Therapeutic efficacy of propranolol for infantile hemangiomas

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Objectives. This was a retrospective study to analyze the clinical therapeutic efficacy of propranolol in patients with infantile hemangioma (IH).

Study Design. Patients with IH were treated with propranolol (2−4.5 mg/kg/day). Those patients who did not have a good response to propranolol underwent intertumoral injection of pingyangmycin or surgery.

Results. Relative therapeutic responses to propranolol among the 51 patients were as follows: excellent in 31.37% (16 of 51); good in 39.21% (20 of 51); poor in 23.53% (12 of 51); and nonresponsive in 3.92% (3 of 51). Of the 15 patients who had a poor or no response to propranolol, 2 received injected pingyangmycin, and 3 underwent surgical resection; the remaining 10 patients received no further therapy. The relevance of many clinical factors (sex, age, dose, depth, and diameter) to the efficacy of propranolol was assessed with univariate and multivariate ordinal logistic regression models, which indicated that young age (≤5 months) was significantly associated with better efficacy ($P < .05$). The most common side effect was diarrhea (52.2%). There was no significant association between dose of propranolol and side effects ($P = .12$).

Conclusions. The effect of oral propranolol was better in younger patients. A 3- to 4.5-mg/kg/day dose may not be more effective than the conventional recommended dose of 2 to 3 mg/kg/day. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:132−138)

Infantile hemangiomas (IHs) are congenital benign tumors originating from vascular endothelial cells. The incidence of IHs among infants is around 3% to 10%;[1-3] 33% to 60% of IHs occur in the head and neck region,[1,4] thus affecting the child's appearance and possibly quality of life. Twenty-four percent of IHs are present at birth, and the majority of cases occur before age 5 months.[1,5] IH usually undergo a proliferative phase in the first year and then gradually enter an involution phase.[6] Because 50%, 70%, and 90% of the lesions regress by ages 5, 7, and 9 years,[4] respectively, most clinicians tend to take a wait-and-observe approach (without any specific treatment). However, untreated IHs may be associated with ulceration, bleeding, infections, and even potentially life-threatening consequences.[4,7] In addition, after the untreated tumor shrinks, residual skin degeneration, manifesting as pigmentation, scars, or skin relaxation,[8] seriously affects the appearance of the skin. Therefore, interventional treatment may be more appropriate for IHs.

According to the International Society for the Study of Vascular Anomalies Guidelines (2018 edition),[9] treatment of IHs is mainly based on local and systemic medications that inhibit vascular endothelial cell proliferation, promote tumor regression, and reduce tumor residues. In cases of high-risk and moderate-risk IHs, prompt treatment is recommended.

The first-line treatment for IHs is propranolol, a nonselective β-adrenergic receptor blocker.[10-12] Propranolol is a highly effective and safe medication for shrinking hemangiomas.[11,13,14] According to a survey of 31 hospitals in China where propranolol was administered to patients with IHs, the dose ranged from 1 to 3 mg/kg/day, and the duration of therapy ranged from 1 to 24 months.[15] Some centers hospitalized all children during treatment, but most infants were treated in an outpatient setting. Some hospitals administered a single treatment, whereas others used a comprehensive sequence of treatments. However, because not all patients respond well to propranolol, it is important to carefully consider the choice of treatment, dose escalation, and safety monitoring. This study retrospectively analyzed the clinical therapeutic efficacy of propranolol in patients with IHs.

MATERIAL AND METHODS

Patients

Fifty-one children with IHs treated in Guangzhou Women and Children's Medical Center in Guangzhou, China, from January 2015 to December 2017, were enrolled in this study. The recruitment criteria excluded patients with any of the following conditions: history of IH treatment, tumors with clear boundaries (these patients underwent surgery), cardiovascular disorders, and other congenital malformations. All the patients were of Han Chinese

Statement of Clinical Relevance

Propranolol is still the first candidate for the treatment of infantile hemangiomas. Early intervention is associated with better efficacy. The conventional dose of propranolol (2−3 mg/kg/day) is suitable for clinical use. Gastrointestinal reactions were the most frequent side effects observed.

