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Original Article

A survey on clinical use of propranolol for infantile hemangiomas in mainland China

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Abstract: Objective: To provide a guideline for Chinese clinicians regarding oral propranolol treatment on infantile hemangioma (IH). Methods: A survey for management of propranolol therapy (clinical consultation, dosage initiation, dosage changing, monitoring of complications and effectiveness evaluation) was performed and was delivered to the Division of Vascular Anomalies (DVA), Chinese Stomatological Association (CSA), and to the Division of Hemangioma and Vascular Malformations (DHVM), Chinese Society of Plastic and Reconstructive Surgery. Results: Data from 31 hospitals were collected and analyzed. In all hospitals, IH patients were treated with oral propranolol as a routine. Twenty-two (71%) of the 31 hospitals treated patients with IH as part of a multidisciplinary strategy. Cardiology consultation was routinely sought in 21 (95%) of these 22 hospitals before initiation of propranolol therapy. Sixteen hospitals (52%) recommend an initial propranolol dose of 1 to 1.5 mg/kg/day, in most cases 1.0 mg/kg/day. The dosage frequency of once a day was recommended in 18 (58%) of the surveyed hospitals. The maximum dose of 1.5 mg/kg/day or 2.0 mg/kg/day was suggested in 10 (32%) and 13 (42%) hospitals, respectively. Similarly, the optimal dose of 1.5 mg/kg/day or 2.0 mg/kg/day was recommended in 11 (37%) and 9 (30%) hospitals, respectively. The duration of therapy varied from 1 to 24 months. Tapering was advised by 10 (40%) hospitals and immediate discontinuation was applied in 13 (52%) hospitals. Complications were emphasized by all hospitals. The most common complications were gastrointestinal symptoms (17 of 31 hospitals), whereas the complication most commonly monitored for was changes in heart rate. No rebound effects were reported. Conclusions: Propranolol has become the first-line agent for IH in mainland China. This is a practical survey which is helpful to standardize and develop a guideline for propranolol therapy.

Keywords: Propranolol, infantile hemangioma, medication, side effects

Introduction

Infantile hemangioma (IH) is a common benign vascular tumor with a unique growth pattern [1, 2], characterized by an early proliferative phase during the neonatal period or early infancy followed by a spontaneous involution that begins immediately after the proliferation phase, or after a plateau period of several weeks to months [3]. About 60% of IH are located in the head and neck area [4]. The majority of the cases are uncomplicated and do not require treatment. However, intervention may be necessary for IH that are located in life- or function-endangering locations, which cause disfiguring, and/or result in ulceration.

Léauté-Labrèze et al first fortuitously discovered the efficacy of propranolol for the treatment of IH in 2008 [5]. Since then, the effectiveness of oral propranolol for IH of all types has been documented in multiple publications. Its ability to rapidly decrease the size of proliferating hemangioma has dramatically changed the management of cutaneous and systemic infantile hemangioma [6-9]. However, there are currently no consensus guidelines on proper dosing and monitoring requirements when using propranolol for IH. A consensus conference on this subject was held in December 2011, from which guidelines were published in January 2013 [10]. Up to date, there is still a wide variation in practices for initiation and monitoring of propranolol use in IH patients, with little evidence to validate many of the protocols.

In order to develop a standardized and consensus-derived set of best practices for the treatment of IH for clinicians in mainland China,

Table 1. Questions used for survey

Aspect surveyed	Related questions	Example
Clinical consultation	1-4	1. Whether any clinical departments were consulted before initiation of propranolol in infants with IH? 2. Which related departments were consulted before initiation? 3. What examinations were conducted when consulted? 4. Which was your prefer department for consultation?
Dosage initiation	5-6	5. Original dosage and administration. 6. Time of duration.
Dosage changing	7-10	7. Whether or not the medication was interrupted or terminated? 8. And the reason? 9. Standards for medicine withdrawl. 10. Means for medicine withdrawl.
Complication monitoring	11-17	11. Department for propranolol treatment (outpatient / inpatient). 12. Conditions for hospitalization. 13. Time for revisit. 14. Original time for complications monitoring. 15. Items for monitoring. 16. Length of stay in inpatient department. 17. Detailed complications happened when taking propranolol.
Effect evaluation	18-24	18. Whether treated with other types of therapy before? 19. Means of therapy treated before. 20. Which type was treated with oral propranolol based on Waner and Suen classification? 21. Results of effect evaluation by Achauer assessment. 22. Other issues adopted for effect evaluation. 23. Whether or not rebound growth was detected? 24. Time for rebound growth occurred.

