Efficacy and safety of oral propranolol for infantile hemangioma in Japan

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Abstract Background: There have been few reports on the efficacy and safety of oral propranolol at 3 mg/kg/day for infantile hemangioma (IH) in Japanese patients.

Methods: A multicenter, open-label phase III study was conducted to evaluate the efficacy and safety of oral propranolol solution in Japanese infants aged 35–150 days with proliferating IH. Thirty-two patients were enrolled in the study, received propranolol solution for 24 weeks at 3 mg/kg/day, and completed the study.

Results: The success rate (complete or nearly complete resolution) at week 24 (primary endpoint) was 78% (95% CI: 60–91%). The improvement rate since the previous visit was 100% (32/32) after week 5. Overall, the IH surface area, maximum diameter, and color intensity all decreased over time. Consistency in assessment between the centralized and the investigator on-site assessments was observed in 26 patients. Of the 32 patients, 11 needed further treatment other than the study drug. The incidence of adverse events (AE) and drug-related AE was 97% and 31%, respectively. AE that occurred in ≥two patients were either typical of propranolol use (such as blood pressure decrease) or common events in infants. AE that resulted in dose reduction were observed in two patients, but no serious AE or AE that led to study drug discontinuation were observed.

Conclusion: Oral propranolol solution at 3 mg/kg/day is effective and safe in Japanese IH patients.

Key words clinical trial, hemangioma, infant, Japanese, propranolol.
Although laser therapy is indicated for IH, it does not provide satisfactory efficacy, and the treatment is painful. Surgical excision has a relatively limited role in larger, more problematic IH. Therefore, treatment options for IH are insufficient at present.

In 2008, it was first reported that oral propranolol was effective for the treatment of IH that required systemic treatment. Propranolol is considered to act on IH by causing vasoconstriction, growth inhibition of vascular endothelial cells, inhibition of angiogenesis, and induction of apoptosis. The statistically significant efficacy of propranolol and its recommended dosage (3 mg/kg/day) have been reported in a large-scale placebo-controlled randomized clinical study. As a consequence, oral propranolol has become the first-line therapy for the treatment of IH.

Although there are no reports on racial differences in the pathogenesis of IH, there are racial differences in its incidence rate (Caucasian, 8–12%; Japanese, approx. 1%). Due to the small IH patient population in Japan, the efficacy of oral propranolol in Japanese IH patients had been reported in only a few case reports and small-scale clinical studies, and there have been only few reports on oral propranolol at 3 mg/kg/day in Japanese IH patients. Racial differences in the metabolic enzymes involved in propranolol metabolism should also be considered.

Because we did not participate in the global clinical study, the recommended propranolol dosage needs to be clarified in Japanese patients: namely, whether the same dosage (3 mg/kg/day) as in Caucasian patients is suitable for Japanese patients. Therefore, we conducted this clinical phase III trial of oral propranolol in Japanese IH patients to evaluate its efficacy, safety, and recommended dosage.

**Methods**

This study was conducted at 13 study sites in Japan from January 2014 to April 2015 in accordance with the Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and other applicable regulations. The present study and the study protocol were approved by the Pediatric Clinical Trials Network Central Institutional Review Board (for eight institutions) or the Institutional Review Boards of the other five institutions participating in the study. The parent(s) of all patients provided written informed consent before enrollment. This study was registered at the Japan Pharmaceutical Information Center (JapicCTI-142459).

**Participants**

Patients with IH who met all of the following criteria were eligible for this study: age 35–150 days at enrollment; and proliferating IH (target hemangioma) with a minimum diameter of 1.5 cm. A patient was excluded from the study if he or she met any of the following criteria: one or more of the medical conditions including life-threatening IH, congenital hemangioma, Kasabach–Merritt phenomenon, bronchial asthma; bronchospasm, untreated pheochromocytoma, hypoglycemia (<40 mg/dL or at risk), hypotension (systolic blood pressure [SBP] <50/diastolic blood pressure [DBP] <30 mmHg), bradycardia (<80 beats/min), second- or third-degree atrioventricular block, sick sinus syndrome, cardiogenic shock, diabetic ketoacidosis, metabolic acidosis, severe peripheral circulatory disorder, uncontrolled heart failure, and Prinzmetal angina; had previously received at least one of the prohibited medications (systemic steroids, imiquimod, vincristine, IFN-α, and beta-blockers); had previous surgical and/or medical procedures for IH; and clinical uncertainty of the diagnosis of IH. Magnetic resonance imaging was used as needed for difficult-to-diagnose lesions such as cavernous hemangioma.