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ethnicity. The size, extent, and depth of the IHs were determined by using ultrasonography. Patients with congenital malformations were identified by using cardiac ultrasonography and electrocardiography and were excluded from the study. General information, including patient sex and age, tumor diameter and site, treatment method, medication dose, time of treatment, response rate, side effects, and duration of follow-up were recorded both before and after treatment (Table I).

Ethics

This project was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. Propranolol dosage (up to 4.5 mg/kg/day, which was within the indicated range for off-label use of the medicine) and duration (up to age 15 months) were determined after discussion with the regulatory agencies.

Classification of IHs

On the basis of anatomic distribution, IH was divided into 3 groups: superficial IH, located above the dermal papillae with red plaques; subcutaneous IH, located under subcutaneous or mucosal tissue, usually without any skin alteration; and mixed IH (superficial and subcutaneous IHs).

Treatment method

Fifty-one children with IHs were treated preliminarily with oral propranolol (Jiangsu Ya-Bang-Ai-Pu-Sen Pharmaceutical, Yancheng, Jiangsu, China) and hospitalized for the first 4 to 5 days to facilitate adjustments to the dose. The patients who had poor or nonresponsive results received intertumoral injections of pingyangmycin or other treatment. Patients whose lesions had clear boundaries received surgical resection, and others with lesions that had no clear boundaries were administered pingyangmycin.

For those receiving propranolol treatment, a 0.5 mg/kg dose was given every 8 hours on the first day (a total of 1.5 mg/kg/day). The propranolol dosage was then gradually increased to 0.75, to 1.0, to 1.25, and to a maximum of 1.5 mg/kg if the patient had no side effects. The final maximum target dosage was 1.5 mg/kg (4.5 mg/kg/day). During treatment, heart rate was monitored and recorded. If heart rate was less than 100 beats per minute or if there were other complications, such as diarrhea, anorexia, or nausea, then the dosage was reduced by 0.25 mg/kg (total reduced

Table I. Clinical characteristics and therapeutic efficacy to propranolol among the children with infantile hemangiomas (IHs)

Characteristics	*Patients (n = 51)*	*Excellent (n = 16)*	*Good (n = 20)*	*Poor (n = 12)*	*Nonresponsive (n = 3)*
Age at IH occurrence (months) (%)					
≤5	49	16 (32.7)	18 (36.7)	8 (16.3)	1 (2)
>5	3	0	2 (66.7)	0	1 (33.3)
Age at treatment (months) (%)					
≤5	35	14 (40)	14 (40)	6 (17.1)	1 (2.9)
>5	16	2 (12.5)	6 (37.5)	6 (37.5)	2 (12.5)
Gender (%)					
Male	19	8 (42.1)	6 (31.6)	4 (21.1)	1 (5.3)
Female	32	8 (25)	14 (43.8)	8 (25)	2 (6.3)
Dose of propranolol (mg/kg/day) (%)					
<2	2	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)
2−3	12	2 (16.7)	8 (66.7)	2 (16.7)	0 (0.0)
3−4.5	37	14 (37.8)	12 (32.4)	8 (21.6)	3 (8.1)
Location of IHs (%)					
Parotid gland	24	6 (25)	10 (41.7)	7 (29.2)	1 (4.2)
Lips	17	6 (35.3)	8 (47.1)	1 (5.9)	2 (11.8)
Buccal	5	2 (40)	2 (40)	1 (20)	0 (0.0)
Suborbital	2	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Linguae	1	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
Neck	1	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
Chin	1	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
Depth (%)					
Superficial	20	8 (40)	8 (40)	2 (10)	2 (10)
Subcutaneous	27	6 (22.2)	12 (44.4)	8 (29.6)	1 (3.7)
Mixed	4	2 (50)	0 (0.0)	2 (50)	0 (0.0)
Diameter of lesion (cm), n (%)					
≤2	23	10 (43.5)	8 (34.8)	3 (13.0)	2 (8.7)
2−4	16	4 (25)	4 (25)	8 (50)	0 (0.0)
>4	12	2 (16.7)	8 (66.7)	1 (8.3)	1 (8.3)

dose: 0.75 mg/kg/d) and the patient was monitored for 1 day. If the patient was stable and the side effects ceased, then the dosage was increased by 0.25 mg/kg to the maximum target dosage of 1.5 mg/kg (4.5 mg/kg/day). Once the dose response became stable, the patient was treated at home and followed up monthly. The majority (72.5%) of the study patients took 3 to 4.5 mg/kg/day; 23.5% took 2 to 3 mg/kg/day; and 3.9% took less than 2 mg/kg/day.