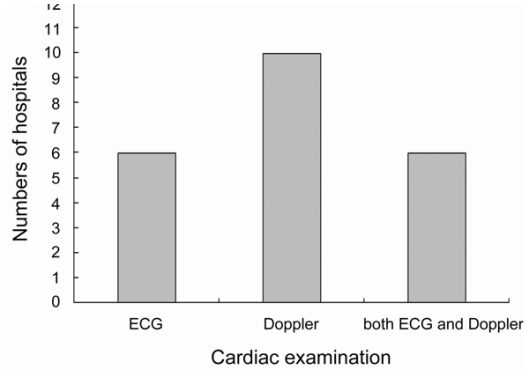

Figure 1. Cardiac examinations adopted as a part of protocol before initiation of propranolol (22 of 31 hospitals recommend consultation of cardiology). ECG: electrocardiography.

Table 2. Cardiac examinations before Propranolol initiation

	Cardiac examination (n (%))		
	ECG	Doppler	Both ECG and Doppler
Hospital (n = 22)	6 (27.3)	10 (45.4)	6 (27.3)

ECG: electrocardiography.

Division of Vascular Anomalies (DVA), Chinese Stomatological Association (CSA), and Division of Hemangioma and Vascular Malformations (DHVM), Chinese Society of Plastic and Reconstructive Surgery, were founded in 2004 and 2012, respectively. DHVM has members with a wide range of expertise, including plastic and reconstructive surgeon, dermatologist, ophthalmologist, laser surgeon, pediatrician, pediatric surgeon, cosmetic surgeon, head and neck surgeon, and interventional radiologist.

Based on the treatment guidelines for hemangioma of the head and neck published in 2009 and 2013 [4, 11], the protocol published was followed by most physicians including pediatricians and plastic surgeons in mainland China. In clinic, propranolol has been found to be rapidly effective for IH, well tolerated, and better than previous therapies at inducing regression. These observations have led to a rapid and widespread adoption of propranolol for IH. Each institution designed unique protocols for clinical administration of propranolol. However, a proposed treatment modality has not been established so far. We undertook this present survey to provide an update on the clinical use of propranolol.

Methods

Questionnaire and surveys

Our questionnaire surveys were conducted as follows:

(1) A questionnaire was developed to evaluate the clinical administration of propranolol as treatment of IH. It consisted of 24 questions,

