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ORIGINAL ARTICLE

Treatment With Propranolol for Infantile Hemangioma in 13 Taiwanese Newborns and Young Infants

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Background: Hemangioma in infants has a benign self-limited course, but the 10% of cases with complications need further treatment. Successful treatment with propranolol in western countries has been reported over the past few years. We evaluated the efficacy of propranolol for treating infantile hemangioma in Taiwanese newborns and young infants.
Methods: Patients below 1 year of age treated with propanolol between November 2009 and March 2011 were enrolled. Demographic data, clinical features, imaging findings, treatment regimens of propranolol, and outcome were investigated.
Results: Thirteen patients were treated with propranolol at a dose of 2–3 mg/kg/day. Seven (53.8%) patients had solitary hemangioma and six had multiple ones. The indications for treatment were risk of local event in nine patients, functional risk in four, local complication in one, and life-threatening complication in one. The median age for starting propranolol was 4 months (range: 1–11 months). Responses to propranolol, such as decolorization, regression in tumor size, or improvement of hemangioma-associated complications were observed in all patients within 1–2 weeks after treatment. Propranolol-associated adverse effects occurred in two patients. One infant had occasional tachypnea, and the other had occasional pale-looking appearance. The symptoms resolved after dosage tapering.

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Conclusion: Propranolol may be a promising therapeutic modality for infantile hemangioma. Therapeutic strategies are needed to evaluate the optimal treatment protocol and long-term adverse effects.

1. Introduction

Infantile hemangioma (IH) is the most common benign vascular tumor of infancy, and its onset usually begins during the neonatal period. The incidence is estimated at 4–5%[1] and is higher in girls and premature infants.[2] IH classically manifests as a rapid proliferation phase in the first year after birth, followed by a spontaneous involution phase that lasts for several years.[3] It usually has a self-limited course with minimal sequelae, and the mainstay of therapy is conservative observation. However, even transient cosmetic disfigurement during the long involution phase frequently induces psychological stress in the affected children and their parents.[4] Moreover, approximately 10% of IH cases need further intervention due to local or life-threatening complications.[5,6] Some IH can cause local complications such as ulceration, pain, bleeding, scarring, secondary infection, and permanent disfigurement. Others may cause significant functional impairment, vital organ compromise, or life-threatening complications. For these complicated IH cases, systemic corticosteroids are generally considered to be the first-line of pharmacological therapy. Although there is a 78–89% response rate,[7] a high recurrence rate of up to 36% and adverse effects limit its use.[8] Alternative therapeutic options, such as vincristine,[9] interferon α,[6] and cyclophosphamide,[10] are used for steroid-refractory and critical patients, but their potential toxicities are a major concern.

The dramatic response to propranolol in the treatment of IH was first described by Léauté-Labrèze et al[11] in 2008, and a number of successful cases have been reported worldwide.[12] To the best of our knowledge, the efficacy of propranolol in Taiwanese hemangioma patients has not been evaluated. We investigated the therapeutic effect of propranolol in 13 Taiwanese newborns and young infants with IH at a tertiary pediatric medical center.

2. Patients and Methods

In this retrospective observational study, we reviewed data from Taiwanese patients, aged <1 year, diagnosed with IH and treated with propranolol between November 2009 and March 2011. Demographic data, clinical features, results of imaging for IH, propranolol dosage, treatment outcome, and complications were collected from medical charts.

Before initiation of propranolol treatment, comprehensive history taking, vital signs, and physical examinations were performed in all patients to confirm that there was no associated medical history or contraindications for propranolol, such as past cardiopulmonary disease, hyperactive airway disease, asthma, sinus bradycardia, secondary or third-degree heart block, cardiogenic shock, and allergy to propranolol. Treatment regimens and potential adverse effects of propranolol were explained to the families of the patients. Informed consent for propranolol treatment and use of the patients' photographs was obtained from their parents.

The patients were first treated with 0.5–1 mg/kg/day propranolol divided into two or three doses, and weekly follow-up at the outpatient clinic was arranged. At each clinic visit, baseline heart rate was recorded and the dosage of propranolol was doubled to a maximum of 2–3 mg/kg/day as tolerated. Parental education included: (1) observation for tachypnea, wheezing, symptoms and signs of hypoglycemia, and signs of poor perfusion; (2) advice on taking the drugs with or after a meal to avoid hypoglycemia; (3) monitoring of heart rate and withholding drugs in the event of bradycardia, defined as a heart rate <100 beats/minute,[13] and signs of poor perfusion; (4) withholding drugs temporarily with acute illness; and (5) making a note of any possible propranolol-associated discomfort. During the stable course of treatment, monthly outpatient clinic follow-up was arranged. When IH had regressed and flattened sufficiently, propranolol was gradually tapered over 1 month by halving the dosage each week.

