Propranolol versus atenolol for problematic infantile hemangiomas: a randomized clinical trial (Version 1.3/Final version)

Protocol outline

Title	Propranolol versus atenolol for problematic infantile hemangiomas: a randomized clinical trial
Version date	July 1, 2017
Research Institutions	Six separate investigation sties in China
Principle Investigators	Yi Ji, Siyuan Chen
Purpose	Comparing the efficacy and safety of propranolol versus atenolol in patients with problematic infantile hemangiomas.
Design	A prospective, multicenter, randomized, controlled, open-label clinical trial.
Subjects	Patients with superficial or mixed infantile hemangiomas who require systemic therapy.
Research Duration	Four years
Methods	Participants are randomized to receive either propranolol or atenolol for at least 6 months. Participants complete a baseline survey and a survey at 96 weeks of follow-up. The primary outcome measure is the clinical response at week 24. Secondary outcome measures include Hemangioma Activity Score, successful initial response, complete ulceration healing time, quality of life, rebound rate, and response at week 96. Frequency and severity of adverse events will be recorded.
Expected results and meanings	Evidence supporting the use of atenolol as a first-line treatment of choice in infantile hemangioma.

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Propranolol versus atenolol for problematic infantile hemangiomas: a randomized clinical trial

2 Research institutions and addresses

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-The authors declare that they have no competing interests, either financial or non-financial, that could be perceived as prejudicing the impartiality of the research reported.

-Written informed consent for publication in this study was obtained from the patients' parents. Copies of the signed informed consent forms are available for review by the Journal Editors.

-The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

-All the authors reviewed the manuscript drafts, trial protocol and supplemental data and approved the final version of the manuscript.

-Yi Ji, Kaiying Yang and Siyuan Chen were involved in the integrity of the data and ensuring the completeness and fidelity of reporting the trial protocol.

5 Study background and rationale

IHs are the most common tumors of childhood and occur in approximately 4% to 5% of infants. In the majority of cases, IHs are self-limited and resolve spontaneously without threat or complications. However, in approximately 10% of patients, the lesions can be disfiguring (e.g., facial involvement), destructive (e.g., ulceration), functionally significant (e.g., visual impairment), or even life-threatening (e.g., airway obstruction).[1,2]

Currently, propranolol is the preferred treatment for problematic proliferating IHs.[3-5] Although propranolol is clearly efficacious, rare adverse effects, such as hypoglycemia and bronchial hyperreactivity, may be life-threatening.[6-8] Nonselective β-adrenergic antagonists, such as propranolol, are competitive antagonists of catecholamines at the β_1- and β_2- adrenergic receptors (ARs). β_2-AR blockade may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis, and lipolysis. Moreover, bronchial hyperreactivity is a direct effect of propranolol that results in bronchospasms due to pulmonic β_2-AR blockade. In addition, the lipophilic nature of propranolol is also important. When given to infants, the long-term effects of propranolol may affect the developing central nervous system (CNS), specifically learning and memory.[9]

A solution to minimize some of the side effects of propranolol may be the use of more selective β_1-AR blockers, such as atenolol, which, at low dosages, have little β_2 activity. More importantly, atenolol is a large, hydrophilic compound and may exhibit fewer CNS-related adverse effects (e.g., sleep disturbance and agitation) in the treatment of IHs.[10] Unfortunately, there is a paucity of clinical data comparing the efficacy and safety of propranolol and atenolol.

Several retrospective studies and case reports and two small, prospective trials, including one randomized controlled trial, have demonstrated the efficacy of atenolol in the treatment of IHs.[11-18] However, it is difficult to compare the efficacy and safety of atenolol treatment with those of propranolol treatment since the majority of the previously conducted studies were fragmented, non-large-scale clinical trials. Furthermore, because of the broad heterogeneity of IH (e.g., superficial, mixed or deep, localized or segmental, and proliferating or involuting), confounding by other pharmacologic exposures (e.g., corticosteroids or cardiovascular agents), and associated complications (e.g., ulceration and/or bleeding), observational and retrospective studies may be unable to definitively establish the clinical utility of β-

blockers in IH. Therefore, questions regarding the efficacy and safety of propranolol and atenolol must be answered in large randomized clinical trials, which may represent the only way to overcome selection and ascertainment bias.[19]

6 Overall study design:

This study is a prospective, multicenter, randomized, controlled, open-label clinical trial comparing propranolol and atenolol for the management of problematic IHs. Only patients who had never received IH-specific treatments and had normal heart, liver and renal functions were included. In both groups, patients were admitted and checked for side effects for 8 hours on day 0 and day 7. The patients were observed for therapeutic effects as outpatients during schedule visits. While comparing the efficacy of medication between propranolol and atenolol, the side effects of both drugs were also monitored.

Study Type	Interventional
Study Design	Allocation: Randomized Endpoint Classification: Efficacy/Safety Study Intervention Model: Parallel Assignment Masking: Single Blind (Outcome Assessors) Primary Purpose: Treatment; Efficacy/Safety assessment

7 Approvals and legal aspects

7.1 GCP statement

This study was conducted in compliance with Good Clinical Practice of Pharmaceutical Products and the Declaration of Helsinki and in accordance with applicable legal and regulatory requirements.

7.2 Ethics approvals

Approval was obtained by the Ethics Committee (Institutional Review Board) of West China Hospital of Sichuan University, the study site of the principal investigator, and by the local institution review boards at each participating site.

7.3 Study Registration

The trial has been registered at www.clinicaltrial.gov (NCT02342275).

