Large Doses of Propranolol for the Treatment of Infantile Cephalic and Facial Hemangiomas: A Clinical Report of 38 Cases

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Objective: *Infantile cephalic and facial hemangiomas (IHs) are common and histologically benign vascular lesions in infants. This study investigates the clinical effect of using large doses of Propranolol for the treatment of IHs.* ***Study design:*** *This study contains 38 patients with IHs. All patients received general screening before the treatment. The dosage of Propranolol was increased over the course of treatment, which initiated three days. 1mg/kg on the first day, then increased by 0.5 mg/kg each day. The daily dose was divided into two smaller doses, administered every 12 hours, half an hour after feeding. Patients were hospitalized for six days. In the absence of side effects, treatment was continued at home and patients were reevaluated every month. Generally, one course of treatment lasted six months.* ***Results:*** *With the treatment, the entire group had significant improvement. 6 of them had excellent results. 22 had a good response with considerable lesion reduction. Side effects were limited during or after the treatment.* ***Conclusions:*** *Large doses of oral Propranolol to treat severe IHs patients had great clinical results. The treatment can shorten the natural course of IHs, making it a possible first choice for treatment.*

Key words: Infantile hemangiomas; Propranolol

INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign vascular lesions during infancy[1,2]. Traditionally, first-line treatment for severe infantile hemangiomas is applying large doses of adrenal corticosteroids. Second-line or third-line treatments involve interferon or vincristine as therapeutic agents. However, traditional treatments have various degrees of side effects or may cause secondary deformity, which limits their clinical efficacy. Because of this, looking for safe and effective therapeutic agents for the treatment of severe infantile hemangiomas becomes the goal of clinicians over the years.

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In 2008, Leaute-Labreze and colleagues discovered that using Propranolol could efficiently inhibit the growth of hemangiomas [3,4] . Ever since that discovery, no standard protocol has been developed for the treatment of Hemangiomas. Here, we try to present our experience with Propranolol treatment for cephalic and facial hemangiomas. (In all cases, parents' consent forms were obtained before the treatment.)

MATERIALS AND METHOD

Before Propranolol treatment was initiated, all patients had a comprehensive inquiry about their treatment history, a complete physical examination and a detailed assessment of lesions. These tests included Electrocardiogram (ECG), blood tests, liver function tests, cardia enzyme tests, troponin tests, and fasting blood glucose testing. Patients with following contraindications were excluded from the Propranolol treatement: asthma, allergic rhinitis, tracheobronchitis, pneumonia, bradycardia, cardiac arrhythmia, cardiogenic shock, cardiac failure, severe atrioventricular block, hypertension, hypotension, and liver failure.

All 38 patients were hospitalized before Propranolol was given to them. The dose is gradually increased. The first day of the starting drug dose is 1 mg / kg per day, the second day at a dose of 1.5 mg / kg per day, the third day at a dose of 2mg/kg per day. The daily dose was divided into two smaller doses, administered every 12 hours, half an hour after feeding. Blood glucose, blood pressure and heart rate were monitored within one hour after administration of Propranolol. We also kept patients' dynamic responses and possible side effects on record. Patients were discharged after three days treatment if no side effects were observed. The treatment was continued at home with the dose of 1mg/kg every 12 hours.

After discharge, all the patients were reevaluated after one week of treatment, and then once per month for six months. Monthly evaluations included measuring heart rate, blood pressure, liver and kidney function and cardiac enzymes. Doses were adjusted for increases in weight and relief of side effects. The outcomes of the treatment were based on the reduction of the volume of the hemangiomas, combined with improvement of color and texture. The primary efficacy measure was a quantitative assessment of the reduction in the volume of the hemangiomas. The results were rated using the following scales: 1, poor (0–25%); 2, fair (26–50%); 3, good (51–75%); and 4, excellent (76–100%) (Table 1). After the six month course of treatment, the therapy was tapered off at the end of the last month, and patients were continued on follow-up observation for one month. Based on the evaluation, decisions would be made regarding the need for a second course of treatment. The drug dose was gradually reduced at the end of the treatment. The dosage was reduced to 1.5 mg / kg on the first day (every 12 hours), then to 1 mg / kg on the second day (every 12hours), and finally withdrawn on the third day.