3. Results

Thirteen patients treated with 2–3 mg/kg/day propranolol were identified between November 2009 and March 2011. The demographic data, clinical features, imaging findings, and treatment outcomes of these patients are summarized in Table 1. There was a predominance of female (10/13, 76.9%) and premature (7/13, 53.8%) infants among the patients. Seven patients (53.8%) had solitary hemangioma, whereas the other six had multiple ones. The onset of IH in 12 patients (92.3%) occurred in the neonatal period. These hemangiomas were located on the trunk (6/13, 46.2%), extremity (4/13, 30.8%), face (3/13, 23.1%), scalp (3/13, 23.1%), liver (2/13, 15.4%), retro-orbital, intracranial area and ethmoid sinus (1/13, 7.7%), neck (1/13, 7.7%), hard palate (1/13, 7.7%), and external auditory meatus (1/13, 7.7%). No patients had thrombocytopenia, consumptive coagulopathy or Kasabach–Merritt syndrome.

The indications for treatment in our patients were divided into four categories: (1) risk of local complication, defined as high risk of local complication due to frequent friction or scratching, in nine patients (69.2%, Figure 1A, 1B and 1E); (2) functional risk, defined as impairment of vision, hearing, feeding, or motility caused by IH, in four patients (30.8%, Figure 1C–1E); (3) local complication in one patient (7.7%, painful ulceration and secondary infection with *Pseudomonas aeruginosa* of hemangioma over the left

Table 1 Demographic data, clinical features, image findings, and treatment outcomes in 13 Taiwanese newborns and young infants.

Patient no.	Age at treatment(mo)/ sex	Age of onset of IH (wk)	Clinical features and image finding of IH	Indication for treatment	Propranolol dosage (mg/kg/d)	Treatment response	Treatment duration (mo)	Last IH status/ the interval of discontinuation and last follow-up	Complications
1	1/F	2	Multiple IH over left shoulder blade (5 cm × 5 cm), right eyelid (2 cm × 2 cm), scalp (1 cm × 1 cm)	Risk of local complication	2	Decolorization: 1 wk, regression in size: 1 wk, stable: 5 mo	9	Stable with spot lesions/8 mo	—
2	4/F	2	Huge IH over left hand with painful ulceration and secondary infection (*Pseudomonas aeruginosa*)	Local complication	2	Decolorization: 1 wk, regression in size: 1 wk, wound healing: 2 wk	14	Tumor flattened out with few patch/1 mo	—
3*	1/M	4	Multifocal hepatic IH with hepatomegaly, high output heart failure and respiratory distress with NCPAP support, MDCT finding: diffuse hypervascular tumors, largest two tumors were 4.4 cm and 3.1 cm	Life-threatening complication	3	Signs of heart failure resolved: 1 wk, NCPAP weaned off: 13 d, regression in size: 3 mo, tumor resolved with only heterogenic echogenecity by sonography: 5 mo	7	Stable with tumor resolved completely/ 2 mo	Occasional tachypnea
4	1/F	4	IH with proptosis and lagophthalmos, MRI finding : huge lobulated mass over left retro-orbital area, left ethmoid sinus, left anterior skull base and left posterior aspect of suprasellar cistern	Functional risk	3	Lagophthalmos improved: 1 d, proptosis improved: 4 d, tapering at 7 mo: relapsed 1 wk later and restarted previous dosage	12 (ongoing)	Mild proptosis/—	—
5	11/F	2	IH over left subcostal abdomen, sono finding: 2.6 cm × 0.8 cm, visible blood flow	Risk of local complication	2.5	Decolorization: 1 wk, regression in size: 2 wk	9 (ongoing)	Regressing with one-third previous size/—	—
6	11/F	0	IH over back, sono finding: 3.1 cm×0.8 cm, visible blood flow	Risk of local complication	2	Decolorization: 1-2 wk, regression in size: 2 wk	3	Stable with spot lesions/8 months	Occasional pale looking
7	4/F	2	Huge IH over scalp (parietal, temporal, occipital, preauricular area), sono finding: multiple heterogeneous lesions within subcutaneous layer, maximum 3 cm×0.5 cm, enriched blood flow	Risk of local complication	2	Decolorization: 1 wk, regression in size: 1 wk, stable: 4 mo	4	Stable with spot lesions/2 months	—
8	1/F	0	Multiple IH over liver (focal, sono finding: 1.6 cm × 0.8 cm, enriched blood flow), right zygomatic area (sono finding: 1.1cm × 0.6 cm, visible blood flow), abdomen (2 cm × 3 cm), thorax area, left shoulder, and neck (0.2 cm × 0.3 cm)	Risk of local complication	2	Tumor of liver resolved: 2 mo Decolorization and regression in size of cutaneous hemangioma: 2 wk, stable : 4 mo	4	Stable with spot cutaneous hemangiomas and resolution of liver tumor/3 mo	—