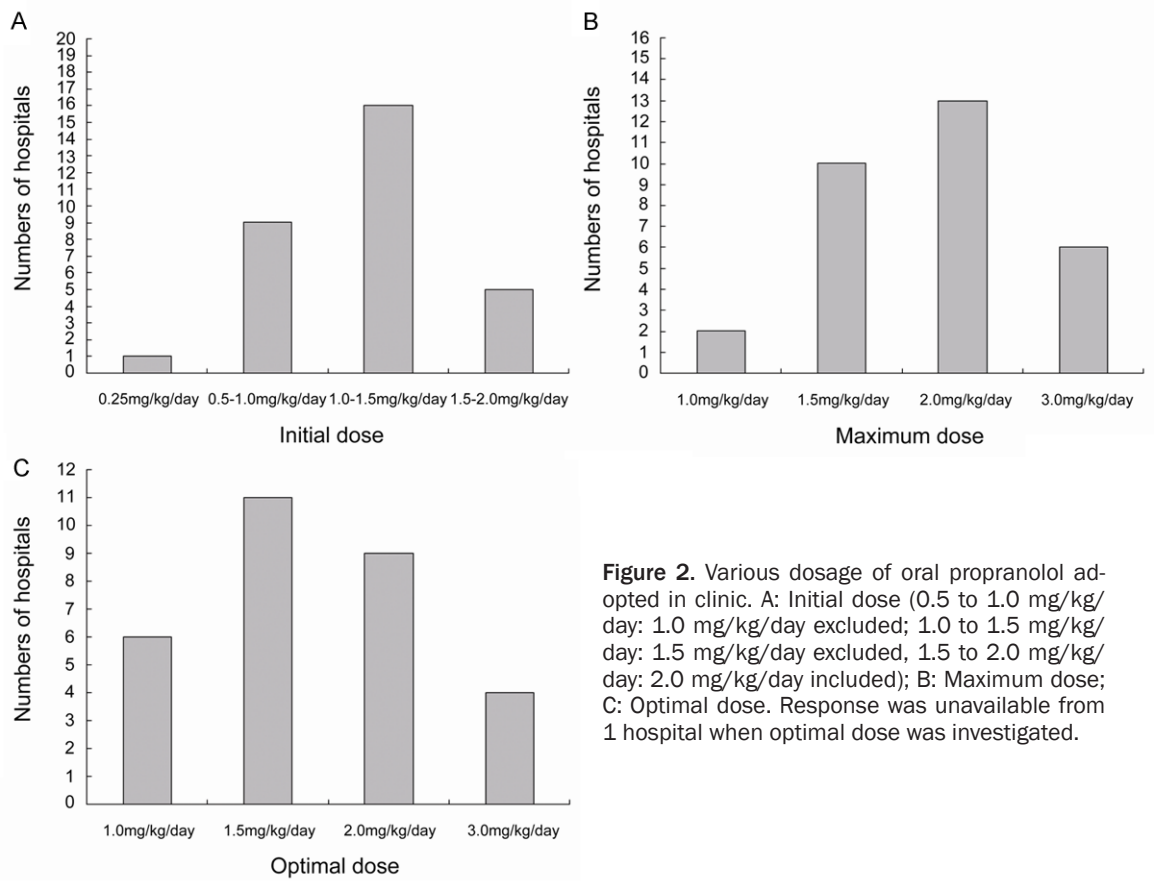

Figure 2. Various dosage of oral propranolol adopted in clinic. A: Initial dose (0.5 to 1.0 mg/kg/day: 1.0 mg/kg/day excluded; 1.0 to 1.5 mg/kg/day: 1.5 mg/kg/day excluded, 1.5 to 2.0 mg/kg/day: 2.0 mg/kg/day included); B: Maximum dose; C: Optimal dose. Response was unavailable from 1 hospital when optimal dose was investigated.

Table 3. Initial dose

	Initial dose (n (%))			
	0.25 mg/kg/day	0.5-1.0 mg/kg/day	1.0-1.5 mg/kg/day	1.5-2.0 mg/kg/day
Hospital (n = 31)	1 (3)	9 (29)	16 (52)	5 (16)

Table 4. Maximum dose

	Maximum dose (n (%))			
	1.0 mg/kg/day	1.5 mg/kg/day	2.0 mg/kg/day	3.0 mg/kg/day
Hospital (n = 31)	2 (6)	10 (32)	13 (42)	6 (19)

Table 5. Optimal dose

	Optimal dose (n (%))			
	1.0 mg/kg/day	1.5 mg/kg/day	2.0 mg/kg/day	3.0 mg/kg/day
Hospital (n = 30)	6 (20)	11 (37)	9 (30)	4 (13)

grouped into five aspects (clinical consultation, dosage initiation, dosage changing, monitoring of complications, and effect evaluation) (**Table 1**).

(2) We delivered 34 questionnaires by email to 20 members of DVA, and 14 members of DHVM. All of them were enquired about the clinical administration completed during the period from January 2009 to December 2013.

(3) The contents of the questionnaires were identical for all the hospitals surveyed.