7.4 Informed consent

Informed written consent was obtained from the parents (or guardians) before enrolment and after the provision of detailed oral and written information concerning the context of the study and its potential benefit to the child and comprehensive safety aspects. The informed consent process was in accordance with Good Clinical Practice of Pharmaceutical Products, the International Council for Harmonization, the Declaration of Helsinki and local regulatory requirements. A patient information sheet containing background information and information about the safety of the study and its possible benefit was provided prior to obtaining consent for the study.

7.5 Confidentiality

The investigators will ensure that the subjects' anonymity is maintained. The medical records will only be reviewed by investigators and will be kept confidential without any identifying information on any study materials. A unique study identification number will be assigned and used on all study materials. On the patient report forms or other documents, participants will be identified not by their names but instead by their assigned identification number. If participant names are included on copies of documents submitted to the principal investigator, the names will be obliterated, and the assigned subject numbers will be added to the documents.

8 Target disease and subjects

The target disease of this study is problematic IH. Patients who are diagnosed with problematic IH in the Department of Pediatric Surgery, Department of Dermatology, Department of Dermatology, and/or Department of Pediatrics in six separate investigation sites in China are subjects. Only patients who voluntarily consent to participate in the study after the study has been fully explained are subjects of the research.

Volunteer recruitment posters will be released in the hospitals, and patients who volunteer to participate after fully understanding the study are targets.

Before explaining the study and receiving consent, the investigators will explain to the parents or guardian that digital photographs will be used to measure the treatment response.

9 Expected duration

Research duration: 4 years.

Recruitment period: 2 years.

After enrolment, each study subject was followed up for 96 weeks following the start of study treatment.

10 Eligibility/Inclusion criteria:

Ages Eligible for Study:	Between 5 and 20 weeks of age
Sexes Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Presenting an infantile hemangioma with the following characteristics:

(1) Superficial or mixed IHs.

(2) Proliferating hemangioma lesions impairing function (including vision, eating and hearing), in cosmetically sensitive regions, or with ulceration and/or bleeding.

(3) The minimum diameter of the lesion was 1.5 cm on the face and 3 cm outside the face (or 1.5 cm if it was ulcerated).

(4) Consent of parents (or the person with parental authority in families): signed and dated written informed consent.

11 Exclusion Criteria:

(1) Patients contraindicated for the administration of β-blockers, such as those with an allergy or hypersensitivity to propranolol; hypoglycemia (<40 mg/dL); hypotension (<50/30 mmHg); severe bradycardia (<80 bmp); second- to third-grade atrioventricular block; heart failure; bronchial asthma or bronchial obstruction.

(2) Patients with any acute illness or gastrointestinal diseases, especially one interfering with normal oral intake.

(4) Patients with inadequate liver function:

Total bilirubin higher than or equal to 1.5 × the upper limit of the normal (ULN) for age and alanine aminotransferase and aspartate aminotransferase higher than or equal to 2.5 × the ULN for age.

(5) Patients with inadequate renal function:

Serum creatinine higher than or equal to 0.8 (mg/dL).

(6) Patients diagnosed with deep IH, congenital hemangioma, Kaposiform hemangioendothelioma, tufted angioma, or other vascular anomalies.

(7) Patients previously treated with any IH therapies, including corticosteroids, propranolol, atenolol, topical timolol, captopril, itraconazole, imiquimod, vincristine, interferon-α, laser therapy or other treatments.

(8) Indication for treatment with corticosteroids, captopril, itraconazole, imiquimod, vincristine, interferon-α, sirolimus, or tacrolimus for an indication other than IH.

(9) Indication for treatment with a beta-blocker for an indication other than IH.

(10) Patients who received the following drugs within the 1 week before enrollment: β-AR agonists, such as epinephrine, norepinephrine and salbutamol, etc.; or other cardiovascular agents, including but not limited to calcium channel blockers, ACE inhibitors and inotropic agents, etc.

(11) Patients with an inability to participate in or follow-up during the study treatment and assessment plan.

12 Sample size determination

In this trial, propranolol was used as the control group to evaluate the efficacy and safety of the atenolol group (experimental group). The treatment response after 6 months of medication was used as the key therapeutic index. To calculate the sample size for this trial, we used the following assumptions:

(1) A 2-sided 0.05 significance level;

(2) Ratio of the propranolol group: atenolol group = 1:1;

(3) A statistical power of 90%;

(4) A 20% dropout rate due to ineligibility;

(5) A follow-up of at least 96 weeks;

(6) A 24-month recruitment period; and

(7) In this trial, the atenolol group's evaluation variables were compared with the propranolol group's evaluation variables to test for noninferiority. The hypotheses are listed below:

-H0: Twenty-four weeks after therapy initiation, compared to the treatment response of propranolol therapy, that of atenolol was inferior; and

-H1: Twenty-four weeks after therapy initiation, compared to the treatment response of propranolol therapy, that of atenolol was non-inferior.

(8) Very limited data are available in the literature that can be used to set hypotheses for atenolol treatment. Existing case studies are mainly based on small single-center experiences. According to previous studies, propranolol's total treatment response is assumed to be 70-100%, and atenolol's total treatment response is assumed to be 70-100%.[4,5,13,20-22] In addition, assuming that the atenolol on propranolol response rate does not fall by greater than 15%, the noninferiority margin was selected to be -15%.

(9) Assuming the ulceration rate in both groups to be 10%.

(10) A sample size of 180 patients was determined to be required for each group (a total of 360 patients).

13 Enrollment/Randomization:

Before enrollment, the parents or guardians could decide if they wanted to be included the study. Each eligible subject whose parent or guardian provided informed consent for either drug was assigned a unique subject number. Randomization was 1:1 according to computer-generated randomization sequences with blocks in random order. Statistical Analysis Software was used to produce random numbers, and there was no stratification factor in this study.