(*continued on next page*)

Table 1 (*continued*)

Patient no.	Age at treatment(mo)/ sex	Age of onset of IH (wk)	Clinical features and image finding of IH	Indication for treatment	Propranolol dosage (mg/kg/d)	Treatment response	Treatment duration (mo)	Last IH status/ the interval of discontinuation and last follow-up	Complications
9*	11/F	0	Huge hemagioma over right chest wall involving breast, sono finding: 6.7 cm × 1.6 cm, enriched blood flow	Risk of local complication	2	Decolorization: 1 wk, regression in size: 2 wk	5 (ongoing)	Regressing/—	—
10	3/M	0	Multiple IH over back, medial aspect of left thigh (2 cm × 2 cm), lower half of left leg and ankle (sono finding: 5.7 cm × 0.5 cm, visible blood flow)	Functional risk and risk of local complication	2	Decolorization: 10 d, regression in size: 1 wk	5 (ongoing)	Regressing/—	—
11	6/M	0	IH over scalp, sono finding: 2.3 cm × 0.6 cm,enriched blood flow	Risk of local complication	2	Decolorization: 3 d, regression in size: 1 wk	3 (ongoing)	Regressing/—	—
12	4/F	0	Multiple IH over left hard palate (3 cm × 2 cm) and back (5 cm × 3 cm)	Functional risk and risk of local complication	2	Decolorization: 3 d, regression in size: 3 d	3 (ongoing)	Regressing/—	—
13	8/F	8	Multiple IH over left eyelid (sono finding: 1.7 cm × 0.9 cm,enriched blood flow, MRI finding: lobulated mass over the left side eyelid without orbital cavity involvement) and left external auditory meatus impacted totally	Functional risk	2	Decolorization: 5 d, regression in size: 6 d	3 (ongoing)	Regressing/—	

* Patients previously treated with corticosteroids. F = female; IH = infantile hemangioma; M = male; MDCT = multi-detector computed tomography; NCPAP = nasal continuous positive airway pressure; MRI = magnetic resonance imaging; sono = ultrasonographic.

