Low-dose propranolol for infantile hemangioma of the head and neck: Analysis of 23 consecutive patients

Wenhao Ren,1,2 Shaoming Li,1,2 Ling Gao,1,2 Shuo Huang,1 Linmei Zhang,1 Cui Qiang,1 Chunxi Liu3 and Keqian Zhi1,2

1Department of Oral and Maxillofacial Surgery, Affiliated Hospital of Qingdao University, Qingdao, Shandong,
2Department of Oral and Maxillofacial Surgery, Stomatolohy Hospital of Xi’an Jiaotong University College of Medicine, and 3Department of Stomatolohy, Xi’an No. 4 Hospital, Xi’an, Shaanxi, China

Abstract  Background: More and more infantile hemangiomas (IH) are being treated with propranolol, but the effectiveness, dosage, and treatment course are still in dispute. The aim of this observational study was to describe the therapeutic response, tolerance, and safety of low-dose propranolol in 23 children with IH of the head and neck.

Methods: Data were collected from the medical charts of patients treated with low-dose propranolol from December 2009 through November 2011. Oral dose was 1–1.5 mg/kg once per day. Blood pressure and heart rate were monitored during the first 24 h of treatment. In the absence of side-effects, treatment was continued at home and the child was re-evaluated every month.

Results: All patients had a good response, even if treated with corticosteroid previously. Color and growth changes within 1 week were noted. Treatment continued for a mean total duration of 6 months until the IH had totally disappeared or stabilized. There were no severe adverse reactions. Side-effects were limited and mild, including blood pressure decrease, somnolence, and nausea. No relapse was noted.

Conclusions: Low-dose propranolol appears to be effective and safe for IH, especially for those patients previously treated with corticosteroid and who had no response or severe side-effects.

Key words  corticosteroid, head and neck, infantile hemangioma, propranolol.

Infantile hemangioma (IH) is the most common benign tumor in infancy, affecting approximately 10% of infants. Of these, approximately 60% involve the head and neck.1 A total of 85–90% of IH resolve without intervention,2,3 but problematic hemangiomas are associated with significant functional and esthetic impairment. Complications such as bleeding, pain, and disability are also common.4 IH on the face could lead to permanent disfigurement. All of these have a psychological impact on both children and parents, therefore the wait-and-see policy should be re-evaluated and early treatment initiated if necessary.

The conventional approach in complicated cases is to use systemic corticosteroids. Rate of response ranges from 30% to 60%, with response appearing in the first 2 or 3 weeks of treatment.5,6 Side-effects are multiple. Most of them are transient and limited, such as cushingoid facies, insomnia, irritability, stunted growth, and gastrointestinal symptoms. Some side-effects, however, may become much more serious, such as hypertension and hypertrophic obstructive cardiomyopathy.

In 2008, Léauté-Labrèze et al. first reported the exceptional effectiveness of propranolol for IH.7 This has been confirmed by a growing number of reports. On the basis of the reported experiences, we treated IH with propranolol, including some children who were previously treated with corticosteroid and who had no response or had severe side-effects. The purpose of this study was to report our initial experience of oral propranolol treatment in a series of 23 children with IH of the head and neck.

Methods

A total of 23 consecutive pediatric patients (15 girls, eight boys) with IH were treated at Xi’an Jiaotong University Stomatolohy Hospital between November 2008 and July 2012 with propranolol. Eleven patients (seven girls, four boys) took propranolol only, while 12 patients (eight girls, four boys) used propranolol after 1–3 months’ ineffective treatment with corticosteroid (seven girls, two boys) or severe side-effects (one girl, two boys). Age ranged from 2 months to 12 years (average, 32 months). The study was approved by the Ethics Committee of the Xi’an Jiaotong University College of Medicine, and informed consent was obtained from each patient.

The IH locations included the eyelid (n = 3), ear (n = 1), nose (n = 2), lips (n = 5), cheek (n = 3), tongue (n = 5) and neck (n = 4). There were 17 patients with IH in the proliferative stage, and six patients with stabilized IH. None of the
infants had Kasabach–Merritt syndrome, which is caused by kaposiform hemangioendothelioma. A total of 19 patients had single IH, and four had multiple IH. Seven patients had cutaneous tumor, and seven had subcutaneous tumor. The remaining nine patients had both cutaneous and subcutaneous lesions. The side-effects of corticosteroid were hypertension (n = 1) and hypertrophic obstructive cardiomyopathy (n = 2). There were no complications of IH before propranolol.

Informed consent to treat with propranolol and document the disease response was received from all parents with infants and children participating in this study. Before treatment, a careful patient history and physical examination were performed. We excluded pneumonia, tracheobronchitis, cardiovascular disorders and other systemic diseases. For subcutaneous IH and mixed IH, color-coded duplex ultrasound or magnetic resonance imaging (MRI) was done to ascertain the location, size and depth of IH. For those treated with corticosteroid, this was stopped 1–3 months before propranolol treatment.