Table 1. Patients characteristics

Patient Characteristics	
Sex	
Female	**21**
Male	**17**
Age	**1month-13month**
Tumor Location	
Cheek	**15**
Neck	**5**
Eye	**18**
Tumor Size	**1.5cm x 1.0 cm – 6.0 x 7.0cm**
Result	**Poor 1** **Fair 9** **Good 22** **Excellent 6**

RESULTS

All patients showed therapeutic effects within 48 hours to 96 hours after the initiation of Propranolol treatment. The color of hemangiomas changed from bright red to dark purple, associated with reduced engorgement and release level of turgidity of the veins. The surface area of the hemangiomas had shrunk and the skin surface temperature had significantly decreased. The release changes above were more noticeable when the hemangiomas were more severe. There were not any cases in the study where hypoglycemia and significantly decreased heart rate occurred during the treatment.

After one month of treatment, the size and the scope of hemangiomas reduced in all 38 patients. The skin temperature of the lesion had significantly decreased, and the area the hemangiomas were softer, had reduced surface tension, and had a more natural skin texture.

Drug resistance was noted in one case three months after the initiation of Propranolol treatment. We changed the therapy, treating with a combination of prednisone and Propranolol. One patient, younger than three months, needed to stop treatment because of side effects. This patient's Creatine Kinase MB (CKMB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and Gamma-glutamyl transpeptidase (GGT) levels continued to rise. We followed up with this patient one month later and the lesion had improved.

In our study, 28 cases with HIs had significantly improved after six months of treatment. The hemangiomas nearly became flat, the lesion skin texture and skin temperature returned to normal. (Figures 1, 2, 3) No relapse was observed. Propranolol treatments lasted less than six months in four cases.

DISCUSSION

Infantile hemangiomas are the most common benign vascular lesions of infants and young children, with an incidence rate of up to 1%-10% [5]. IHs have special growth characterized by proliferation and regression. The duration of the rapid proliferative phase lasts about one year, and then moves into the period of regression for several years [6,7]. Most of them do not need special treatment since they are self-limiting. But infants with head and face hemangiomas could also develop ulcers. For instance, ulceration of the mouth or lips could impair patients' eating ability. The lesions may regress in the future if it is not treated in time, it could leave permanent disfiguring scars on patients' head and face. IHs may affect other vital organs. For example, it could cause amblyopia or strabismus by blocking the line of vision; IHs could also cause dyspnea by blocking the respiratory tract and become a severe life threatening issue.

Traditionally, the first-line therapy for IHs is applying large doses (2-3 mg/kg daily) of adrenal corticosteroids orally or by intralesional injection. The effective rate for this treatment is about 84%. The relapse rate after withdrawal of treatment is about 36%[8]. However, the side effects of this treatment cannot be ignored. About 1/3 of children will have Cushing-like facial appearance, emotional disorders, and/or gastrointestinal irritation. 35% of children will have growth retardation or stop gaining weight, and 12% of children may have permanent developmental defects [9,10].

Propranolol is a β- receptor blocking agent, mainly used in the treatment of various tachyarrhythmias, angina, hypertension, and pheochromocytoma. The mechanism of Propranolol treatment for infantile hemangiomas is still unclear; however, many cases have already shown the significant advantages and therapeutic effects of Propranolol on IHs. This treatment is safe, shows quick results, is non-invasive and does not cause any secondary deformity. In our case study, 38 patients showed significant results 24 hours after the treatment, with lighter color, thinner lesion skin, and decreased skin temperature. Based upon such remarkable effects, we agreed with the hypothesis of Dr. Léauté-Labrèze et al, that the mechanism of Propranolol treatment for infantile hemangiomas is through changing the hemodynamic of the lesions vessels, thereby reducing the local blood supply [3,4]. However, in our case study, 18 patients completed one full course of treatment with no IH relapse; one patient discontinued the treatment due to side effects, but the lesions continued to shrink. Those phenomena cannot be simply explained by the mechanism of hemodynamics.

Many early reports have demonstrated that vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are involved in the IHs development [3,4,11]. Recent detailed molecule studies had illustrated the mechanism of Propranolol treatment

could be related to endothelial cells, vascular tone, angiogenesis and apoptosis [12]. The early effects of Propranolol, such as color changes within 1-3 days, could related to vasoconstriction due to decreased release of nitric oxide; the intermediate effects on growth arrest are due to Propranolol's character on down-regulate levels of proangiogenic signals, (such as VEGF, bFGF); the long-term effects on lesion regression are because of Propranolol's induction of apoptosis in proliferating endothelial cells [13].