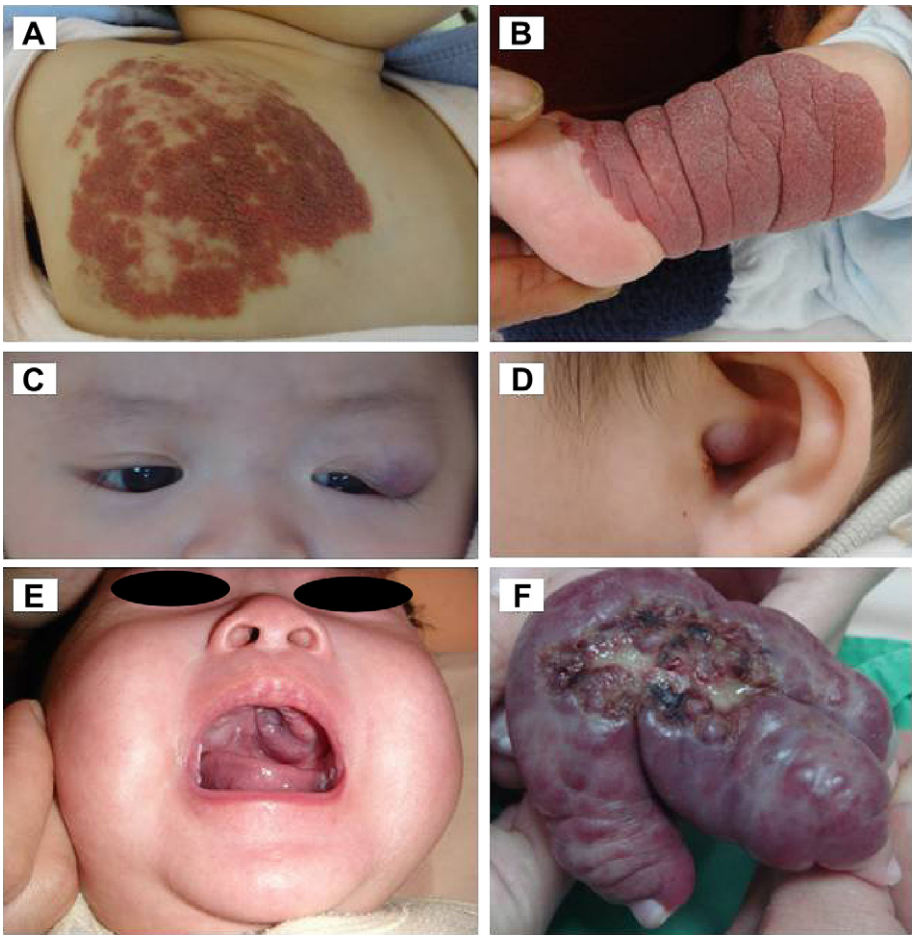

Figure 1 Indications of propranolol treatment in infantile hemangiomas. (A) Risk of local complication: large hemangioma over right chest wall involving breast in Patient 9. (B) Risk of local complication and functional risk of motility: large hemangioma over left ankle and foot in Patient 10. (C) Functional risk of vision: ptosis and visual field defect caused by hemangioma over the left eyelid in Patient 13. (D) Functional risk to hearing: total hemangioma impaction of left external auditory meatus in Patient 13. (E) Risk of local complication and functional risk of feeding: hemangioma over the left hard palate caused sucking difficulty in Patient 12. (F) Local complication: infantile hemangioma with painful ulceration and secondary infection with *Pseudomonas aeruginosa* over the left hand in Patient 2.

hand, fever, and leukocytosis in Patient 2, Figure 1F); and (4) life-threatening complication in one patient (7.7%, high-output heart failure with respiratory distress due to large multifocal hepatic hemangioma in Patient 3).

Diagnostic imaging studies were performed in 10 patients. Ultrasonography in eight patients revealed a mass with visible or enriched blood flow. Multi-detector computed tomography in Patient 3 revealed diffuse hypervascular tumors over the liver (Figure 2A and 2B). Two tumors caused significant arteriovenous shunting. Magnetic resonance imaging in Patient 4 showed a huge lobulated mass over the left orbital cavity, left ethmoid sinus, left anterior skull base, and left posterior aspect of the suprasellar cistern (Figure 2C—2E).

The median age for starting propranolol treatment was 4 months, ranging from 1 to 11 months. Patients 3 and 9 were treated with 2 mg/kg/day prednisolone for 1 week and 3 weeks, respectively. The former patient was administered with propranolol due to progression of hemangioma-associated heart failure, whereas the latter was shifted to propranolol due to progressive growth of hemangioma. For the other 11 patients, propranolol was the sole treatment. Immediate therapeutic response of superficial cutaneous hemangiomas to propranolol, manifested as decolorization and regression in tumor size, was observed in all patients within 1—2 weeks after treatment. These cutaneous his underwent further regression under current propranolol treatment.

Therapeutic effects of propranolol on deep or visceral IH were also seen in three patients. Patient 3 had multifocal hepatic IH, and signs of heart failure resolved after 1 week of treatment. The patient was weaned off continuous positive airway pressure support after 13 days. Serial ultrasonography was used for follow-up and revealed that the size of the multifocal tumor had regressed after 3 months of treatment, and only heterogenic echogenicity over the liver without nodular lesions was noted after 5 months. Patient 4 had left retro-orbital IH, and after 1 day of treatment, lagophthalmos improved. After 4 days, there was also an improvement in proptosis. Treatment