**Study design**

The present multicenter, open-label phase III study consisted of the treatment period of 24 weeks (Fig. 1), with propranolol solution 3.75 mg/mL (propranolol base; Hemangiol® Syrup for Pediatric 0.375%; Pierre Fabre Dermatologie, Boulogne-Billancourt, France), which included a 6 day titration period and a dose maintenance period.

After a patient’s eligibility was confirmed and written informed consent was obtained, treatment with propranolol solution was started at 1 mg/kg/day divided into two daily doses, which was increased in 1 mg/kg/day increments to 3 mg/kg/day every second day during the titration period. Before increasing the dosage, the investigator confirmed the tolerability in each patient. Propranolol solution was given with or immediately after a meal. To ensure the safety of all patients, they were hospitalized until 1 day after treatment of the first maintenance dose of 3 mg/kg/day. After discharge from hospital, patients visited the study site at the end of weeks 1, 2, 3, 5, 8, 12, 16, 20, and 24. During the 12 week survey period, after the completion of the 24 week treatment period, the investigator recorded the presence or absence of further treatment of the target IH every 4 weeks.

**Photographic assessment**

At least two digital photographs of the target IH were taken by the site investigators at each visit from week 1 to week 24, following the standardized procedures. The first photograph was taken in an image plane parallel to the target IH (front-on view) and the second photograph in an image plane at a different angle to that of the first photograph (side-on view) so that the thickness of the lesion could clearly be visualized. All photographs included a color chart to enable color and size calibration. Photographs taken at the study site were transferred to the contract research organization. The contract research organization performed quality control and color calibration of each photograph. The image data were forwarded to the assessment committee office where photograph-based centralized assessment was performed by two independent and trained readers. Detailed procedures for photographs and
photo-based centralized assessment, and the validation of readers and investigators were conducted in accordance with those described in a previous placebo-controlled randomized clinical study. The Japanese centralized assessment readers were trained by the centralized assessment readers of the previous study using the previous study photographs. All investigators received training by Japanese centralized assessment readers, and their assessments were validated before the initiation of the investigator on-site assessment.

**Study endpoints**

The primary efficacy endpoint was evaluation of the target IH from baseline to week 24, expressed as centralized assessment of success rate. Treatment success was defined as centralized assessment of complete or nearly complete resolution of the target IH at week 24. Nearly complete resolution was defined as minimum degree of telangiectasia, erythema, skin thickening, soft-tissue swelling and/or distortion of anatomical landmarks.

Major secondary endpoints of centralized assessments included the improvement rate of IH since the previous visit at weeks 5, 8, 12, 16, 20, and 24, the entire target IH surface area, and the maximum diameter and color intensity (International Commission on Illumination [CIE2000] color difference formula: \( \Delta E^*_{2000} \)) at weeks 12 and 24. Other major secondary endpoints were the investigator on-site assessment, which included the success rate and the improvement rate of IH since the previous visit at weeks 1, 2, 3, 5, 8, 12, 16, 20, and 24.

The safety assessments included adverse events (AE), vital signs, pinprick blood glucose, laboratory tests (hematology and clinical chemistry), physical examination, and electrocardiogram. Significant AE, including AE leading to study drug discontinuation, hypotension, bradycardia, congestive heart failure, atrioventricular block, asthma excluding infectious diseases, bronchospasm and hypoglycemia, were also assessed.

If further treatment was carried out after the completion of the treatment period with propranolol, the treatment method and the treatment start date were also recorded.

**Statistical analysis**

Although a placebo group was not planned in this study, propranolol was determined to be effective when the lower limit of the 95%CI of the success rate exceeded 12%; which is the maximized estimate of the placebo success rate based on the results of the previous placebo-controlled randomized clinical study. The simulation was performed to estimate the probability that the lower limit of the 95%CI (exact) would exceed 12% assuming a success rate of 30–60%, with the number of patients at 30. Based on the results of simulation, a sample size of 30 patients was considered adequate for efficacy assessment.

The efficacy analyses were performed on the full analysis set (FAS), which included patients who received the study drug and had efficacy data. The per-protocol set (PPS) was defined as a subset of the FAS without any major protocol deviations that might have affected the efficacy evaluation. The safety results were analyzed in the safety population of patients who received the study drug and had safety data.