Ethics committee review

All of the answers were provided by clinical physicians non-anonymously. The use of propranolol for IH was approved by the Hospital Review Boards according to the Declaration of Helsinki [12]. The questionnaire survey was approved by DVA.

Results

Response rates of questionnaire surveys

Thirty-one hospitals (general response rate: 91%) submitted completed surveys, of which 19 and 12 were members of DVA and DHVM, respectively. Three hospitals did not respond to our survey, due to insufficient data of IH patients.

Clinical consultation

Twenty-two (71%) of the 31 hospitals treated patients with IH as part of a multidisciplinary strategy. Among these 22 hospitals, cardiology consultation was routinely sought in 21 (95%) hospitals before initiation of propranolol therapy. Pediatrics instead of cardiology department was consulted in only 1 (5%) hospital. As a routine, cardiac examination was performed. Only electrocardiographic and only ultrasound echocolor Doppler examination were performed in 6 (27%) and 10 (45%) of the 22 hospitals, respectively. Both of the two examinations were carried out in 6 (27%) hospitals (**Figure 1**; **Table 2**). In the hospitals in which pediatric department was consulted, no cardiac examination was conducted.

Dosage initiation

For propranolol dose used for IH, there were three questions, i.e. what initial dose, maximal dose and optimal dose were recommended, including the duration of each dose. Propranolol was used as first-line treatment in all the hospitals. Dose at initiation varied from 0.25 to 2.0 mg/kg/day administered one to three times a day. The patients were treated at a dose of 0.25 mg/kg/day in 1 (3%) hospital, 0.5 to 1.0 mg/kg/day (1.0 mg/kg/day excluded) in 9 (29%) hospitals, 1.0 to 1.5 mg/kg/day (1.5 mg/kg/day excluded) in 16 (52%) hospitals, and 1.5 to 2.0 mg/kg/day (2.0 mg/kg/day included) in 5 (16%) hospitals (**Figure 2A**; **Table 3**). Propranolol was taken postprandially, one to three times a day. The number of hospitals recommending one, two, or three doses a day was 18 (58%), 8 (26%), and 5 (16%), respectively. The maximum dose level ranged from 1.0 to 3.0 mg/kg/day. In 2 (6%) hospitals, propranolol was taken at a maximum dose of 1.0 mg/kg/day. Ten (32%) hospitals used 1.5 mg/kg/day, 13 (42%) hospitals used 2.0 mg/kg/day, and 6 (19%) hospitals used 3.0 mg/kg/day (**Figure 2B**; **Table 4**). The recommended optimal dose level was 1.0 mg/kg/day in 6 hospitals, 1.5 mg/kg/day in 11 hospitals, 2.0 mg/kg/day in 9 hospitals and 3.0 mg/kg/day in 4 hospitals. One hospital offered no response regarding optimal dose level (**Figure 2C**; **Table 5**).

Duration of therapy varied between 1 and 24 months. The treatment had to be interrupted or terminated due to various reasons. No answer came from 8 hospitals. The interruption was mainly caused by adverse events of propranolol, such as severe diarrhea, fever, bronchospasm and bradycardia, in 14 (61%) of 23 hospitals. The other causes included continuous drug inefficiency for 3 months, discompliance, or refusal of the patient or parents to take the drug.

Dosage change

During treatment, dosage reduction was reported in all the 31 hospitals. We set the standard for propranolol discontinuation as color (color fading to be similar to normal skin), volume (volume reduction to the degree of no significant bulge) and infant age. A comprehensive standard which confirms the recovery with the evidence of ultrasound or magnetic resonance imaging (MRI) examination and which takes color, volume and age into account was adopted by 19 (76%) hospitals. In 3 (12%), 2 (8%) and 1 (4%) of the hospitals, color, volume and age was solely considered for drug discontinuation, respectively. Regarding drug discontinuation, gradual tapering was employed by 10 (40%) hospitals and immediate drug withdrawal was by 13 (52%) hospitals. In 2 (8%) hospitals, gradual reduction was used for the patients with a large lesion or with a long treatment duration of more than 3 months and immediate withdrawal was used for a smaller lesion and a shorter therapeutic duration of less than 3 months.