The patients were given oral propranolol once per day at 1–1.5 mg/kg/day.8 Treatment was initiated during a hospitalization of 7 days. We monitored blood pressure and heart rate every 2 h during the first 24 h and then three times per day of treatment. In the absence of side-effects, treatment was continued at home and the child was re-evaluated every month. Regular clinical examinations were performed (heart rate and blood pressure). Serial photographs were also obtained to evaluate the efficacy of propranolol. The course of treatment was at least 3 months, extended to 9–10 months in severe cases. Final results were determined based on improvement in volume, color, and texture of the IH. The results were classified as non-response (I), partial response (II), or total response (III).

Results

Data for the 23 children who received propranolol treatment are summarized in Tables 1, 2. We noted rapid therapeutic effects in all cases within 24 h after the initiation of propranolol treatment. The color and texture had changed macroscopically within 1 week, especially in the first 24 h. Cutaneous tumor had changed in color from bright red to purple, and subcutaneous tumor had changed in texture from hard to soft. After the dramatic initial response, IH continued to improve progressively with respect to both color and thickness. Seven children were treated with propranolol for 3 months, seven continued to 6 months, three for 7 months, five for 9 months, and one for 10 months. Propranolol was continued until the IH disappeared or were stabilized. On periodic (6–12 month) follow up, no relapse was observed in any of the patients. According to the results classification, six patients had grade III response (26.1%); 17, grade II (73.9%), and no patients had grade I (0.0%), indicating an effectiveness of 100% (Fig 1).

There were no severe or obvious adverse reactions noted during the treatment course, such as severe decreased heart rate, bronchospasm, or hypoglycemia. For two patients, mildly transient decreased heart rate and lower blood pressure were noted after taking the drug, but no clinical symptoms appeared. One patient had somnolence during the treatment course, and another one had mild nausea. All the side-effects were minor and required no intervention. No other side-effects were observed during treatment. When the treatment was finished, all of the symptoms had resolved and no obvious weight loss was noted compared with their peers.

Discussion

Propranolol is a non-selective beta-blocker primarily used for hypertension, supraventricular tachycardia, long Q-T syndrome, congestive heart failure, and thyrotoxicosis. It was first reported by Léauté-Labrèze et al. to cure IH.7 Later, use of propranolol to treat IH became more common, but the underlying mechanism of the curative effect is still not clear. A number of hypotheses have been suggested, including that propranolol can induce vasoconstriction, inhibition of angiogenesis, or induce vascular endothelial cell apoptosis, or all three mechanisms combined, to lighten the color, soften the texture, and reduce the IH lesion.9

There is still no consensus on propranolol dose. Following the Léauté-Labrèze et al. report, similar results of propranolol treatment have been reported at an empirical dosage of 2–3 mg/kg/day.10 Holmes et al. treated 31 cases of rapidly proliferating IH with oral propranolol; the initial dose was 0.5 mg/kg, with close monitoring; if the vital signs were stable, dose was increased up to a maximum of 3 mg/kg (t.i.d.).11 Rapid halt in hemangiomma growth was seen in all of the patients, and significant regression in 87%. The treatment had no severe complications. Propranolol was also found to reduce tumor stem cells and placental endothelial cell proliferation in vitro in a dose-dependent manner.12,13 This suggests that clinical therapeutic effect may vary with propranolol dose.

Although the use of beta-blockers in pediatric patients is extensive, the safety profile and side-effects with regard to this new indication, have not been established. The side-effects of propranolol are well known; these include hypotension and transient bradycardia. Propranolol can also decrease lipolysis, glycogenolysis, and gluconeogenesis, predisposing to hypoglycemia, which is particularly relevant in very young infants with potential adverse neurologic sequelae.14,15 Consequently, divided dosing and non-precipitous dose escalation may improve the margin of safety and facilitate use of minimum dosage to achieve the desired effect.16 Tan et al. prescribed oral propranolol 1.5–2.0 mg/kg/day to 15 IH patients, and recorded the size, texture, color changes over 3 months.17 They noted that a subcardiovascular dose 1.5–2.0 mg/kg/day in divided doses with gradual increase was effective and safe.18 The drug sensitivity, however, appears to vary with ethnicity. Zhou et al. noted that Chinese patients had a higher propranolol sensitivity than US patients,19 therefore this needs to be taken into account when determining the safety range and dose. In the present series, we used low-dose propranolol (1–1.5 mg/kg once per day) for IH, and noted a difference within 24 h: the color became lighter, and the texture became soft. All of the children had curative effect. It is similar to
Table 1  Clinical characteristics: propranolol treatment in patients treated previously with corticosteroid (n = 12)