The following statistical analyses were carried out to analyze the data obtained by the centralized assessments and the investigator on-site assessments. For the success rate and the improvement rate since the previous visit, the 95% CI (exact) were calculated. For the time to the first sustained complete/nearly complete resolution of the target IH, Kaplan–Meier estimates were provided. As sensitivity analysis, the same analysis was carried out on the PPS.

Sub-analyses were carried out by stratifying the results according to target IH ulceration, possible target IH functional impairment, sex, age at first treatment, IH site, and clinical type of target IH (superficial, mixed, or deep).

For the analysis of AE, the number of patients, the incidence rate and the number of events were investigated according to occurrence of AE, severity, seriousness, and significance. For the analysis of electrocardiogram, QT intervals were corrected for heart rate using both the Bazett (QTcB) and Fridericia (QTcF) methods. QT interval was also corrected using the pediatric formula (QTcP).

**Results**

**Patients**

Thirty-two patients were enrolled in the study, received propranolol solution, and completed 24 weeks of the treatment period (Fig. 2). All patients completed a further 12 weeks of the survey period. Four patients had six protocol deviations (prohibited treatment taken by the lactating mother, two patients; insufficient exposure to study drug, one patient; prohibited concomitant treatment, insufficient study drug compliance <70%, insufficient exposure to the study drug, all in one
patient), of whom the one patient who received a prohibited concomitant treatment was excluded from the PPS. Baseline patient characteristics are listed in Table 1. There were more female patients (n = 23, 72%) than male patients (n = 9, 28%). The mean age at the first propranolol treatment was 107.9 days. More patients had IH of the facial area (63%, 20/32) than non-facial areas (38%, 12/32). According to the International Society for the Study of Vascular Anomalies classification, the superficial (flat or elevated) type was found in 69% (22/32) than non-facial areas (38%, 12/32). According to the International Society for the Study of Vascular Anomalies classification, the superficial (flat or elevated) type was found in 69% (22/32) than non-facial areas (38%, 12/32).

The maintenance dosage of propranolol was 3 mg/kg/day in all patients, and the mean (±SD) number of treatment days during the maintenance dose period was 168.3 ± 3.5 days (range, 161–175 days). No patients had extension of the titration period or reduction of the dose for safety reasons.

Efficacy

The success rate of propranolol at week 24 is summarized in Table 2. According to the centralized assessments, the success rate at week 24 from baseline was 78% (95%CI: 60–91%), and the lower limit of the 95%CI exceeded the efficacy criteria of 12%. Similar results were obtained in the PPS. The improvement rate of IH since the previous visit was 100% (32/32) after week 5, and was sustained until week 24, excluding one patient each at week 8 and at week 16. The median surface area (7.3 cm² at week 0, 4.0 cm² at week 12, and 2.7 cm² at week 24; Fig. 3a), maximum diameter (3.4 cm at week 0, 2.8 cm at week 12, and 2.5 cm at week 24; Fig. 3b), and color intensity (26.2 at week 0, 18.4 at week 12, and 12.8 at week 24; Fig. 3c) decreased over time. Representative examples of IH in patients treated with propranolol are shown before treatment (Fig. 4a1–c1), at week 2 (Fig. 4a2–c2), and at week 24 (Fig. 4a3–c3). Target IH ulceration or possible functional impairment did not affect success rate when the results were stratified by these factors (present, 10/12, 83%; absent, 15/20, 75%). A similar success rate was also found when the data were stratified by sex (male, 7/9, 78%; female, 18/23, 78%); age at first treatment (35–90 days, 8/11, 73%; 91–150 days, 17/21, 81%); IH site (facial, 16/20, 80%; non-facial, 9/12, 75%); or clinical type of target IH (superficial, 17/22, 77%; mixed, 6/8, 75%; deep, 2/2, 100%). According to the investigator on-site assessments, the success rate at week 24 was 78% (25/32). The improvement rate in IH since the previous visit was 78% (25/32) after 1 week, and 100% (32/32) after 5 weeks. Improvement was sustained until week 24. Consistent assessment results were obtained in approximately 80% of patients (n = 26: success, n = 22; failure, n = 4) between the centralized and the investigator on-site assessments. Discrepancy in assessment was observed in six patients between the centralized and the investigator on-site assessments (success in the centralized assessment and failure in the investigator on-site assessment, n = 3; failure in the centralized assessment and success in the investigator on-site assessment, n = 3).