Monitoring of complications

IH patients were treated exclusively at an outpatient clinic in 12 (44%) of 27 responding hospitals, while in 7 (26%) hospitals the treatment was started only on an inpatient basis. In the remaining 8 (30%) hospitals, the therapy was conducted on an outpatient or inpatient basis. No response regarding this issue was available from 4 hospitals. Ten (37%) of the hospitals had

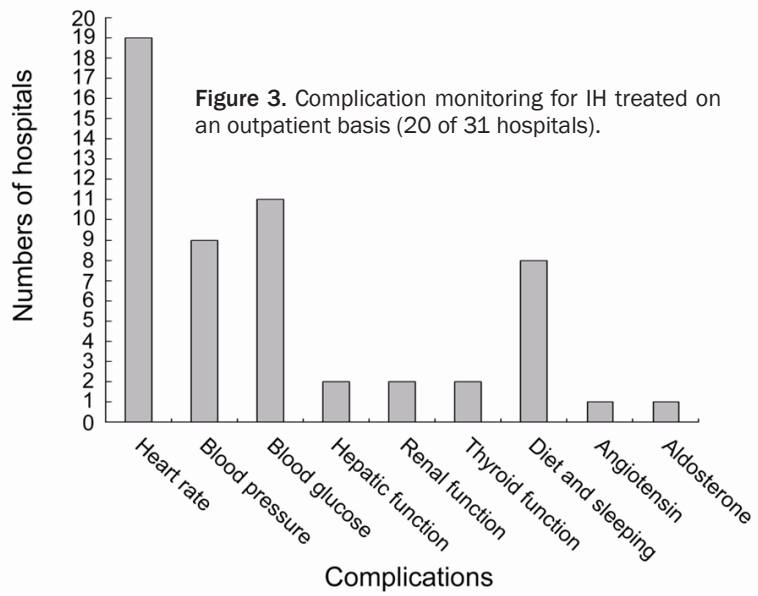

Figure 3. Complication monitoring for IH treated on an outpatient basis (20 of 31 hospitals).

Table 6. Complications monitored in outpatient department

	Hospital (n = 20) (n (%))	
Heart rate	19	(95)
Blood pressure	9	(45)
Blood glucose	11	(55)
Hepatic function	2	(10)
Renal function	2	(10)
Thyroid function	2	(10)
Diet and sleeping	8	(40)
Angiotensin	1	(5)
Aldosterone	1	(5)

specific criteria for hospitalization. Hemangiomas with a more than 10 cm^2 area, located in the face, head, perineum, trunk or extremities were treated on an inpatient basis in 4 (15%) hospitals. Age was considered in 4 (15%) hospitals.

In 20 hospitals in which IH patients were treated at an outpatient clinic, revisit for the first time was recommended 1 day (in 20% of the hospitals), 3 days (5%), 7 days (15%), 14 days (10%) or 30 days (50%) after the first dose of propranolol. However, the first time for complications monitoring was earlier. Half an hour after the first dose was reported from 1 (5%) hospital, 1 hour from 11 (55%), 2 hours from 3 (15%), 6 hours from 1 (5%), and 24 hours from 4 (20%) hospitals. The factors monitored for included heart rate (95%), blood pressure (45%), blood glucose (55%), hepatic function (10%), renal function (10%), thyroid function (10%), diet and sleeping (40%), angiotensin levels (5%) and aldosterone levels (5%) (**Figure 3**; **Table 6**).