The West China Hospital of Sichuan University is the central investigative site (CIS). The CIS generated a randomization list and implemented randomization using an interactive web-based system. The CIS was in charge of randomization data management and application. In addition, randomization information was independently managed, and access was limited for investigators who treated the patients. Two randomized sequences were used for each center so that enrollment could be stratified by exposure to either propranolol or atenolol. Subjects who were randomized to a treatment had their subject number linked to a corresponding drug kit.

14 Trial schedules

Contents	Schedule (Study period: 192 weeks)							
	24	48	72	96	120	144	168	192
Recruitment of participants	→							
Primary and secondary outcome measurement	→							
Adverse event measurement	→							

15 Pretreatment evaluations

(1) At the initial visit, investigators collected demographic and clinical data. The patients' parents who opted for oral β-blocker therapy provided a thorough medical history (e.g., existence of comorbidities) and family history (e.g., cardiovascular disease).

Acquisition of general information:

-Sex;

-Gestational age;

-Date of birth;

-Age,

-Body weight.

Hemangioma histories were also taken from families, including:

-Age when the hemangioma appeared;

-Changes in the color of the hemangioma; and

-The period during which the hemangioma showed the greatest growth before referral.

(2) In all infants, the following inspections were performed before enrollment:

-Heart rate;

-Blood pressure;

-Blood glucose;

-Full blood count;

-Liver function tests;

-Renal function

-Electrocardiogram (ECG); and

-Echocardiogram.

If cardiovascular abnormalities were detected, the patient were evaluated by pediatric cardiologists to ensure that it would be safe to initiate β-blocker treatment. Echocardiographic findings, such as a false tendon in the left ventricle, a patent ovale, left superior vena cava to the coronary sinus, and small systemic-to-pulmonary arterial collateral vessels, were considered normal variants and are not reported as anomalies.

(3) When patients had more than one IH, detailed information was obtained for the most clinically important hemangioma (typically the largest or most ulcerated lesion). Hemangioma assessments included lesion size, lesion location, stage of growth,

morphologic subtypes, depth of involvement, and treatment indication.

(4) According to Chang et al., lesion size was recorded using 'hemispheric' measurement.[23] A soft tape measure was draped over the hemangioma, and the longest diameter and a measurement perpendicular to it were noted to obtain a measurement in cm^2.

(5) Hemangioma lesions were classified by morphologic subtypes:

-Localized: well-defined focal lesions;

-Segmental: a hemangioma involving an anatomic region that was often plaque-like and often measured at >5 cm in diameter; or

-Indeterminate: neither clearly localized nor segmental.

(6) Hemangioma lesions were also be classified by soft-tissue depth:

-Superficial, which was defined as red with little or no evidence of a subcutaneous component;

-Deep, which was defined as blue and located below the skin surface (deep lesions were not considered target hemangiomas in this study); of

-Mixed, which was defined as having both superficial and deep components.

Investigators at all sites received standardized training on hemangioma assessments, including training in measurement techniques and the classification of hemangiomas.

(7) Treatment indications included:

-Disfigurement: Segmental IH; Head or facial IH ≥1.5 cm; Neck, truck or extremity IH ≥3.0 cm.

-Causing functional disturbance: Periocular IH with threat to vision, nasal tip and lip (≥1.5 cm). If functional concerns were documented, indication for treatment was not classified as disfigurement (facial IH ≥1.5 cm).

-Ulceration (IH ≥1.5 cm): ulcerated IH appearing anywhere on the body surface.

-Bleeding (IH ≥1.5 cm): Bleeding IH appearing anywhere on the body surface.

16 Study visits

Study visits were scheduled at enrolment; at 1, 4, 12, and 24 weeks after treatment; and then every 12 weeks until the end of the study or if there was any specific need after enrolment. Body weight, height, heart rate, blood pressure, blood glucose, full blood count, liver function tests, renal function and ECG were obtained during protocol visits and in-between periods if needed. All adverse events, which were identified by the investigators as at least possibly treatment-related during the 24-week treatment phase, were collected by the investigator. At each visit, the drug will be handed over to the parent/guardian in an amount sufficient to last the interim duration.

17 Treatment

17.1 Standard case management

Arms	Assigned Interventions
Active Comparator: Propranolol	Drug: Propranolol Initiated at a dosage of 1 mg/kg per day divided 3 times daily for 1 week and then increased to 2 mg/kg per day divided 3 times daily from week 2. *2 mg/kg per day in 3 doses from week 2 after a gradual increase in the dose in the first week.* Other Name: None
Active Comparator: Atenolol	Drug: Atenolol Initiated at a dosage of 0.5 mg/kg per day in a single dose for 1 week and then increased to 1 mg/kg per day in a single dose from week 2. *1 mg/kg per day in a single dose from week 2 after a gradual increase in the dose in the first week* Other Name: None

In the propranolol group, propranolol was initiated at a dosage of 1.0 mg/kg per day divided 3 times daily for 1 week and then increased to 2 mg/kg per day divided 3 times daily from week 2. The treatment schedule was at least 6 months.

In the atenolol group, atenolol was initiated at a dosage of 0.5 mg/kg per day in a single dose for 1 week and then increased to 1 mg/kg per day in a single dose from week 2. The treatment schedule was at least 6 months.

Patients were administered the first dose of β-blocker at 8:00 am. During β-blocker treatments, the dose was adjusted for weight gain. At the end of treatment, the drug dose was adjusted according to the tapering schedule, which was determined by investigators and was supposed to be 4 weeks.