Further treatment

Of the 32 patients who completed the survey period, a total of 11 patients received further treatment other than the study drug during the 12 week survey period, after the completion of the 24 week treatment period. A lower incidence of further treatment was observed in patients who were assessed as successful in the primary analysis (success, 7/25, 28%; failure, 4/7, 57%). The mean time to further treatment in patients with success was 50.0 ± 31.6 days, which was longer than for the patients with failure (21.3 ± 13.3 days). Ten of 11 patients received another formulation of oral propranolol (e.g. tablets) and one patient was treated with pulsed dye laser after the 24 week treatment period. There was no association between time to further treatment and age at the time of the last propranolol treatment in the further treatment group. There was also no association between the primary endpoint and age at last propranolol treatment in patients without further treatment. Further treatment was given to the following among the high-risk patients: two of six patients with ulceration; three of 10 patients with a risk of functional impairment; and one of four patients who had both.

Safety

The incidence of AE was 97% (31/32 patients). The AE were either mild or moderate in severity (Table 3). The incidence
of drug-related AE was 31% (10/32 patients), and all drug-related AE were mild in severity. There were no serious AE or AE that led to discontinuation of the study drug. AE that led to a dose reduction were observed in two patients (bronchitis in one patient, and upper respiratory tract inflammation and wheezing in one patient). A causal relationship with the study drug was denied for bronchitis and upper respiratory tract inflammation, but not for wheezing. Bronchitis was moderate, and upper respiratory tract inflammation and wheezing were mild in severity. Both patients recovered with treatment.

Propranolol-related AE that carried important risk consisted of decreases in DBP, SBP and BP (i.e. decrease in both SBP and DBP in the same measurement), and occurred in 3/32 patients, but they were mild in severity and the patients recovered without any treatment. Another propranolol-related AE that carried important risk was wheezing, which occurred in one patient, but it was mild in severity and resolved with treatment. AE that occurred in ≥ two patients, such as

Table 1  Baseline patient characteristics

|                  | n (%) | mean ± SD (range), or median (range) |
|------------------|-------|-------------------------------------|
|                  |       |                                     |
| FAS              | 32    |                                     |
| Sex              |       |                                     |
| Male             | 9 (28) |                                     |
| Female           | 23 (72)|                                     |
| Age at first treatment (days) | 107.9 ± 28.7 (53–150) | |
| IH site          |       |                                     |
| Facial†          | 20 (63)|                                     |
| Non-facial       | 12 (38)|                                     |
| Clinical type of target IH |       |                                     |
| Superficial (flat or elevated) | 22 (69) | |
| Mixed (superficial and deep) | 8 (25) | |
| Deep             | 2 (6)  |                                     |
| Target IH ulceration‡ |       |                                     |
| Yes              | 6 (19) |                                     |
| No               | 26 (81)|                                     |
| Target IH functional impairment§ |       |                                     |
| Yes              | 10 (31)|                                     |
| No               | 22 (69)|                                     |
| Concomitant disease |       |                                     |
| Yes              | 20 (63)|                                     |
| No               | 12 (38)|                                     |
| Target IH surface area (cm²) | 7.3 (1.1–50.9) (IQR, 3.1–18.0) | |
| Target IH maximum diameter (cm) | 3.4 (1.3–10.8) (IQR, 2.3–5.8) | |
| Target IH color intensity (dE*2000) | 26.2 (4.8–56.6) (IQR, 18.0–36.1) | |

†Includes the head and neck. ‡Head and neck area with lesion size 627–2,263 mm² in five patients; body area with lesion size 3,290 mm² in one patient. §Head and neck area such as under ears, eyelids, and lips, with a risk of causing hearing, vision, and eating impairment in all 10 patients. dE*2000, International Commission on Illumination (CIE2000) color difference formula; FAS, full analysis set; IH, infantile hemangioma.

Table 2  Centralized assessment of target IH at week 24 from baseline

|        | Success† | Failure | Success rate (%) | 95% CI |
|--------|----------|---------|------------------|--------|
| FAS    | n (%)    | n (%)   |                  |        |
| 32     | 25 (78)  | 7 (22)  | 78               | 60–91  |

†Complete or nearly complete resolution of the target IH at week 24. †No. patients with success on propranolol 3 mg/kg/day 6 months/no. patients in FAS × 100. FAS, full analysis set; IH, infantile hemangioma.