<table>
<thead>
<tr>
<th>Patient ID no.</th>
<th>Gender</th>
<th>Location of IH</th>
<th>Age at initiation of corticosteroid (months)</th>
<th>Corticosteroid dosage (mg/kg/day)</th>
<th>Age at end of corticosteroid treatment (months)</th>
<th>Complications</th>
<th>Reason for cessation</th>
<th>Age at initiation of propranolol (months)</th>
<th>Propranolol dosage (mg/kg/day)</th>
<th>Treatment duration (months)</th>
<th>Efficiency†</th>
<th>Side-effects</th>
<th>Follow up (months)</th>
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<td>M</td>
<td>Lips</td>
<td>2</td>
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<td>No response</td>
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<td>3</td>
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IH, infantile hemangioma. †I, non-response; II, partial response; III, total response.
On periodic (6–12 months) follow up, no relapse was observed in any of the patients. There were no severe or obvious adverse reactions noted during treatment, indicating that low-dose propranolol 1.5–2.0 mg/kg/day is effective and safe in Chinese patients.

The course of treatment was at least 3 months, extended to 9–10 months in severe cases. All of the present patients had good response, but the length of treatment was not well-defined: it was continued according to lesion response. Sans et al. used propranolol for 2–10 months until the lesions were nearly flat, and again for lesion recurrence.10 Buckmiller et al. carried out treatment according to lesion phase.20 In patients with proliferating lesions, treatment proceeded from the proliferative phase to the theoretic conclusion of hemangioma growth at 12 months of age. Patients in the involution phase remained on propranolol for at least 6 months and until resolution or observation of benefit ceased.20 In order to avoid hemangioma rebound growth, treatment time should cover most of the proliferation phrase, if not the whole proliferative phase. There is no “one size fits all” approach to the management of IH. The location and size of IH, and age and general condition of the patient, all have a dramatic impact on treatment choice.

Some of the children were treated previously with corticosteroid, with unsatisfactory results. After corticosteroid was stopped for several months, they were then given low-dose propranolol, and all of them had good response. This was also observed in other studies.21,22 The critical period between corticosteroid and propranolol treatment, however, has not been clarified. We considered that it was safe to begin propranolol 1–3 months after corticosteroid cessation.

During the follow-up period (3–7 months after withdrawal of oral propranolol), no recurrence was noted in any of the children. This may be because the proliferative phase was included in the duration of treatment, or the lesion were small or not too deep. Bagazgoitia et al. noted a recurrence rate of 19%.23 They suggested that this was due to the fact that the treatment was withdrawn before the proliferative phase of the IH was finished, or because the lesions were deep or the overall treatment time was short. They also noted that recurrence was often seen in patients treated with corticosteroids, and that this may have been due to corticosteroid and propranolol dose differences, but that re-treatment with propranolol was satisfactory.23 In the present study, there were no recurrences

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<th>Propranolol dosage (mg/kg/day)</th>
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IH, infantile hemangioma. †I, non-response; II, partial response; III, total response.

Fig. 1 Hemangioma on the lower lip of a girl (a) at the age of 6 months, before starting propranolol treatment, and (b) after 6 months of low-dose propranolol.

other studies.10,18,20 On periodic (6–12 months) follow up, no relapse was observed in any of the patients. There were no severe or obvious adverse reactions noted during treatment,
in the children treated previously with corticosteroid. The reason for this is not clear, and it may be that there is no relationship between recurrence and corticosteroid or propranolol treatment.

In conclusion, 2 mg/kg/day has been reported as effective in some centers.24 A higher dose of 3 mg/kg/day has been used at Alder Hey Children’s Hospital, Liverpool.12 In the present series, low-dose oral propranolol (1–1.5 mg/kg/day) for IH of the head and neck was effective and safe, and even produced good results in corticosteroid-treated hemangiomas. The side-effects were limited and mild, and none of the present 23 children had severe side-effects. After 3–10 months’ treatment, which would cover the proliferation phase, the entire lesion became flat, and the rate of effectiveness in the present study was 100%. Before the wide application of propranolol treatment for IH, however, large-scale prospective, randomized controlled clinical trials are needed, to determine the optimal dosage and regimen. Low-dose propranolol is recommended for the first-line treatment of IH.

Disclosure
The authors declare no conflict of interest.

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Authors’ contributions
K.Z. and W.R. contributed to the conception and design of this study, critically reviewed the manuscript and supervised the whole study process; S.L. and S.H. performed the clinic treatment. L.Z. and C.Q. collected and analyzed data. W.R. and L.G. wrote the manuscript; C.L. gave technical support. All authors read and approved the final manuscript.

References

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