To monitor and evaluate the therapeutic efficacy of propranolol, we took photographs and conducted ultrasound examinations of the lesions at 1, 3, and 6 months until age 15 months. Once the size of the IH became reduced, the dosage of propranolol was gradually reduced until the medication was completely withdrawn.

Surgical resection

Patients whose lesions had already completely shrunken after treatment with propranolol but had remaining appearance defects with a clear boundary and a diameter of less than 1.5 cm then received surgical resection. All operations were performed under cover of general anesthesia. The biggest advantage of surgical resection was that it was a one-time treatment resulting in complete cure with a good prognosis. However, to prevent tumor recurrence, strict selection of patients on the basis of clear indications and a 1-year follow-up visit were necessary.

Evaluation of response to treatment

Therapeutic response was evaluated by using the following grades: excellent, good, poor, and nonresponsive. If a lesion had totally disappeared, as clinically observed, or if the lesion's original size had become reduced by greater than 75%, as seen on ultrasonography, then the response was considered "excellent". Reduction in size by greater than 50% of the original volume of the lesion was considered a "good" response. Reduction by less than 50% of the original size was considered a "poor" response, and a 0% change was considered "nonresponsive."[15,16]

Statistical analysis

Univariate and multivariate ordinal logistic regression models were applied to evaluate the potential factors associated with the therapeutic efficacy of propranolol in IHs. The χ^2 test was used to assess the associations between doses of propranolol and side effects, as well as between treatment and efficacy. A P value less than .05 was considered statistically significant. All analyses were performed by using SPSS version 21.0 software (SPSS Inc., Chicago, IL).

RESULTS

General data

The median age of the 51 patients with IHs was 4 months (range 1−14 months). Nineteen patients (37.25%) were males and 32 (67.75%) were females. Age at initial occurrence of IH ranged from 1 month to 7 months. Mean age at first visit to a specialist was 4 months; 96.08% (49 of 51) of lesions occurred before age 5 months (see Table I). A good response to propranolol treatment was usually achieved in the first week (Figure 1); 31.37% (16 of 51) of the patients had an excellent result; 39.21% (20 of 51) had a good result; 23.53% (12 of 51) had a poor result; and 3.92% (3 of 51) were nonresponsive to therapy, respectively (see Table I). Because of either nonresponsiveness or poor efficacy of propranolol treatment, 3 patients received further treatment with pingyangmycin (Figure 2), and 2 patients underwent surgical resections (Figure 3). Other children with IHs (10 cases) who had poor or no response to propranolol treatment did not receive any further treatment. Most IHs were located in the parotid gland (47.1%) (Figure 4) and lips (33.3%) (see Figure 1); 52.9% were subcutaneous; and 45.1% had a tumor diameter less than 2 cm (45.1%) (see Table I).

Analysis of relevance factors regarding the therapeutic efficacy of propranolol

Relevance factors regarding the therapeutic efficacy of propranolol and other factors were analyzed by using univariate ordinal logistic regression analyses, which indicated that age 5 months or less was significantly associated with better efficacy (Table II). No association was found between sex, dose of propranolol, tumor depth, or tumor size and the therapeutic efficacy of propranolol. The variates (factors) with a P value less than .15 in the univariate models were then analyzed with a multivariate model, which indicated that age 5 months or less (odds ratio = 3.65; 95% confidence interval = 1.11−12.04; P = .03) was still significantly associated with better treatment efficacy (see Table II).

Adverse reactions to propranolol

Twenty-three of the 51 patients who received propranolol treatment experienced side effects. The most common

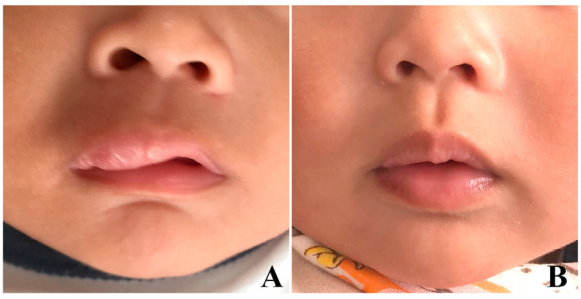

Fig. 1. Propranolol treatment given to an infant with infantile hemangioma (IH). **A**, A 2-month-old male infant with IH on the upper lip was treated with propranolol (4.5 mg/kg/day). **B**, Same child after 9 months of treatment with oral propranolol; the lesion has almost completely shrunken.