Fig. 3  Change in (a) entire target infantile hemangioma (IH) surface area; (b) maximum diameter; and (c) color intensity at weeks 12 and week 24 from baseline. Box, IQR; whiskers, minimum and maximum. n = 31 throughout, because one patient who received a prohibited concomitant treatment was excluded. dE*2000, International Commission on Illumination (CIE2000) color difference formula.
nasopharyngitis, diarrhea, infantile eczema, pyrexia, upper respiratory tract inflammation, and eczema, were either typically associated with propranolol use or were common events in infants. Drug-related AE that occurred in ≥two patients were diarrhea, pyrexia, alanine aminotransferase increase, and aspartate aminotransferase increase. No deaths or serious AE occurred throughout the study.

No clinically meaningful changes were observed on laboratory tests. During the titration period, decreases in heart rate, BP, and respiratory rate were observed, but there was no association between the size of the decrease in these parameters and the dose. Although DBP, SBP and BP decreased in three patients (reported AE), the decrease from baseline was small in almost all cases (range, 4–54 mmHg), and a consistent tendency was not observed. These changes were asymptomatic and not serious, and did not lead to discontinuation of the study drug in any patients. During the treatment period, two patients had QTc (QTcF, QTcP) prolongation ≥60 ms from

Fig. 4  Photographs of target infantile hemangioma (IH) at (a1-c1) before treatment, (a2-c2) at week 2, and (a3-c3) week 24. Photographs were adjusted to be equal in size and were trimmed to focus on the target IH lesion area.

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Table 3 Incidence of AE in the safety group

| AE‡ | Drug-related AE§ |
|-----|------------------|
| n (%) | n (%) |
| No. patients in the safety group | 32 | 32 |
| Any AE | 31 (97) | 10 (31) |
| Severe | 0 | 0 |
| Moderate | 4 (13) | 0 |
| Mild | 31 (97) | 10 (31) |
| Serious AE | 0 | 0 |
| AE leading to discontinuation of the study drug | 0 | 0 |

Known important risks associated with propranolol

- DBP decrease: 2 (6) vs. 2 (6)
- SBP decrease: 2 (6) vs. 2 (6)
- BP decrease: 1 (3) vs. 1 (3)
- Wheezing: 1 (3) vs. 1 (3)

AE occurring in ≥2 patients

- Diarrhea: 9 (28) vs. 4 (13)
- Constipation: 2 (6) vs. 0
- Pyrexia: 6 (19) vs. 1 (3)
- Nasopharyngitis: 10 (31) vs. 0
- Conjunctivitis: 3 (9) vs. 0
- Excoriation: 3 (9) vs. 0
- ALT increase: 2 (6) vs. 2 (6)
- AST increase: 2 (6) vs. 2 (6)
- URT inflammation: 6 (19) vs. 0
- Rhinorrhea: 3 (9) vs. 0
- Eczema infantile: 8 (25) vs. 0
- Eczema: 4 (13) vs. 0
- Dry skin: 3 (9) vs. 0
- Erythema: 3 (9) vs. 0
- Urticaria: 2 (6) vs. 0

†Tabulated according to the preferred terms from the Medical Dictionary for Regulatory Activities, version 18.0. ‡Defined as any undesirable and unintended signs, symptoms, or diseases that occurred during the treatment period. §Defined as occurring during the treatment period, for which study drug causality could not be ruled out. ¶The investigator reported “decreased blood pressure,” because both DBP and SBP decreased in one patient in the same measurement. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; URT, upper respiratory tract.

Discussion

The present study has shown the efficacy of oral propranolol at 3 mg/kg/day for 24 weeks in Japanese IH patients. The incidence rate of IH in the Japanese population is one-tenth that in the Caucasian population. In addition to the limitation on recruiting a large number of IH patients, it was unethical to include a placebo-controlled group in this study, because it involved high-risk IH such as ulcerated IH and possible functional impairment. Such high-risk patients, who need effective treatment, were included in this study because ulcerated IH is painful and accompanied by bleeding and infection, and possible functional impairment may result in vision, hearing, and eating impairment. Although corticosteroids have been the mainstay of IH therapy, they are not approved for IH in Japan. We therefore did not set a control group and referred to the results of a previous placebo-controlled randomized clinical study in which the same study drug was used,§ to interpret the present results.