Tapering schedules of drug discontinuance

Week	Propranolol	Atenolol

1	1.5 mg/kg per day divided 3 times daily	0.75 mg/kg per day in a single dose
2	1.0 mg/kg per day divided 3 times daily	0.5 mg/kg per day in a single dose
3	0.5 mg/kg per day divided 3 times daily	0.25 mg/kg per day in a single dose
4	2.5 mg/kg per day divided 3 times daily	0.125 mg/kg per day in a single dose
5	Discontinued	Discontinued

17.2 Rebound management

Significant rebound after stopping the medication was treated by reinstitution of daily therapy with either propranolol (2 mg/kg per day) or atenolol (1 mg/kg per day) until hemangioma remission.

17.3 Other co-interventions

In both arms, oral antibiotics (cefaclor suspension), topical ointment antibiotics (mupirocin) and/or wound dressings were permitted to treat ulcerated IH and were recorded. The requirement for any additional IH-specific intervention was considered treatment failure.

18 Collection and assessment of series of digital photographs

Digital photographs of each target hemangioma were acquired by the site investigators at baseline and at 1, 4, 12, 24 and 96 weeks after treatment. The detailed procedures are listed below:

(1) The investigators used a unified camera model. The acquisition procedures ensured consistency in lighting, exposure and distance from the camera. All digital photographs were obtained using digital single-lens reflex cameras (Nikon D7000 or Nikon D7100, Nikon Inc., Melville, NY).

(2) For each participant site, the series images were taken in the same room. The room was a naturally well-lit room. The acquisition of digital photographs was performed carefully to avoid glare and direct light deep into the room.

(3) The background behind the patient when the images are acquired was either the parent's (or guardian's) chest or shoulder or an examination couch. The parents and patients wore light-color, nonreflective clothes. Similarly, the examination couch was covered with a light blue, non-reflective bed sheet.

(4) For each patient, at least one photograph (a front-on view with or without side-on view) was taken at each visit. If the patient had a mixed hemangioma, front-on view and side-on view photographs were taken (not mandatory).

(5) The quality of all the photographs was verified by site investigators before they were transferred to the CIS. If the photographs were not compliant with the acquisition protocol, repeated acquisition of the images was immediately performed.

(6) Each photograph was uploaded with the following information: patient ID number and date of photograph acquisition. The central investigators assessed the quality of the digital photograph once more.

(7) Digital photographs were independently assessed by three investigators (research assistants) working in the CIS who were unknown to the study group assignment and blinded to the clinical information. None of these investigators was involved in the clinical management of patients with IH. They were trained specifically to assess hemangioma evolution (response or nonresponse), hemangioma size and hemangioma color using a series of digital photographs.

19 Primary outcome measures

The primary outcome measure was the clinical response at 6 months in the intention-to-treat population. The intention-to-treat population was defined as all patients who had undergone randomization. If after assignment, a patient did not receive a drug administration or if an evaluation was never made after drug administration, the patient was excluded from the intention-to-treat population.

Digital photographs of IHs were independently obtained by three investigators who were unknown to the study group assignment. In the case of multiple IHs, only the most clinically important IH (typically the largest or most ulcerated IH) was documented.

Changes in IH size and color were classified as a complete response, nearly complete response, partial response or no response. The primary outcome measure was any response or nonresponse at 6 months in the intention-to-treat population of all patients who underwent randomization. The any response included compete, nearly complete and good responses; the nonresponse included stable or deteriorated:

-A complete response was defined as no redundant tissue or telangiectasia was identified.

-A nearly complete response was defined as a minimal degree of telangiectasis, erythema and skin thickening.[5]

-A partial response was defined as a size reduction or change in color that did not meet the nearly complete resolution criteria.

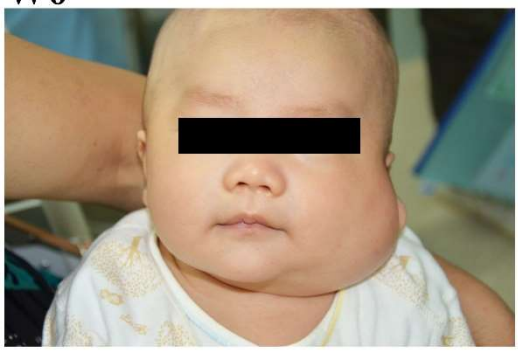
-Stable was defined as no changes in size or color between baseline and month 6.

-Deterioration was defined as further growth of the target hemangioma.

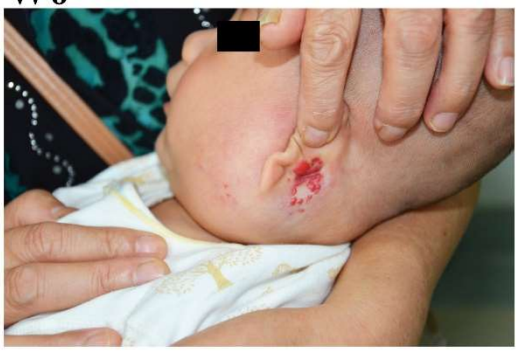
Treatment failure was defined as patients withdrawing from trial treatment due to nonresponse and/or severe adverse events.