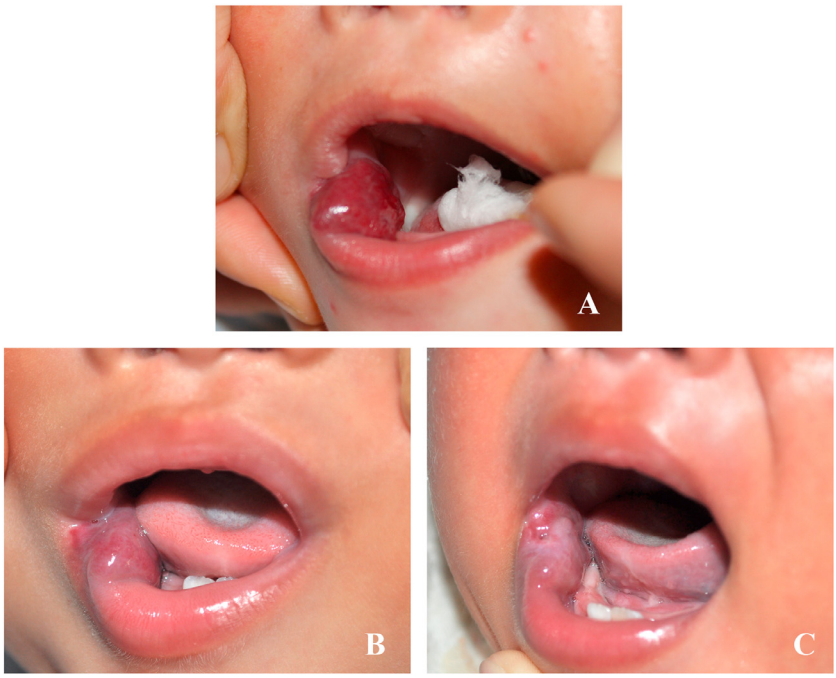

Fig. 2. Pingyangmycin treatment given to an infant with infantile hemangiomas (IHs) on the buccal cavity and lower lip. **A**, A 5-month-old male infant before treatment; an IH is located on the right side of the buccal cavity plus lower lip. **B**, The same patient's appearance at the 2-month follow-up visit after receiving oral propranolol. **C**, Because the propranolol treatment had poor efficacy, the infant then received an intertumoral injection with pingyangmycin (1.6 mg), which caused the lesion to shrink to a relatively smaller size after 1 month.

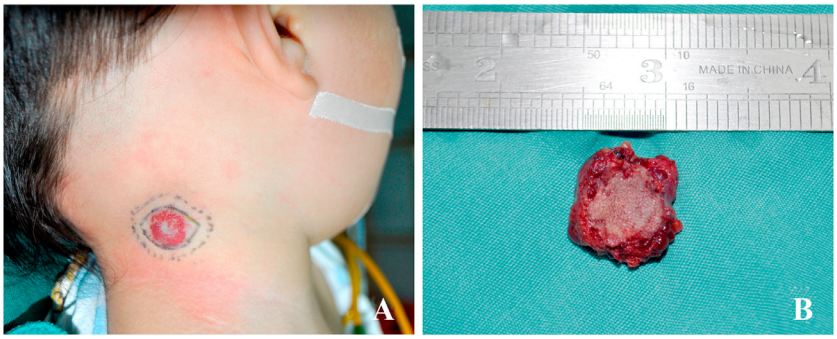

Fig. 3. Surgical resection in an infant with infantile hemangioma (IH) with no response to propranolol treatment. **A**, An 11-month-old female infant (with IH on the neck) who had a poor response to propranolol. **B**, The resected tumor. Tumor size was significantly reduced, but complete resolution was not achieved.

side effect was diarrhea (52.2%), followed by pulmonary symptoms (bronchitis and cough) (21.7%), decreased heart rate (17.4%), constipation (4.3%), and vomiting (4.3%). There was no significant association between dose of propranolol and side effects ($P = .12$) (Table III).

