.

Exclusion criteria included sinus bradycardia, hypopiesia, cardiac shock, heart block (second- and third-degree atrioventricular block), severe or acute heart failure, tracheobronchitis, pneumonia, bronchial asthma, altered liver and kidney function, abnormal glucose tolerance or diabetes mellitus and unwillingness to attend follow-up visits.

Preparation for treatment

Basic vital signs (temperature, pulse, respirations, blood pressure) and weight were measured in patients before initiation of propranolol treatment. Routine blood tests, liver and kidney function tests and blood glucose levels were also obtained. To exclude infants with cardiovascular disorders contraindicative to propranolol use, all patients underwent a 12-lead electrocardiogram with an Automatic Analysis Machine (FX-7402, Beijing Futian Electronic Medical Instrument, Economic and Technological Development Zone, Beijing, China) and an echocardiogram with the Diagnostic Ultrasound System (iE33, Philips Ultrasound, Bothell, WA, USA) while quiet in a supine position.

Photographic clinical evaluation and an ultrasound examination of the hemangiomas were performed while infants were in a quiet state. It should be noted that chloral hydrate was administered to keep the crying infants quiet.

Ultrasound examination

Ultrasound examination was performed in all patients by an ultrasound specialist. The study was performed with a Siemens Diagnostic Ultrasound System (S2000 VC25, Siemens Medical Solutions USA, Mountain View, CA, USA) equipped with a broadband (9–14 MHz) linear transducer. The ultrasound transducer was applied on hemangiomas using a sterile medical ultrasonic coupling agent. Color Doppler sonograms were obtained with low-pulse repetition frequency (1220–2448 Hz) and a wall filter (50–100 kHz). Pulse repetition frequency was increased only if aliasing occurred.

Ultrasound measurements were set to the superficial organ examination. Gray-scale sonography was used to observe IH size, morphology, thickness and boundaries, as well as relationships with its surrounding tissues. Vessel density was estimated by color Doppler sonography, and the number of vessels per square centimeter outlined on color Doppler imaging was counted (Dubois et al. 1998). Arteriovenous blood flow signals, arteriovenous spectrum, blood flow velocity (arterial and venous) and arterial peak systolic blood flow velocity were determined by pulse Doppler ultrasonography. The resistance index (RI) was calculated with the formula RI = (PSV–EDV)/PSV, where PSV = peak systolic velocity and EDV = end-diastolic velocity. Doppler spectrograms were also used to measure the PSV and EDV (according to arterial blood flow waves) and the S/D blood velocity ratio (S = peak systolic velocity, D = end-diastolic blood flow velocity) of hemangiomas.

Propranolol therapy

Propranolol was administered orally on a daily basis. Treatment was started at a dose of 0.67 mg/kg/d for 2 d; increased to 1.35 mg/kg/d in two divided doses for the next 2 d; and finally increased to 2.0 mg/kg/d in three divided doses until the end of treatment. If the patient tolerated the total dosage well, then the dose was maintained at 2.0 mg/kg/d, with a follow-up at an outpatient clinic once a week. Heart rate was monitored with a stethoscope at each visit. Ultrasound evaluation was performed 3 mo after treatment and on a monthly basis thereafter until the end of the treatment. During the course of treatment, weight was measured to adjust dosage. If patients experienced adverse effects such as a cold, diarrhea, vomiting, shortness of breath, and changes in sleeping patterns, the dose of propranolol was either reduced or temporarily discontinued depending on the severity of the symptoms. Once the symptoms disappeared, propranolol therapy was re-instituted and continued at the dosage of 2.0 mg/kg/d. When the hemangioma disappeared and ultrasound revealed that the internal blood flow of the lesion was normal or close to normal, the dose of propranolol was gradually lessened over 1 mo and subsequently discontinued. If propranolol treatment reached 6 mo but the hemangioma had not yet completely disappeared or the ultrasound revealed blood flow signals, propranolol treatment was continued and ultrasound assessment of the IH was continued on a monthly basis. Propranolol treatment was discontinued when the hemangioma remained stable and there were no obvious blood flow signals on ultrasound or when the duration of treatment reached 11 mo.

Indicators of the efficacy of propranolol therapy

Clinical evaluation of the efficacy of therapy consisted of measuring the size and superficial thickness of