Examples of baseline and primary endpoint photographs (any response):

W0



W0

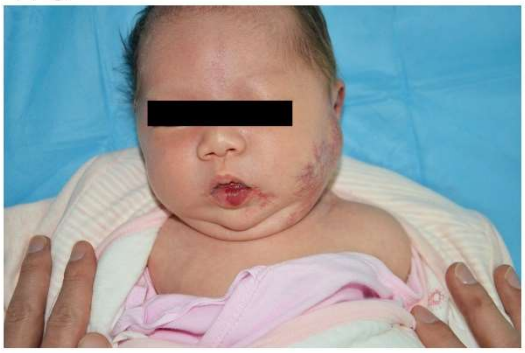


W24

W24

Examples of baseline and primary endpoint photographs (nonresponse):

W0



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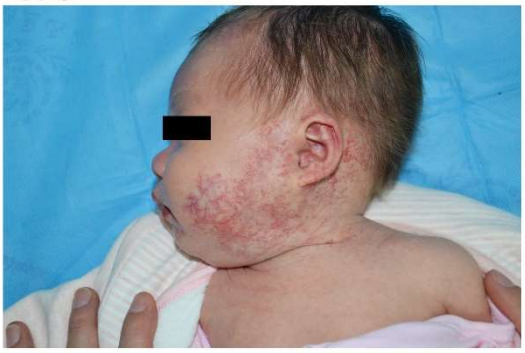

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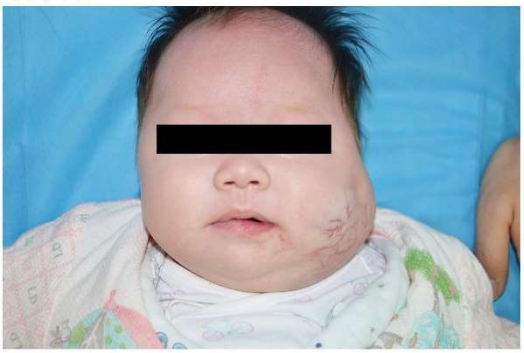

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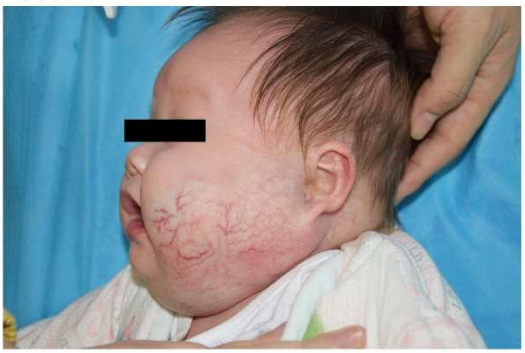

20 Secondary outcome measures

20.1 Hemangioma Activity Score

The key secondary outcome measure was the Hemangioma Activity Score (HAS), which was measured at baseline and at 1, 4, 12 and 24 weeks using digital photographs. The photographs of the target hemangioma acquired at each visit were sent to the CIS. The consecutive digital photographs were assessed by centralized evaluation at West China Hospital of Sichuan University. Three trained investigators who were unknown to the study group assignments independently evaluated the digital photographs taken at baseline and the follow-up visits. According to previous reports, changes in an individual HAS could be used to evaluate the effect of treatment. Baseline scores were subtracted from posttreatment scores to obtain the change in HAS or the decrease in hemangioma proliferative activity after treatment.[24,25]

The HAS system has three scoring forms, including the degree of deep swelling, the color of the hemangioma, and the ulceration assessment:

(1) Assessment of the degree of swelling (or protrusion or elevation). A proliferating superficial or mixed IH can present as a protrusion with an overlying red tint. If there is visible swelling (or protrusion or elevation), it was scored as follows:

-Six points if the swelling (or protrusion or elevation) was tense;

-Four points if the swelling (or protrusion or elevation) was 'neutral' (i.e., not tense or less tense) at baseline or had <50% reduction at follow-up;

-Two points when the swelling (or protrusion or elevation) was reduced by 50% or more at follow-up; or

-Zero points when there was no more visible swelling (or protrusion or elevation) at a follow-up.

If the patient had superficial IH and showed no visible evidence of swelling (or protrusion or elevation) at baseline, this step was omitted or we set the point as 0. However, the score for no swelling (which was zero) affected the final score.

(2) Assessment of the color of the IH. The hemangioma color was assessed by blinded central investigators. A bright-red (or shining-red) color suggested that the hemangioma was very actively proliferating. A diminishing red color on the surface was seen during the phases of involution. It is therefore possible that different scores might have been applied to different phases of the same hemangioma. A bright-red hemangioma received the highest score.

The intensities of hemangioma color were rated from 5 through 0:

-Five points if the hemangioma lesion was bright red all over;

-Four points if only the edge of the hemangioma lesion was bright-red;

-Three points if the hemangioma lesion was matte red or reddish-purple (totally or partially) or if the hemangioma lesion was matte red only at the edge;

-Two points if the hemangioma lesion was totally or partially blue or showed blue shining through in deep lesions;

-One point if the hemangioma lesion was totally or partially gray;

-Zero points if the hemangioma lesion was totally or partially skin-colored after involution. At this stage, the hemangioma color was imperceptible.

If the hemangioma lesion was bright red, whereas the edge was not scored, then a bright-red edge was only be scored when the rest of the hemangioma lesion was not bright red. The total number was divided by the number of items scored to give to the mean score. Even the score for a normal skin color (which will be zero) would have an effect on the final score and thus was scored only if the hemangioma lesion had previously been another color.

(2) Assessment of the ulceration. If ulcerations were visible, additional points were given. The scoring system for an ulcerated hemangioma was as follows:

-0.5 point for an ulcer ≤ 1.0 cm^2;

-One point for an ulcer >1.0 cm^2 but <25 cm^2;

-Two points for an ulcer ≥ 25 cm^2.

Overall, for an individual hemangioma lesion, the HAS scale ranges from 0 to 8. Several examples of HAS system scoring are shown in eFigures 8 and 9. The HAS system scoring for these digital photographs is illustrated in eTable 3.

20.2 Successful initial response

A successful initial response was assessed by using HAS in the intention-to-treat population. A successful initial response was defined as an HAS decrease at 1 week after treatment. Previous studies demonstrated that HAS decreases over time after β-blocker treatment, with a dramatic drop occurring in the first week, indicating an immediate therapeutic response.[24,25] HAS can reflect the rapid effect of β-blocker (either propranolol or atenolol) therapy shortly after initiation.