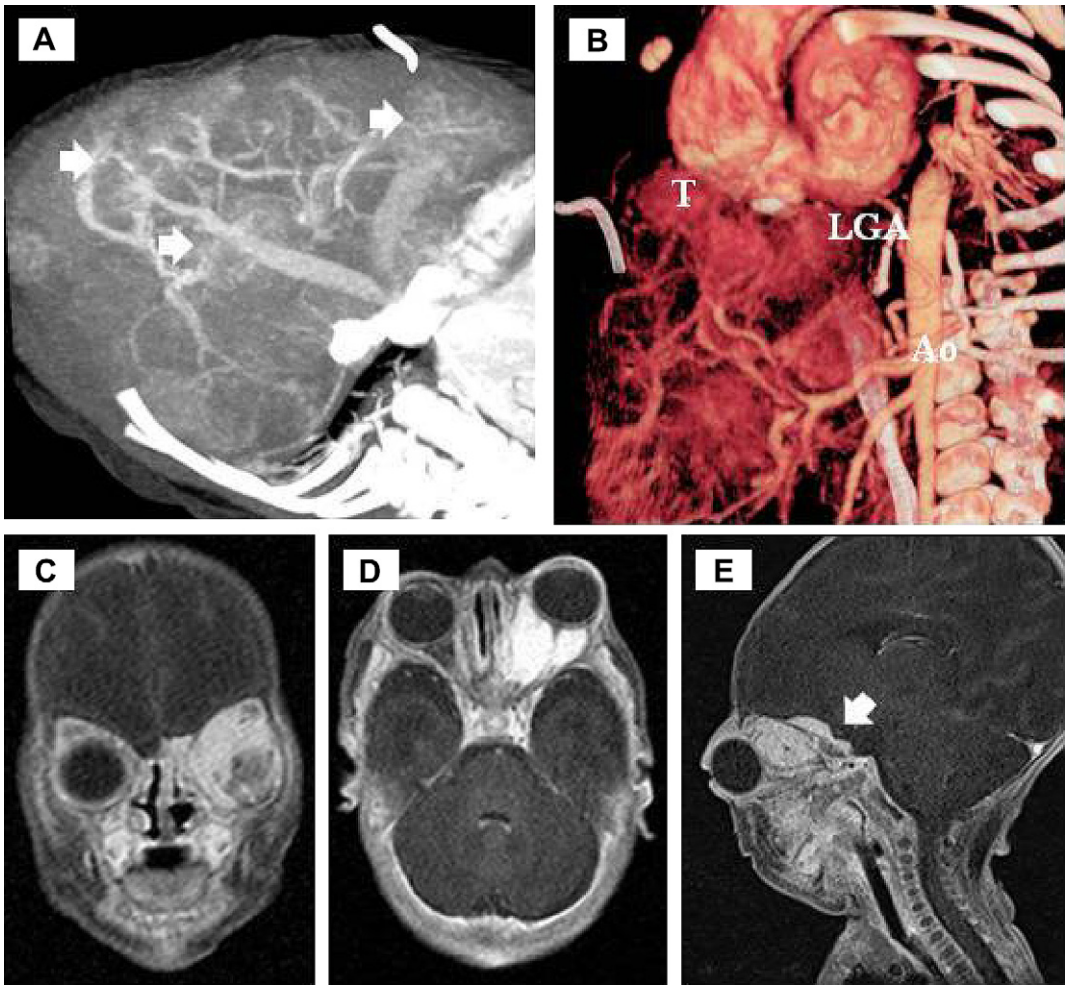

Figure 2 Diagnostic imaging studies for infantile hemangioma in two patients. (A) Multifocal liver hemangioma in Patient 3. Diffuse hypervascular tumors (white arrows) were mostly supplied by hepatic arteries on cross-section of multi-detector computed tomography. (B) Some multifocal liver hemangiomas (T) in Patient 3 were seen supplied by the left gastric artery on multi-detector computed tomography. Patient 4 had (C) huge lobulated mass with iso-signal intensity on T1-weighted imaging magnetic resonance imaging over the left orbital cavity and left ethmoid sinus, (D) left retro-orbital hemangioma with strong contrast enhancement on magnetic resonance imaging, and (E) similar enhancement revealed left retro-orbital hemangioma at the left anterior skull base and left posterior aspect of suprasellar cistern (white arrow). Ao = aorta; LGA = left gastric artery.

with 3 mg/kg/day propranolol was maintained. Dosage was tapered at 7 months after treatment, but relapse with aggravation of proptosis was noted 1 week later. After restarting the previous dosage of 3 mg/kg/day propranolol, proptosis improved again.

Six patients completed the treatment course, with a median treatment duration of 5.5 months (range: 3—14 months) (Table 1). No recurrence of IH was noted in any of these patients during follow-up (range: 1—8 months). Seven patients continued to receive the treatment, with a median duration of 5 months (range: 3—12 months).