In total, there were 15 hospitals undertaking IH treatment on an inpatient basis. The first time for complications monitoring was immediately after propranolol administration in 2 (13%) hospitals. Half an hour after taking propranolol was reported from 1 hospital (7%), 1 hour from 9 (60%), 2 hours from 2 (13%), and 24 hours from 1 (7%) hospital. Heart rate (evaluated in 93% of the hospitals), blood pressure (73%), blood glucose (53%), hepatic function (33%), renal function (33%), thyroid function (13%), saturation of peripheral oxygen (20%), diet and sleeping (67%), angiotensin (7%), aldosterone (7%), skin eruption (7%), routine blood test (7%) and psychiatric condition (33%) were examined and recorded (**Figure 4**; **Table 7**). The patients were treated in inpatient department for 3 days in 10 (67%) hospitals and 7 days in 5 (33%) hospitals. The patients were asked to revisit 7 days after being discharged in 3 (20%) hospitals, and 1 month after discharge in 12 (80%) hospitals.

In 17 (55%) of the 31 hospitals surveyed, gastrointestinal symptoms, such as diarrhea, reflux, vomit, loss of appetite and occasional constipation, were the most common complications. Cardiovascular complications, such as bradycardia and hypotension, and sleeping alterations, such as somnolence and prone to wake were reported in 12 (39%) hospitals. Bronchospasm was reported from only 3 (10%) hospitals and hypoglycemia from 2 (6%) hospitals.

Effect evaluation

Both primary IH and those after treatment with other modalities such as corticosteroids, topical medication, laser and isotopic therapy, were admitted in 26 (84%) hospitals and only primary IH were admitted in the remaining 5 (16%)

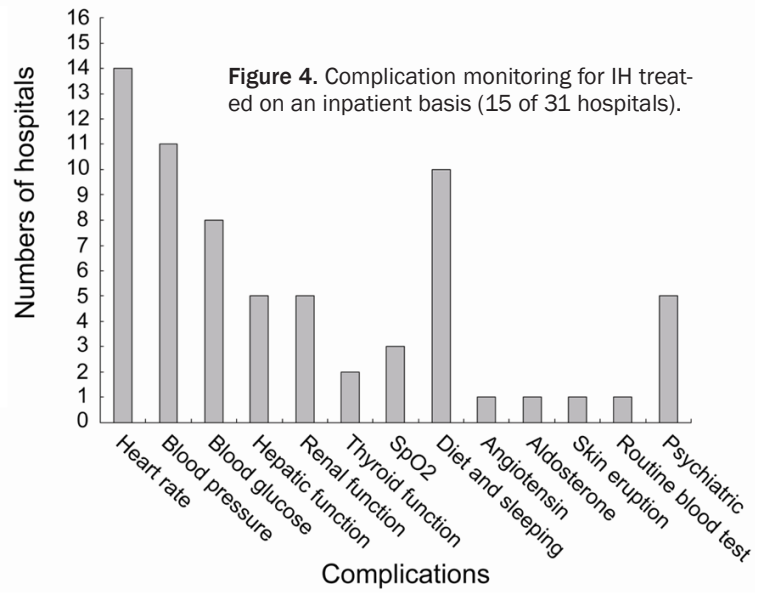

Figure 4. Complication monitoring for IH treated on an inpatient basis (15 of 31 hospitals).

Table 7. Complications monitored in inpatient department

	Hospital (n = 15) (n (%))	
Heart rate	14	(93)
Blood pressure	11	(73)
Blood glucose	8	(53)
Hepatic function	5	(33)
Renal function	5	(33)
Thyroid function	2	(13)
SpO_2	3	(20)
Diet and sleeping	10	(67)
Angiotensin	1	(7)
Aldosterone	1	(7)
Skin eruption	1	(7)
Routine blood test	1	(7)
Psychiatric	5	(33)

SpO_2: saturation of peripheral oxygen.

hospitals. IH of 3 clinical types, superficial, deep and mixed, were treated [13]. Scale proposed by Achauer et al [14] based on improvement of volume was adopted to assess the efficiency of propranolol therapy. In all the 31 hospitals, approximately 80%-90% of propranolol therapy resulted in excellent response (76%-100% volume decrease) and 60%-80% resulted in good response (51%-75% volume decrease). About 10% achieved the result of fair (26%-50% volume decrease) or poor (0-25% volume decrease) response. In addition to the volume changes, color alterations were also considered for evaluation in 22 (71%) hospitals. Only 1 (3%) hospital used examinations of heart rate, blood pressure, blood glucose, electrocardiograph and ultrasound in the treatment evaluation. No rebound growth was reported in 26 hospitals and the remaining 5 hospitals provided no respond to this issue.