20.3 Quality of life

Quality of life (QOL) was measured at baseline and week 48.

20.3.1 Quality of life instrument for IH

The Quality of life instrument for IH (IH-QOL), which was developed by Sarah L Chamlin et al,[26] was designed to measure the impact of treatment on IH patients and their parents. This module consists of 4 domains and 29 items. The domains include physical symptoms of the patient (4 items), social functioning of the patient (5 items), social and psychological functioning of the caregiver (10 items), and emotional functioning of the caregiver (10 items). IH-QOL is self-administered by the patients' parents and takes approximately 5 minutes to complete. The Chinese Mandarin Version of IH-QOL has previously been translated according to standardized procedures, which consist of 4 steps: forward translation (Chinese), backward translation (English), preliminary test and field test. The Chinese version of the IH-QOL has been demonstrated to have good internal consistency in patients with IH.[27]

20.3.2 Pediatric Quality of Life Inventory 4.0 family impact module

The Pediatric Quality of Life Inventory 4.0 family impact module (PedsQL^{TM} 4.0 FIM), which was developed by Varni et al.,[28] is used to measure the impact of pediatric chronic disease on family functioning. The PedsQL^{TM} FIM can stand alone or be integrated into the other measurement model, allowing an overall assessment of QOL in children and their parents. Chen et al. translated it cross-culturally into a Chinese version.[29] The Chinese version of the PedsQL^{TM} FIM demonstrates good internal consistency and discriminant and construct validity. The FIM is a parent-reported instrument that measures the impact of chronic health conditions on children's health-related QOL (HRQOL) and their family functioning. This instrument is composed of 9 dimensions and 37 items. The dimensions include physical functioning (6 items), emotional functioning (5 items), social functioning (4 items), cognitive functioning (5 items), communication (3 items), worry (5 items), daily activities (3 items), family relationships (5 items) and financial issues (1 item). The first six dimensions measure parent self-reported HRQOL, while the latter three dimensions measure parent-reported family functions.

20.3.3 Procedures

The site investigators are trained by the project managers to guarantee the quality of the investigation. Before completing the questionnaires, the site investigators provided a good explanation of the purpose and significance of the questionnaires. Under the supervision of site investigators, when necessary, the site investigators

explained the study to the parents individually. If the parents had questions related to semantic or conceptual understanding, the site investigators assisted the parents in completing the questionnaires. In addition, the site investigators were responsible for ensuring that there were no missing data in the questionnaires.

In two questionnaires, standardized response choices consisted of five categories scored from 0 to 4. Likert-type scale responses were provided for each item: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. The items were then linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 =50, 3 = 25, 4 = 0), with higher scores indicating better HRQOL. The dimension scores are computed as the sum of the items divided by the number of items answered within a particular dimension.

20.4 Complete healing time of ulceration

Additional information was collected by site investigators for patients with ulceration. Ulceration is defined as a break in the integrity of the hemangioma surface epithelium (or skin) with or without infection. The information included the extent of ulceration, complications of ulceration, prior duration of ulceration (before treatment), concurrent treatments, and complete healing time. Prior duration of ulceration was defined as the time from the first sign of ulceration until before β-blocker treatment. The complete healing time of the ulceration was defined as the time from the first dosage of propranolol or atenolol until complete healing of the hemangioma ulceration. Concurrent treatments, including oral pain medication, oral antibiotics, topical ointment antibiotics and/or wound dressings, were permitted to treat ulcerated IH and were recorded.

20.5 Rebound rate

Regrowth of more than 20% in hemangioma appearance (including changes in color and/or volume) after stopping the medication was considered significant rebound. The inclusion criteria for rebound analysis were as follows: (1) patients who completed 6 months of treatment and (2) patients who discontinued therapy or were tapering treatment after achieving an any response. The exclusion criteria were as follows: (1) patients who were noncompliant with treatment and (2) patients who did not respond to treatment. Whether a patient had hemangioma rebound was based on the site investigators' assessments after the week 24 treatment. In patients with

significant rebound, reinitiation of systemic therapy (either propranolol or atenolol) was recommended. Minor rebound, which was defined as those patients in whose rebound was noted but no reinitiation of systemic therapy or further treatment was necessary, was not included in the analysis.

20.6 Responses at Week 96

A complete/nearly complete response at week 96 was considered median-term efficacy. The digital photographs of the target hemangioma were assessed by centralized evaluation at West China Hospital of Sichuan University. Three trained investigators who were unknown of the study-group assignments independently evaluated the digital photographs taken at baseline and week 96 after the initial treatment. For more details regarding the procedures for median-term efficacy, refer to the **Collection and Assessment of Series Digital Photographs** section.

21 Safety assessments

21.1 In-house monitoring

All patients were monitored as in-house patients for 8 hours with hourly measurements of cardiovascular examination at day 0 (week 0) and day 7 (week 1). Continuous bedside monitoring was performed on all infants during hospitalization by using a noninvasive multiparameter monitor. Blood pressure and heart rate were obtained before (baseline) and at 1, 2, 3, 4 and 6 hours following the first dose of β-blocker therapy. The blood glucose level was measured by fingerstick using an automated glucometer and obtained before (baseline) and at 4 hours after the first dose of propranolol or atenolol during hospitalization. These values were also recorded before and following the first dose of β-blocker on day 7 (week 1) after dose escalation. Blood pressure and heart rate values were compared with age-related reference ranges.