DISCUSSION

This study included 51 patients with IHs treated with different dosages of propranolol (2−4.5 mg/kg/day) for an average of 14 months. The results indicated that propranolol dose, tumor location, tumor depth, and tumor size did not affect the rate of therapeutic efficiency. However, therapeutic efficacy significantly increased in patients with IHs age 5 months or less.

Most IHs do not require specific treatment because they are small and self-limiting. For IHs with bleeding, infection, or affected vital structures (including eye, airway tract, and nerve system), a specific treatment, such as medication or surgery, is necessary.[17] Traditional medical treatments, including glucocorticoids, interferon-α, or vincristine, have many side effects.[18-20]

Propranolol is a nonselective β-adrenergic receptor inhibitor, which used in the treatment of patients with hypertension or other cardiac disorders and is recognized as being safe for use in infants.[21] In 2008,

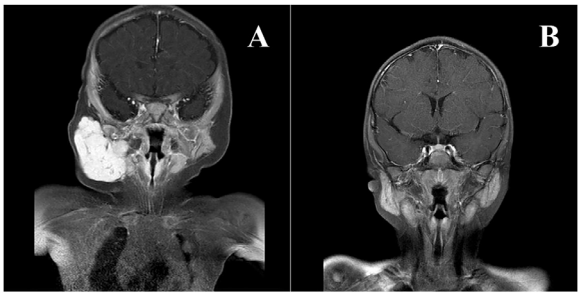

Fig. 4. An infant with infantile hemangioma (IH) at the parotid gland. **A**, 1-month-old female infant with a hemangioma located on the left parotid gland before treatment with oral propranolol (4.5 mg/kg/day) for 15 months. **B**, The lesion had almost completely shrunken at the follow-up visit at age 3 years. If the lesion did not respond well to propranolol after 2 months of observation or if the lesion had already obviously shrunken but not completely resolved after a long period, then the propranolol therapy was replaced by intertumoral injection of pingyangmycin (Ha'erbin Lai-Bo-Tong Pharmaceutical, Ha'erbin, China). All injections were performed under cover of general anesthesia in an operating room and the patients were observed for 30 minutes after the injection. Each injection dosage was maintained at 0.1 to 0.2 mg/kg until the surface of the lesion became pale. The maximum dose was no greater than 4 mg per injection, and the entire treatment was 2 to 3 injections for each patient. An interval of 4 weeks was applied between the 2 injections (to minimize the risk of pulmonary fibrosis). All potential adverse reactions and prognoses were recorded during the follow-up visits.

Léaute-Labreze et al.[22] first introduced propranolol treatment in an infant with obstructive hypertrophic myocardiopathy and reported good efficacy. Thereafter, propranolol was extensively administered in the treatment of IHs.[23-25] Inhibition of tumor cells, control of endothelial proliferation, and vasoconstriction are believed to be the therapeutic mechanisms involved in IH treatment.[25] However, not all patients respond well to propranolol. On the basis of the findings from a study by Östman-Smith et al., who found that high-dose propranolol (>4.5 mg/kg/day) yields good results (5-year survival rate for high-risk infants improved from 54% to 93%)[26] and is safe for treating pediatric hypertrophic cardiomyopathies, we used high-dose propranolol (4.5 mg/kg/day) to treat the patients with IHs in this study.

Our data showed no difference in therapeutic efficacy between the 2 mg/kg/day and 4.5/kg/day dosages in infants with IHs who received an average of 14 months of treatment. Therefore, the conventional recommended dose of propranolol (2−3 mg/kg/day) remains suitable for clinical use.

To explore the relationship between the therapeutic efficacy of propranolol and clinical characteristics in detail, we investigated whether patient age and sex, tumor location, tumor size, and tumor depth influence the therapeutic effect of propranolol in infants with IHs. Interestingly, age less than 5 months was the only characteristic that significantly increased the therapeutic efficacy rate ($P < .05$), according to our observations. This finding is very similar to those reported by Kim et al., who found excellent therapeutic efficacy for propranolol in infants age less than 6 months.[23] Kim et al. also stated that the incidence of IH was higher in female infants (20 of 23 infants [86.97%]). Our data support this finding, even though the sex rate among female infants with IHs was