Discussion

In recent years, propranolol therapy has been increasingly used in the management of IH that require intervention. The investigators questioned in this study reported a remarkable flattening and fading of the IH when propranolol therapy was initiated. The investigators subsequently documented the drug's efficacy as a first-line, as well as second-line (after steroid use) therapy. However, rare side effects, a few of which may be life-threatening, are cause for concern. In mainland China, IH are mainly treated by surgeons of oral and maxillofacial surgery and plastic and reconstructive surgery, which is why DVA and DHVM were founded for the purpose of treating IH. Until now, most clinicians treat IH with propranolol following the guidelines established in 2009 and 2013 [4, 11], while the off-label use of propranolol has led to variability in pre-treatment work-up, treatment dosing (initiation, goal, and frequency), duration, and monitoring. We undertook this survey in order to reach a consensus on understanding and controlling IH treatment.

At the annual conference of Chinese Society of Oral and Maxillofacial Surgery in 2002, it was agreed that the classification and nomenclature of Waner and Suen [13] and the evaluation scale of Achauer et al [14] were adopted and applied in clinic for IH. These criteria have been applied till now in mainland China. One significant finding of our systemic survey is that 80%-90% of IH in all the 31 surveyed hospitals can reach the excellent response level which means 76%-100% volume decreased and no rebound growth after treatment with propranolol. Most therapeutic results are ranked as excellent and good, with an overall accumulative success rate of more than 90% for patients treated with

propranolol alone. By viewing these cases as a whole, with more than 1,500 patients included in total, a more definitive determination of efficacy is possible. Such a high response is noteworthy for any medical treatment, and even more impressive when considering that the patients included in this survey varied in age at treatment initiation, therapy duration, size and anatomic site. There is a possibility that such improvement in some cases would have occurred as a result of spontaneous involution even without propranolol treatment. However, the mean age of less than 6 months at time of initial treatment is far younger than the age at which spontaneous involution typically occurs, suggesting that the medication, and not spontaneous involution, explains this high efficacy.

With regard to indications for therapy with propranolol, IH leading to severe complications, such as ulceration, bleeding, visual compromise and deformity, should be considered for treatment. Some PHACE syndromes (PHACE = posterior fossa, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities; a cutaneous neurovascular syndrome characterized by large, segmental hemangiomas of the head and neck along with congenital anomalies of the brain, heart, eyes and/or chest wall) should also be included. Risk evaluation of IH patients including medical history enquiry, examination of heart rate, blood pressure and assessment on cardiac and pulmonary function should be performed before the initiation of propranolol therapy. Heart failure, cardiogenic shock, sinus bradycardia, hypotension, bronchospasm and drug allergy are usually contraindications for treatment.

Most severe IH patients are suggested to be treated early in the proliferative phase to prevent sequelae. Propranolol may be initiated on an outpatient or an inpatient basis. Our study suggests that most hospitals (20 of 31) treat IH with uncomplicated disease courses on an outpatient basis. Among them, 12 hospitals admitted all IH only in outpatient department. In contrast, IH was treated in 15 hospitals on an inpatient basis and in 7 of these 15 hospitals all the patients were hospitalized. Although not specifically addressed in our survey, many physicians considered admission for infants younger than 3 months or those whose custodians may be unable to provide the necessary monitoring or render care.

Currently, many uncertainties exist regarding the appropriate and optimal use of propranolol in IH treatment, including optimal dosing, frequency of dosing, duration of therapy, age of therapy initiation, and timing and method of tapering to minimize the opportunity of rebound. An ongoing multicenter survey may shed light on these issues.

