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Original paper

Propranolol intervention therapy for infants with facial hemangioma

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Aim of the study: The current study aimed to evaluate the clinical efficacy and adverse effects of small doses of propranolol intervention therapy for infants with infantile facial hemangioma in the proliferation stage.

Material and methods: A total of 22 patients including 9 males and 13 females with an average age of 5.5 months were enrolled. These patients were diagnosed with facial hemangioma. During the first week of hospitalization, the patients were requested to take propranolol according to their weight (1.0 mg/kg to 1.5 mg/kg once daily). After hospital discharge, the patients were requested to take propranolol consistently and were reassessed every two weeks. We closely observed the process, recorded information about the size, color, and texture of the hemangioma, coped with the adverse effect during the treatment, and evaluated the clinical efficacy of propranolol.

Results: The color of the hemangioma faded 24 h after taking propranolol. After 3 months to 9 months of observation, we obtained the following clinical efficacies: level I, 0; level II, 2; level III, 13; and level IV, 7. The effective rate was 100%. The heart rate of 22 patients became slower than before treatment, 2 patients had slight diarrhea that disappeared after treatment, and there was no serious adverse effect during the entire process.

Conclusions: With the advantages of minor side effects, convenience, safety, and evident efficacy, the administration of small doses of propranolol is a good method for treating hemangioma in infants.

Key words: infants, propranolol, hemangioma.

Introduction

Hemangioma is a congenital benign tumor originating from residual embryonic angioblasts. Among all hemangioma cases, 60% are facial hemangioma, which usually appears on the face, subcutaneous tissue, and oral mucosae, such as the tongue, lips, and floor of the mouth. Generally, active surgical treatment was not recommended for hemangioma. However, treatment is necessary when the hemangioma appears on the mouth, eyes, and respiratory tract, when complications such as bleeding, infection, and ulcer arise, or when the hemangioma is rapidly growing. Normally, nine months after birth is the growth period of hemangioma. Thereafter, the hemangioma starts to shrink at a speed of 10% annually until it disappears. Although hemangioma is benign, it may still cause great facial damage. Thus, a proper intervention therapy is necessary to accelerate the disappearance of hemangioma and reduce potential complications. Contemporary conventional treatments have obvious side effects. Based on related literature, our group used the method of propranolol administration to treat facial hemangioma in 22 patients, and achieved ideal results.

Material and methods

Patients

A total of 22 patients including 9 males and 13 females with an average age of 5.5 months (45 days to 15 months) were included in the current study. These patients were admitted to our department from January 2010 to September 2010 and were diagnosed with facial hemangioma. The lesion sites included cheek (6 patients), lip (7 patients), temporal region (5 patients), eyelid (3 patients), and auricle (1 patient) with a minimum size of 1.0 cm × 0.5 cm and a maximum size of 3.5 cm × 3.0 cm. Among the 22 patients, there were 9 patients who received such treatments as laser, cryotherapy, isotope applicator, and hormone treatments. One patient had hemangioma near the lips combined with ulcer and bleeding, as well as a related eating disorder. Hormone and anti-inflammatory treatments did not achieve the ideal treatment goals. The tissue defect also caused a visible deformity on the lips. Before treatment, all patients underwent routine blood, cardiac ultrasound, liver function, kidney function, and blood glucose tests. Patients with organic diseases and pneumonia were excluded from the current study.

Treatment protocol

Informed consent was obtained from the parents of the infants after informing them of the treatment protocol and side effects of propranolol. The propranolol (10 mg) used in the current study was obtained from Xing De An, Changzhou Kangpu Pharmaceutical Co., Ltd., China. Propranolol was administered orally at about 10.00 o'clock once daily at a dose of 1.0 mg/kg (for patients

younger than 3 months) or 1.5 mg/kg (for patients older than 3 months). For 7 days of hospitalization, the heart rates and blood pressures of the patients were examined 1, 3, and 6 h after propranolol use. Blood sugar levels were recorded 3, 7, 14, and 28 days after propranolol use. The side effects including diarrhea, mental irritability, and sleep disorder were monitored and conservatively treated during hospitalization. The period of propranolol use did not exceed 5 months. After hospital discharge, the patients visited our clinic monthly until the discontinuation of propranolol. The size, color, and hardness of the hemangioma, the blood routine, cardiac ultrasound, liver function, kidney function, and blood glucose tests, as well as the complications were recorded during each clinical visit.

Evaluation criteria

The evaluation criteria were as follows: level I, tumor size decrease by less than 25%; level II, tumor size decrease by 26% to 50%; level III, tumor size decrease by 51% to 75%; and level IV, tumor size decrease by 76% to 100%.