Propranolol-associated adverse effects were suspected in two patients (15.4%). Patient 3 had occasional tachypnea at 3 months after treatment. Patient 6 had occasional pale-looking appearance at 1 month after treatment. These symptoms resolved after propranolol dosage reduction. No patient was reported to have bradycardia with poor perfusion, and neither hypoglycemia nor hypotension was observed.

4. Discussion

Propranolol is a nonselective β-blocker and is usually used in children for treating cardiac dysrhythmias, hypertension, congestive heart failure, tetralogy of Fallot, thyrotoxicosis, and migraine headache.[14] In 2008, Léauté-Labrèze et al used propranolol to treat obstructive hypertrophic myocardiopathy in a young infant with coexisting nasal IH, and the hemangioma regressed rapidly and serendipitously.[11] The dramatic efficacy was replicated in the other 10 infants in the same trial and in another 21 infants with severe hemangiomas in a large follow-up observational study.[15] Propranolol was equally effective for treatment of superficial cutaneous IH as well as for deep or visceral IH.[16—18] Rapid tumor regression within days in infants with severe or life-threatening hemangiomas has been demonstrated in several recent studies.[12,19—23] In addition, propranolol has been shown to be effective in cases with IH resistant to conventional treatment with high-dose

corticosteriods, vincristine, cyclophosphamide, or interferon α.[24,25]

Our study showed that the onset of IH was usually in the neonatal period and all patients had received propranolol treatment during the proliferation phase of IH. Both superficial cutaneous and visceral hemangioma were dramatically responsive to propranolol treatment, which was consistent with the findings of previous studies.[11,15–23] In superficial IH, decolorization and regression in tumor size occurred within 1–2 weeks after treatment. In visceral or deep IH, the hemangioma-associated complications improved within 1 week. All of our IH patients continued to show tumor regression under propranolol treatment, or were stabilized after discontinuation of treatment.

The exact mechanism of propranolol action on IH remains to be clarified. It has been speculated that three different pharmacological mechanisms of propranolol lead to early, intermediate and long-term effects on IH.[26] Early effects are ascribed to decreased release of nitric oxide and subsequent vasoconstriction. Intermediate effects are believed to result from the blocking of angiogenesis factors, including vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase 2 and 9. Long-term effects of propranolol are thought to be caused by the induction of apoptosis in proliferating capillary endothelial cells. Another possible mechanism of propranolol-induced accelerated involution proposed by Itinteang et al involves the reduction in expression of components of the renin–angiotensin system, especially renin and angiotensin II.[27]

The optimal duration of propranolol treatment in IH has yet to be established. It is reasonable to maintain propranolol treatment after the first year of life when the proliferation phase is usually completed.[20,21] Some investigators have evaluated the effects of discontinuation of propranolol before the first year of age, when IH had completely resolved.[15,19] Recurrence of IH in a few patients was reported,[15,18,19] especially with abrupt withdrawal of propranolol.[23] However, reintroduction of propranolol for recurrent growth of IH was still effective in most patients.[19] In our study, four patients completed the treatment course of propranolol before the first year of age and two discontinued propranolol after the proliferation phase. Although no recurrences of IH were noted in all our patients, larger studies are required to determine how long the treatment should be continued.

To date, no documented death or serious cardiovascular event has been reported for children under 6 years of age as a direct result of β-blocker exposure.[14] A few case reports have described adverse effects of propranolol treatment for IH, including hypoglycemia,[28–30] wheezing,[15] transient hypotension,[15,19,20] asymptomatic and transient bradycardia,[25] and hyperkalemia.[31] Except for one preterm infant with potential life-threatening hyperkalemia,[31] other adverse effects have been shown to resolve without specific therapy. In our study, the patient with occasional tachypnea after propranolol treatment had no subsequent respiratory distress or desaturation even though the tachypnea was thought to be related to propranolol-induced bronchospasm. Another patient had occasional and transient pale-looking appearance with no signs of poor perfusion. Thus, the side effects found in our patients were not serious. Compared with conventional agents such as systemic corticosteroids, vincristine, and interferon α, propranolol is a safer drug at the therapeutic dosage for IH. However, more clinical trials are needed to provide a guide for better monitoring of hemodynamics, blood glucose and electrolyte status in infants with IH during the treatment period, to prevent potential adverse effects.

Propranolol use in IH is a promising therapeutic option with few complications. Randomized controlled studies are necessary to determine the appropriate patient populations, treatment dosage, treatment duration, and long-term prognosis, as well as to investigate any long-term adverse effects of propranolol.

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