21.2 Outpatient monitoring

The patients' parents or guardians were asked to inform the investigators about adverse events at any time to ensure that potential adverse events could be handled promptly and appropriately. Parents or guardians were also provided with a patient booklet to record any possible adverse events during treatment. Data on adverse events was obtained at scheduled or unscheduled study visits based on information spontaneously provided by the subject and/or through questioning of the participant.
Each scheduled visit included an evaluation of efficacy and routine examination. Routine examinations included physical examination, electrocardiography, routine blood tests, and blood glucose measurement.

21.3 Collection and management of adverse events

The frequency of adverse events (e.g., sleep disturbance, cool or mottled extremities, diarrhea, etc.) were collected by the investigator and reported by parents. The investigators collected any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerged or worsened relative to baseline assessment. All adverse events that were identified by the investigators as at least possibly treatment-related (treatment-emergent adverse events or adverse events that have worsened since baseline) were included in the analysis. For each adverse event, the percentage of subjects who experienced at least 1

occurrence of the given event was summarized by treatment group. Adverse events during the initial 24-week treatment phase were compared between the two groups.

21.4 Definition of adverse events

Identified adverse events were coded using the latest version of the Medical Dictionary for Regulatory Activities. Adverse events included suspected adverse drug reactions, other medical experiences, regardless of their relationship with the investigative drugs, such as infections, injury, surgery, accidents, extensions of symptoms or apparently unrelated illness, and significant abnormalities in clinical laboratory values or physical examination findings. These medical conditions relate to the disease under study whose changes during the study are consistent with natural disease progression. Therefore, they are not considered adverse events, but they shall be recorded by the investigators. Medical conditions that were present at baseline shall not be considered adverse events unless worsening occurred.

Blood pressure and heart rate values were compared with age-related reference ranges: hypotension was defined as an SBP less than 50 mmHg and/or a DBP less than 30 mmHg; bradycardia was defined as an HR less than 80 beats per minute (bpm) while awake or less than 60 bpm while asleep.

Intolerable CNS-related adverse effects (e.g., sleep disturbance and agitation) were defined as adverse events that did not disappear or were not relieved after treatment administration was altered (e.g., earlier evening dose or a decrease in daily dose). Sleep disturbance was characterized by difficulty in falling sleep and/or remaining sleep, or development of increased waking or night terrors. Agitation was characterized by a state of restlessness associated with unpleasant feeling of irritability and tension.

Bronchial irritation was classified as hyperreactivity, bronchospasm, bronchiolitis, and cold-induced wheezing.

21.5 Relationship of adverse events

All adverse events were collected and graded according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). The investigators evaluated each adverse event that occurred after administration of β-blockers regarding the relationship with the administration of β-blockers. The causality of the adverse event was determined by the investigators and classified as definitively not related,

probably not related, possibly related, probably related, or definitively related. Only patients with events that were at least possibly treatment-related were taken into consideration:

(1) Definitively not related: only a remote connection exists between the administration of β-blocker and the reported adverse event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication, appear to explain the reported adverse event.

(2) Most likely, not related: an adverse event that does not follow a reasonable temporal sequence related to the administration of β-blocker and is likely to have been produced by the patient's clinical state, other modes of treatment or other known etiology.

(3) Possible related: an adverse event that has a reasonable possibility that the event may have been caused by the administration of β-blocker. The adverse event has a timely relationship to the administration of β-blockers. However, the pattern of response is atypical, and an alternative cause seemed more likely, or there is significant uncertainly about the cause of the event.

(4) Probable related: an adverse event that has a reasonable possibility that the event is likely to have been caused by the administration of β-blocker. The adverse event has a timely relationship and follows a known pattern of response, but a potential alternative cause may be presented.

(5) Definitely related: there is a reasonable possibility that the event might have been caused by the administration of β-blocker. A certain event has a strong temporal relationship, and an alternative cause is unlikely.

21.6 Grade of adverse events

Grade referred to the severity of the adverse event. CTCAE v4.0 displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on the general guidelines. A serious adverse event is defined as any of the following toxicities identified during the 6 months of treatment:

-Grade ≥3 of any adverse events;

-Persistent hypotension;

-Persistent bradycardia; and

-Intolerable CNS-related adverse effects.

21.7 Preventing and managing adverse events

(1) Before treatment, all of the parents were advised by investigators of the potential risk of side effects and educated on relative evocative signs, which included but were not limited to weakness, unusual tiredness, losing consciousness, trouble awakening, difficulty feeding, respiratory difficulty, and severe diarrhea.

(2) To avoid the risk of hypoglycemia, we requested that β-blockers should be administered within 30 min after the patients were fed. The patients' parents were instructed to ensure that their children were free to eat as often they desired. If there were any possible hypoglycemia alteration, the parents were instructed to administer oral liquids containing sugar and seek medical support in the case of persistence of these signs.

(3) In patients in whom severe complication symptoms were observed, medical support from site investigators or pediatricians was sought immediately.

(4) In cases of mild hypoglycemia, bronchitis with dyspnea, bronchial hyperreactivity or mild to moderate bronchospasms, treatment was suggested to be temporarily discontinued based on the patients' symptoms.

(5) Mild CNS-related adverse effects (e.g., sleep disturbance and agitation) might have subsided without any interventions, or they often resolved when the treatment administration was altered (e.g., earlier evening dose or a decrease in daily dose). In patients associated with intolerable CNS-related adverse effects, discontinuation of β-blocker administration was recommended.

(6) Any dose reductions, interruptions, or cessations enacted at the discretion of the investigators were recorded.

21.8 Termination of the study

All participants were informed that they had the right to withdraw from the study at any time without prejudice to their medical care and that they were not obliged to state their reasons. Follow-up was considered complete when the participant completed all study procedures and assessments up to the 96-week visit. Termination of the study was mandatory in the following situations:

-Any grade ≥4 adverse event;

-Recurrent or persistent cases of hypoglycemia, bronchitis with dyspnea, bronchial hyperreactivity or bronchospasms.