Results

After 3 months to 9 months of follow-up, the final results were as follows: level I, 0 patients; level II, 2 patients (9%); level III, 13 patients (59.1%); and level IV, 7 patients (31.9%). All heart rates decreased 1 h after propranolol use. Blood pressures slightly decreased in five patients. Two patients had moderate diarrhea that was relieved after conservative intervention. No severe adverse effect was observed. The hemangiomas were well controlled in all cases. The patient with lip damage recovered very well. Before hospitalization, this patient took a hormone (prednisolone acetate tablets, 5 mg/day) and antibiotics, which did not yield any clinical response. After 4 weeks of propranolol use, the ulcer on the lips healed. Four months later, the mucosa regenerated and the majority of the tumor disappeared, resulting in an overall improved deformity status.

Routine blood, cardiac ultrasound, liver function, kidney function, and blood glucose tests were recorded 3, 7, 14, and 28 days after propranolol use and monthly thereafter. The side effects are shown in Table 1.

Discussion

Hemangioma is a common benign tumor in infants that may disappear spontaneously. However, the development of hemangioma is unpredictable. Hemangiomas can grow very rapidly and even cause great damage to facial tissues, which may cause psychological stress to the family of affected patients. Thus, intervention therapy is necessary to accelerate the process of hemangioma treatment [1].

There are many methods for treating a hemangioma. A precise diagnosis as well as a proper and comprehensive treatment can achieve ideal outcomes and improve the quality of life of patients. The currently available treatments for hemangioma mainly include the injection of a sclerosing agent, surgery, freezing, laser treatment, hormone therapy, and imiquimod medication [2]. Most researchers have focused on comprehensive treatments such as medication, surgery and injection combination, as well as laser and drug applications. However, although novel treatment combinations have some advantages, the risk for complications or side effects also has to be taken into account [3].

Hormone therapy is the most important treatment for serious hemangioma. However, it may cause such adverse effects as high blood glucose level, osteoporosis, infection, and growth delay. In 2008, Léauté-Labrèze *et al.* used propranolol (2 mg/kg/day) to treat hypertrophic cardiomyopathy, and accidentally discovered that propranolol controls hemangioma in the nasal cavity very effectively [4]. The same result has been observed in nine other patients with facial hemangioma. Propranolol is a non-selective competitive inhibitor of the adrenergic β-blocker. It can inhibit β1 and β2 receptors in the heart as well as decreasing sympathetic nervous activity, blood catecholamine levels, myocardial contractility and force of contraction, and the heart rate. Consequently, propranolol is widely used for angina pectoris. The underlying mechanism of hemangioma possibly involves the β receptor antagonist, which can induce endothelial cell apoptosis, down-regulate the gene expression of VEGF and bFGF, and prevent vasoconstriction. Therefore, the novel finding of Léauté-Labrèze *et al.* on propranolol is considered a milestone in hemangioma treatment [5].

In the study of Léauté-Labrèze *et al.* (2008), a dose of 2 mg/kg to 2.5 mg/kg propranolol was used. In the current research, based on the study of Qing *et al.* [6] from the Shandong Linyi Tumor Hospital, age-dependent doses of 1.0 mg/kg to 1.5 mg/kg propranolol were administered and comparable results were obtained. The short-term results were excellent and the side effects were minimal.

Propranolol is a non-selective competitive antagonist of the adrenergic β-blocker and is usually used for arrhythmia. Common adverse effects of propranolol include bradycardia and hypotension. Diarrhea and hypoglycemia are less often reported. Propranolol has side effects on the nervous system, which may cause symptoms such as dizziness, sleepiness,

Table 1. Follow-up of adverse reactions in children after treatment [cases (%)]

Group	Heart rate slows down	Sleep change	Blood sugar decrease	Diarrhea	Thrombocyt openia	Blood pressure decrease
3 d	22 (100)	5 (22.7)	2 (9.1)	2 (9.1)	0	5 (22.7)
1 wk	15 (68.2)	2 (9.1)	0	2 (9.1)	0	5 (22.7)
2 wk	4 (18.2)	1 (4.5)	0	0	1 (4.5)	3 (13.6)
4 wk	1 (4.5)	0	0	0	0	0
2 month	0	0	0	0	0	0

or insomnia [7]. Thus, changes in blood pressure, heart rhythm, and blood glucose level need to be monitored carefully. In the current work, decreased heart rates were observed in all patients. The platelet count of one patient decreased. The condition of four patients improved. Four patients manifested temporary sleep disorder. Diarrhea occurred in two patients and resolved after appropriate treatment. There was no severe effect related to the heart, lung, liver, or kidney.

Buckmiller *et al.* [8] reported a higher incidence of withdrawal symptoms such as angina pectoris, and even worse, myocardial infarction. Thus, they strongly recommended gradual termination of propranolol use within 2 weeks. In the current study, the gradual termination period lasted for 4 months without recurrence of hemangioma within a short-term follow-up. Our results were consistent with the research of Menezes *et al.* [9] showing that propranolol is an attractive alternative to other treatments for hemangioma. Long-term result analyses, withdrawal symptom observations, and comparison studies are required in future research.

In conclusion, a small dose of propranolol for facial hemangioma in infants yields remarkable clinical results and rare side effects. Propranolol use is safe, simple, and effective for the treatment of hemangioma in infants.

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