Table II. Ordinal logistic regression analysis of the factors associated with therapeutic efficacy of propranolol in the children with infantile hemangioma (IH)

Characteristics	*Crude OR (95% CI)*	*P value*	*Adjusted OR (95% CI)*	*P value*
Age at treatment (months)				
≤5	4.27 (1.35−13.53)	.01	3.65 (1.11−12.04)	.03
>5	Reference	–	Reference	–
Dose of propranolol (mg/kg/day)				
<2	0.13 (0.01−1.93)	.14	0.29 (0.02−4.77)	.39
2−3	0.86 (0.26−2.83)	.80	0.81 (0.24−2.73)	.74
3−4.5	Reference	–	Reference	–
Gender*				
Male	1.71 (0.60−4.90)	.32	–	–
Female	Reference	–	–	–
Depth*				
Superficial	1.36 (0.19−9.77)	.76	–	–
Subcutaneous	0.71 (0.10−4.87)	.73	–	–
Mixed	Reference	–	–	–
Diameter (cm)*				
≤2	1.74 (0.48−6.35)	.40	–	–
2−4	0.63 (0.16−2.50)	.51	–	–
>4	Reference	–	–	–

*These variates were not included in the multivariate ordinal logistic regression analysis.*CI,* confidence interval; *OR,* odds ratio.

Table III. Side effects of propranolol treatment in the children with infantile hemangioma (IH) (N = 23)

Side effects	*N*	*Dose of propranolol (mg/kg/day)*			*P value*
		<2 (n = 1)	*2−3 (n = 7)*	*3−4.5 (n = 15)*	
Diarrhea, n (%)	12	0 (0.0)	3 (25)	9 (75)	.12
Decreased heart rate, n (%)	4	1 (25)	3 (75)	0 (0.0)	
Pulmonary symptoms (bronchitis, cough), n (%)	5	0 (0.0)	1 (20)	4 (80)	
Vomiting, n (%)	1	0 (0.0)	0 (0.0)	1 (100)	
Constipation, n (%)	1	0 (0.0)	0 (0.0)	1 (100)	

62.75% (32 of 51) in our investigation. However, unlike Kim et al.'s result, in our study, sex distribution did not influence the therapeutic efficacy of propranolol. Their data showed that better efficacy was seen in male infants than in female infants. However, only 2 male infants were observed in Kim et al.'s study. On this point, our data may be more robust because our study included a higher number of male infants (n = 19). Kim et al. also found that propranolol was more effective in infants with single-site IHs than in those with multisite IHs. Our study, however, did not focus on this point. Our results also indicate that the size, depth, and location of IHs did not affect the therapeutic efficacy of propranolol.

A total of 23 study patients with IHs treated with propranolol experienced side effects. Our data also indicated that side effects associated with propranolol may not be dose dependent. Gastrointestinal reactions (52.2%) were the most frequent side effects of oral propranolol, according to our observations, which is similar but higher than the rate reported by Wang et al.,[27] who recorded 22.6% of their subjects with gastrointestinal reactions. Our data included pulmonary symptoms (21.7%) and decreased heart rate (17.4%) as adverse reactions. Wang et al. reported hypoglycemia, bronchospasm, bradycardia, and hypotension as other adverse reactions. Some authors did not report bradycardia as a side effect in the treatment of IH with doses up to 4 mg/kg/day.[28] Decrease in diastolic blood pressure was noted in 1 patient in our study. In our clinical observations, we also found that a decrease in heart rate occurred within 24 hours after taking a propranolol dose but was quickly restored after temporary withdrawal of the medication. Love et al. reported that hypoglycemia may be the most serious complication in children and that hypoglycemia associated with propranolol may not be dose dependent[29]; however, we did not find these adverse reactions in our study patients. However, it did remind us that we need to closely monitor patients with IH taking propranolol. It is hard to recruit healthy infants as normal controls, and this was a limitation of our study.

CONCLUSIONS

Our study showed that propranolol is still the first-choice treatment for IHs. Early intervention with propranolol for IHs was associated with better efficacy. The conventional recommended dose of propranolol (2−3 mg/kg/day) was found to be still suitable for clinical use, as indicated by our data. Gastrointestinal reactions were the more frequent side effects of oral propranolol. Although side effects may not often be associated with propranolol treatment, patients still need to be closely monitored.

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