Statistically significant efficacy of propranolol was reported in the previous placebo-controlled randomized clinical study, which provided convincing evidence for the therapeutic efficacy of propranolol. In the previous study the proportion of female infants was 71%, mean age at inclusion was 104 days, and facial IH comprised 70%. The patient baseline characteristics in the present and the previous study are similar except that the present study consisted of Japanese patients and included high-risk IH. The efficacy in the present and previous studies was evaluated using the same methods at the same time. Therefore, comparison of the results of the previous and present studies is acceptable.

Given that these baseline characteristics are consistent with the general epidemiological characteristics of IH patients requiring systemic treatment, the present results can likely be generalized.

With regard to the primary outcome, approximately 80% of the patients had complete or nearly complete resolution after 24 weeks of treatment. This percentage was higher than in the previous study (60%). This might be at least partly related to differences in study design. The time course of changes in efficacy followed a similar pattern to the previous study: efficacy was observed even at 1 week after the start of treatment, and the efficacy that was observed at 5 weeks after the start of treatment lasted up to week 24. Such efficacy was observed not only in the high-risk patients, but also in all patients irrespective of IH lesion area, IH type, and age at the time of treatment initiation, indicating that treatment with oral propranolol is effective in Japanese IH patients.

Discrepancies in assessment were observed only in six of 32 patients between the investigators and the centralized assessment in this study. This low discrepancy rate is likely due to the fact that the centralized assessment readers directly instructed the investigators on assessment before the initiation of this study, and also that this study was conducted only in Japan. In contrast, a substantial number of discrepancies have been reported in the assessment of the efficacy in the previous study, in which the on-site investigators did not receive specific training in the assessment of complete/nearly complete resolution.

Although it was planned to treat patients with propranolol at 1 or 2 mg/kg/day if they had tolerance issues, no patients had any such issues, and all patients were therefore treated at 3 mg/kg/day. Expected AE associated with propranolol use, such as decrease in BP and heart rate, were observed in a few patients, but these were all mild in severity and resolved without any treatment. No clinically significant serious
drug-related AE were observed in Japanese IH patients. Therefore, oral propranolol was well-tolerated in Japanese IH patients in the present study.

Overall, propranolol at 3 mg/kg/day is effective and well-tolerated in Japanese IH patients, and the same dosage and treatment duration used in other countries are also recommended in Japan.

In the present study approximately one-third of the patients were further treated with another propranolol treatment, independent of the 6 month treatment result. One of the reasons for requiring the further treatment is that the proliferative phase of IH could have still been on going after the 24 weeks of treatment in those patients. Furthermore, the rate of further treatment in the high-risk patients was not high and, therefore, the study drug was likely effective even in the high-risk patients. Given that IH can relapse after completion of propranolol treatment in some patients,24 and that some patients are treated with propranolol for an extended period,25,26 treatment longer than 24 weeks may be required in some patients. To clarify the optimal treatment duration, and to assess the efficacy and safety of long-term propranolol treatment, further studies are needed. In addition, given that only 32 patients were included in the present study due to the small number of Japanese IH patients, a large-scale clinical study will be necessary to further evaluate the efficacy and safety.

The superiority of oral propranolol to other pre-existing treatment methods has been reported in the past. In a small-scale clinical study, higher efficacy of oral propranolol at 2 mg/kg/day compared with laser treatment and cryosurgery has been reported.16 Propranolol has also shown better efficacy and fewer AE than corticosteroids.27–29 Given that propranolol appears to offer better efficacy and safety results than conventional therapies, it represents a better treatment option for Japanese IH patients.

In conclusion, propranolol at 3 mg/kg/day is effective and safe in Japanese IH patients, and the same dosage and treatment duration used in other countries are applicable to Japanese patients. It is expected that oral propranolol will become the first-line of therapy for IH in Japan as well.

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Author contributions

T.K. designed and supervised the study, interpreted the data, and drafted and revised the content of the manuscript. S.S. and N.B. evaluated the primary efficacy outcome and drafted the main content of the manuscript. K.K., K.M., H.O., N.H., A.N., K.O., Y.K., A.M., Z.T., M.K., K.K., T.O., and A.S. recruited the participants and collected the data. T.H. designed and coordinated the study. R.K. interpreted the data and did the major preparation of the manuscript. All authors critically read and approved the final manuscript.

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