More than half of the clinicians in this study recommended an initial dose of 1.0 to 1.5 mg/kg/day with most advocating 1.0 mg/kg/day. The dosage frequency of once a day was recommended in 58% of the surveyed hospitals. This fact is different from the standardized, consensus-derived set of best practices for the propranolol use in IH in United States. According to that guideline, a target dose of 1.0 to 3.0 mg/kg/day with most members advocating 2.0 mg/kg/day and frequency of 3 times daily dosing with a minimum of 6 hours between doses are recommended [10]. A study of the pharmacokinetics and pharmacodynamics of propranolol reported that Chinese subjects have at least a twofold greater sensitivity to the beta-blocking effects of propranolol than the white subjects [15]. Also, the free fraction of propranolol in plasma was proved to be 45% higher in Chinese than in American individuals [15]. Therefore, the difference of racial and pharmacokinetic characteristics between Chinese and Caucasian patients might explain the high efficacy resulted from the lower initial dosage in China. Given the fact that dose escalation is required and that IH usually respond rapidly to even low doses, clinicians will often use dose response to decide an individual's optimal target dose. The principle of dose escalation from a low starting dose is always recommended even in the presence of inpatient monitoring. In most hospitals (74%), the maximum dose of 1.5 mg/kg/day (32%) or 2.0 mg/kg/day (42%) was suggested. Meanwhile, the optimal dose of 1.5 mg/kg/day (37%) or 2.0 mg/kg/day (30%) was also recommended. The lower target dose of initiation is of more safety and convenience while showing the same efficacy as the higher target dose in our survey.

The question of how to taper propranolol and when to ultimately stop the medication is still controversial. Many factors, including the age at which the medication is initiated, the size and depth of the IH, and patient adherence to

treatment, all contribute to decisions about tapering or stopping propranolol [16]. It is reported that the average rebound rate was 17% when propranolol was discontinued with IH patients treated for an average of 6.4 months [16]. Another research showed that discontinuation of propranolol before the age of 1 year appeared to increase the risk of rebound [17]. Additionally, larger and deeper IH are known to have a protracted late proliferative phase extending through the first year of life [18]. In our survey, age is not the only factor which can decide propranolol discontinuation. In 76% of these hospitals, the timing for discontinuation was affected by color, volume and age. Means of tapering and direct stopping propranolol was adopted in a ratio of 40% to 52%, however with the same result of no occurrence of rebound. Therefore, the general rule is to continue therapy at least for the whole proliferative phase in order to precipitate the risk of recurrence. It seems that there is no significant difference of therapeutic effect resulted from either tapering or direct discontinuation in our survey.

Although propranolol has revolutionized the approach to IH management and has quickly become a cornerstone in IH therapy, rare side effects, such as symptomatic hypoglycemia, hypotension, bronchial hyperreactivity, seizure, restless sleep, constipation, and cold extremities can occur [19]. Gastrointestinal discomfort, cardiovascular complications, bronchospasm and hypoglycemia were reported in 55%, 39%, 10% and 6% of the total hospitals based on our survey. Diarrhea was the most common symptom in our survey. The onset was generally within 24 hours, and almost resolved spontaneously within one week. In previous research, diarrhea induced by propranolol is well characterized in adults, but experience in infants is limited [20, 21]. The susceptibility of infants to diarrhea from propranolol may be caused by immature hepatic first-pass metabolism and therefore greater bioavailability of infants. Nonetheless, careful complications monitoring, such as heart rate, blood pressure, blood glucose, hepatic function, renal function, thyroid function, saturation of peripheral oxygen, diet and sleeping, and psychiatric condition, should be considered.

In conclusion, propranolol has been proved to be a valuable and effective therapy option for IH. Rapid onset of the propranolol associated with tolerable side effects, and there were no severe adverse reactions were noted during their treatment courses. Despite the widespread use of propranolol, no systematic strategy currently exists for its medication and identification of toxicities of therapy for IH. We anticipate more precise therapeutic managements and a more appropriate surveillance. The recommendations from our survey will provide a platform for trials to determine optimal regimens and long-term safety profiles.

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Disclosure of conflict of interest

None.

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