-Persistent hypotension; or

-Persistent bradycardia.

21.9 Outcome of the adverse event

The outcome of an adverse event at the time of the last observation/assessment was classified as:

(1) Recovered/resolved: All signs and/or symptoms of an adverse event disappeared without any sequelae at the time of the last observation/assessment.

(2) Recovering/resolving: The intensity of signs and symptoms was diminishing and/or their clinical pattern was changing up to the time of the last observation/assessment in a way typical for its resolution.

(3) Not recovered/not resolved: signs and symptoms of an adverse event had mostly unchanged or worsened at the time of the last observation/assessment.

(4) Recovered/resolved with sequelae: actual signs and symptoms of an adverse event disappeared, but there were sequelae related to the adverse event at the time of the last observation/assessment.

(5) Fatal: resulting in death. If there was more than one adverse event, only the adverse event leading to death was characterized as ‘fatal’.

22 Tapering and discontinuation of treatment

Propranolol or atenolol were tapered and stopped at an appropriate time, which was primarily based on the response and lesion regression after treatment. In this trial, the treatment was tapered and discontinued on complete or nearly complete resolution of IH or if no further improvement of IH (for 12 weeks of observation) was observed after month 6. At the end of the treatment period, the drug dose was gradually reduced over 4 weeks and then cease. For more detail regarding the procedures for tapering and discontinuation of treatment, refer to the **Treatment** section.

23 Data management and quality assurance

The site investigators were responsible for recording all study data in the patient report form. All of the clinical and laboratory data were entered in electronic format. The patient report form was completed as soon as possible after the clinical and laboratory data were collected, preferably on the day of the scheduled visit. Double data entry was performed, and the documents were compared. At the visit interval, the data entries were checked for completeness, and the documents were reviewed for errors. For more details regarding the procedures for digital photograph management and quality assurance, refer to the **Collection and Assessment of Series Digital Photographs** section. For more details regarding the procedures for adverse event collection, refer to the **Collection and Management of Adverse Event** section.

24 Missing data

If a patient dropped out of the study, the site investigators at the participant site attempted to ascertain the reason or reasons for the patient not continuing. If a patient missed one of the scheduled visits, the site investigators communicated with the parents or guardians to determine if the patient would come back for the next scheduled visit. As the trial progressed, missing data were monitored to ensure that there was not one data point that, for some reason, was routinely not being captured. If data were missing, the analyses were performed in several ways. The investigators first analyzed the data assumed to be missing completely at random. However, when the missingness depended on the outcome, the parameter estimation was most likely biased. The investigators would then assess the missing data mechanism according to the types of observed outcomes. When the missingness depended on the set of observed outcomes, a correctly specified covariance structure accommodated the situation. However, if the missingness was due to a primary outcome value that should have been obtained at week 24, the investigators performed a sensitivity analysis.

25 Statistical analyses

Statistical analyses were used to assess the recruitment, quality of data, and homogeneity of treatment groups and to evaluate the efficacy and safety of the treatments.

25.1 Descriptive methods

Continuous variables are described using the number of nonmissing values, mean (SD), mean (range), and median (interquartile range), as appropriate. For binary or categorical variables, absolute and relative frequencies (number and percentage) are provided. For comparisons between the groups, descriptive *P*-values are provided to show comparability of the groups in baseline characteristics and to provide a further descriptive measure.

25.2 Baseline characteristics

Both the propranolol and atenolol groups were characterized using descriptive methods based on the intention-to-treat principle. Table 1 gives an overview of what to describe at baseline in the intention-to-treat population.

25.3 Primary outcome analysis

Based on the intention-to-treat principle, the primary outcome analysis was performed in the intention-to-treat population. All patients treated with at least one dose of study medication (propranolol or atenolol) were included and analyzed in the group to which they were randomized.

Primary outcomes were analyzed by sensitivity analysis. Best-case (response) and worse-case (nonresponse) scenarios were evaluated based on the intention-to-treat principle (in the best-case scenario, missing data in the propranolol group were considered failures, and missing data in the atenolol group were considered successes). In addition, missing data in the propranolol group were considered successes, and missing data in the atenolol group were considered failures.

In addition, a per protocol analysis was performed. This means that only patients without major protocol violations are included. These patients fulfilled all inclusion and exclusion criteria and carried out all medical procedures/visits according to the protocol.

25.4 Secondary outcome analyses

Quantitative variables were compared with Student's unpaired t-test, paired t-test, Wilcoxon rank sum test (Mann-Whitney *U* test), or generalized linear mixed models (GLMM). GLMMs were employed to compare the difference between the two groups in HAS changes from baseline to 6 months. Categorical variables were analyzed with Fisher's exact test or a chi-square test, and 95% confidence intervals were calculated. Kaplan-Meier curves were used to visualize the time to treatment discontinuation.

All secondary outcomes were analyzed based on the intention-to-treat principle without imputation of missing values.

25.5 Safety outcome analyses

All safety outcomes were analyzed based on the safety population, which comprises all patients who were treated with at least one dose of trial treatment and included in a treatment group.

All premature study discontinuations are listed along with treatment group, time in study and reason for discontinuation.

Unless specified otherwise, no data imputation was applied for missing safety evaluations. For analysis and reporting purposes, partial dates for adverse events and concomitant therapies were imputed.

25.6 Differences from the trial protocol

Despite the amendment to the protocol, there were no differences from the trial protocol.

25.7 Software

All analyses were performed using SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA).

26 References

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27 Study flow chart