Because of Propranolol's drug safety advantage, it has been widely used in pediatric therapy. The maximum therapeutic dose could be up to 7mg/kg *per* day [14]. The common side effects of Propranolol treatment include bronchospasm, hypoglycemia, emotional disorders, bradycardia, and hypotension[15]. These adverse reactions did not occur in our 38 cases. According to the long-term follow-up data, Propranolol is less toxic for infant patients and there are no fatal side effects. Even though there have been adverse reactions in some cases, these adverse reactions would disappear immediately after the withdrawal of the medication. The treatment did not cause sequelae in our 38 cases either [16]. But, a detailed examination before treatment is still important; it could clarify those patients with potential risks with the Propranolol treatment. In order to detect side effects promptly and adjust drug doses after the patients had been discharged from the hospital, parents of patients were suggested to test their children's heart rate weekly, do liver and kidney function tests and cardiac enzyme tests monthly. Whether the long-term treatments with Propranolol have something to do with the drug accumulation effect or delayed side effects is still unclear. If side effects, such as hypotension or bradycardia occur in patients after they take the drug, the use of epinephrine for emergency treatment should be avoided, as the interaction of these two drugs could have disastrous consequences: causing patients' death or permanent disability[17-19]. There should be verbal and written information for patients' parents; it should also be placed in an obvious location on patients' discharge summaries as a warning to other doctors.

CONCLUSION

Large doses of oral Propranolol therapy for infantile hemangiomas have many advantages: it is well- tolerated in children, has rapid therapeutic effect, fewer side effects, and could considerably shorten the natural course of IHs. This could undoubtedly change the traditional treatment of severe infantile capillary hemangiomas and become the first choice therapy of IHs.

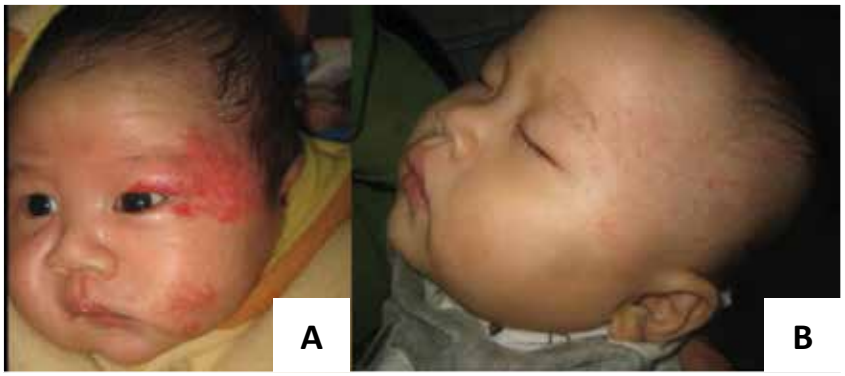

Figure 1
(A) Patient 5, , at two month of age, 1 day before treatment with Propranolol. (B) After 6 months of Propranolol treatment at 2mg/kg per day, Hemangiomas regressed completely.

Figure 2
(A) Patient 6, at four month of age, Hemangiomas over right upper eye lid, before the treatment with Propranolol. (B) After 6 months of Propranolol treatment at 2mg/kg per day, IHs continued to improve progressively.

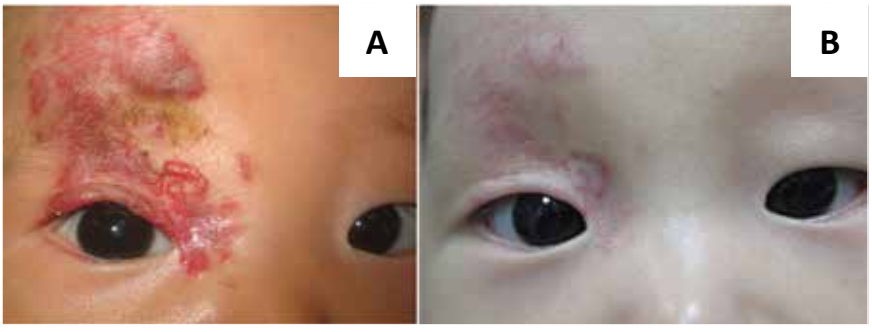

Figure 3
(A) Patient 7, at 3 month of age, large area of Hemangiomas over right upper eye lid and forehead, before treatment with Propranolol. (B) After 6 months of Propranolol treatment at 2mg/kg per day, IHs continued to improve progressively.

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