Treatment of Severe Infantile Hemangiomas With Propranolol: An Evaluation of the Efficacy and Effects of Cardiovascular Parameters in 25 Consecutive Patients

Da-Peng Xu, MS, Rong-Yu Cao, MS,† Lei Xue, DDS,‡ Ning-Ning Sun, DDS,§ Shuang Tong, DDS,‖ and Xu-Kai Wang, DDS, PhD¶*

Purpose: The aim of this study was to investigate the therapeutic results and effects of propranolol on cardiovascular parameters in infants receiving systemic propranolol for complicated infantile hemangiomas (IHs), as well as to evaluate the adverse effects of propranolol throughout the course of treatment.

Materials and Methods: Twenty-five consecutive patients who presented with complicated IHs were prospectively recruited into this study between April 2012 and June 2013. All patients were treated with systemic propranolol at a dose of 1.0 to 1.5 mg/kg, and the drug was taken once per day. The length of treatment was 8.2 months on average and ranged from 6 to 12 months. The follow-up visits were scheduled monthly after discharge. Changes were recorded during the 3-day hospitalization, including systolic and diastolic blood pressures, heart rate, and blood glucose level. The treatment responses were scored according to a 4-point scale system as very good, good, mild, or no response. The adverse effects after medication administration were evaluated and managed accordingly.

Results: Of the 25 patients, 8 (32%) had a very good response, 11 (44%) had a good response, and 6 (24%) had a mild response. When pretreatment and post-treatment values were compared, there was no significant decrease in mean systolic and diastolic blood pressures and mean heart rate (all $P > .05$). The decreases in the cardiovascular parameters were not commonly associated with observable clinical symptoms. No major collateral effects were observed, and no infants were withdrawn from treatment because of side effects.

Conclusions: Fluctuations from the normal ranges of cardiovascular parameters occurred frequently with the initiation of propranolol, but were clinically asymptomatic. Therefore oral propranolol was an effective and safe treatment for IHs, particularly for early intervention suitable for severe IHs.

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*Resident, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, China.

†Resident, Department of Endodontics, School of Stomatology, Shandong University, Jinan, China.

‡Attending Surgeon, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, China.

§Attending Surgeon, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, China.

‖Attending Surgeon, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, China.

¶Professor and Chairman, Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, China.

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Address correspondence and reprint requests to Dr Wang: Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, No. 117, Nan Jing North Street, HePing District, Shenyang 110002, Liaoning Province, PR China; e-mail: wangxukai757892@sina.com

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Infantile hemangiomas (IHs) are the most common tumors of childhood, occurring in 4 to 10% of infants, with a female predominance.[1,2] They appear shortly after birth and usually begin to involute spontaneously in early childhood. A complete regression has been observed in 60% of 4-year-old patients and 76% of 7-year-old patients.[3,4] Although most IHs do not need treatment because of unique biological characteristics, approximately 10% of IHs require treatment because of their growth, local complications, and cosmetic and functional risks. Systemic corticosteroids have traditionally been the mainstay of treatment for severe IHs. However, the potential for treatment-associated morbidity limits their use. Propranolol for the treatment of IHs was a serendipitous finding, which was first reported in 2008 by Léauté-Labrèze et al.[5] Two children with large IHs were treated for high-output cardiac failure with propranolol. Impressive and rapid regression of their hemangiomas was surprisingly noted. Since then, propranolol has largely replaced corticosteroids as the first-line agent. In this study we further evaluate the clinical outcomes and side effects of systemic propranolol treatment in patients with complicated hemangiomas involving the orofacial region, and we investigate the effects of propranolol on cardiovascular parameters in infants.

Materials and Methods

Between April 2012 and June 2013, 25 consecutive patients (13 female and 12 male patients), aged 2 to 9 months (mean, 4.4 months), were enrolled in this study. All of them had hemangiomas in the orofacial area. The patients had been admitted for treatment at the Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, China Medical University, Shenyang, China. According to the classification of hemangioma proposed by Waner and Suen[6] and combined with Doppler ultrasonography scanning, we categorized this lesion into 3 basic subtypes. These comprised superficial hemangioma (located in the papillary dermis) in 15 cases, deep hemangioma (located in the reticular dermis and subcutaneous tissue) in 6 cases, and mixed hemangioma (mixture of superficial and deep components) in 4 cases. The anatomic location of the IHs was as follows: 9 tumors were in the periorbital region, and the remaining IHs were in the parotid area (n = 7), the nasal area (n = 5), and the perioral region (n = 4). The diagnosis of hemangioma was made based on the history, clinical appearance, and Doppler ultrasonography scanning or magnetic resonance imaging findings. The inclusion criteria were the presence of potential problematic hemangiomas that may result in cosmetic disfigurement or functional loss because of their position and size, excluding hemangiomas associated with PHACE syndrome (a congenital syndrome of posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye anomalies, and sternal defects), and ulceration. No infants were given any treatment before propranolol. The exclusion criteria for treatment were the presence of congestive cardiac failure, bradycardia, asthma, and obstructive pulmonary disease. Informed consent was obtained from the parents, and the study protocol was approved by the Institutional Review Board of China Medical University.

Treatment was initiated during a short hospitalization of 72 hours. Before treatment, the electrocardiogram and echocardiogram were reviewed by a pediatric cardiologist to identify contraindications. The baseline values of the systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and blood glucose (BG) level were obtained on the day of admission before the initiation of propranolol. Propranolol (10-mg tablet; Tianjin Lisheng Pharmaceutical, Tianjin, China) was prepared from a tablet to a suitable solution and then given at a dose of 1.0 to 1.5 mg/kg (with 1.0 mg/kg for children aged <3 months and 1.5 mg/kg for those aged >3 months) once per day. The SBP, DBP, HR, and BG level were closely monitored in the course of the 3-day hospitalization and recorded 1 hour after each dose. The SBP, DBP, and HR also were recorded every 3 hours according to the monitoring protocol of the inpatient infant unit. If the blood pressure (BP) or HR were substantially decreased, we repeated the measurement after 1 hour. The ranges of normal BP and HR values were taken from the age-specific published data, and a BG value of less than 60 mg/dL was considered to indicate hypoglycemia.[7,8] The patients who did not have adverse reactions continued to take propranolol orally after discharge. The parents were trained on how to detect side-effects and, if necessary, to discontinue administration when any major side-effects were observed. The first follow-up visit was performed after 2 weeks of therapy, and follow-up was scheduled monthly thereafter. At each clinic visit, the BP, HR, and BG level were measured. Propranolol was stopped when patients had complete regression of lesions, when patients were aged up to 1 year, or when no further improvement could be achieved. Early discontinuation would lead to a relapse, and the dose of the drug was adjusted according to the patient's weight changes and the degree of adverse reaction during the follow-up period. Therefore we usually gave all patients propranolol for at least 6 months to prevent rebound. All patients were followed for a period of 6 to 13 months.

All patients were evaluated by B-scan echography, by clinical examination, and by photographs at the onset of treatment, between treatment intervals, and at the conclusion of treatment. The treatment