An Open-Label Single-Arm Clinical Trial of Propranolol Cream in Infantile Hemangioma

Eiko Nagata (✉ ngt815@gmail.com)

Hamamatsu University Hospital

Yasuharu Kashiwagura

University of Shizuoka

Eisaku Okada

Hamamatsu University School of Medicine

Shimako Tanaka

University of Shizuoka

Shinichiro Sano

Hamamatsu Medical Center

Mitsuhiro Nishida

Hamamatsu Medical Center

Satoshi Hayano

Chutoen General Medical Center

Satoru Iwashima

Chutoen General Medical Center

Akio Hakamata

Fujimi Children's Clinic

Keiichi Odagiri

Hamamatsu University Hospital

Naoki Inui

Hamamatsu University School of Medicine

Hiroshi Watanabe

Hamamatsu University School of Medicine

Kazuo Umemura

Hamamatsu University School of Medicine

Shinya Uchida

University of Shizuoka

Research Article

Keywords: Infantile hemangioma (IH), tumor , Oral propranolol, hypotension, bradycardia, hypoglycemia

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-701185/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Infantile hemangioma (IH) is a common tumor in infants that gradually resolves and is often followed up for observation. However, for cosmetic reasons, parents often opt for treatment. Oral propranolol, the first-line therapy for IH, shows several side effects, including hypotension, bradycardia, and hypoglycemia. No clinical studies on topical propranolol have been conducted using standardized procedures. We evaluated the efficacy and safety of topical propranolol in patients with IH. This multicenter, open-label phase II study was conducted from June 2019 to December 2020 and involved 8 Japanese infants aged 35–150 days with proliferating IH. Patients were treated with 5% propranolol cream twice daily. We examined the efficacy rate based on central evaluation (complete or near-complete healing of the target hemangioma) at weeks 24 and 12, respectively, compared to baseline values. The efficacy rate at week 24 was 68.8% (95% confidence interval: 44.1–85.9%). The surface area, maximum diameter, and color intensity of the target IH decreased over time. Adverse event and drug-related adverse event rates were 87.5% and 0%, respectively. Propranolol cream (5%) is effective and safe in Japanese patients with IH and may be considered a first-choice treatment for small and superficial IHs in cosmetically problematic areas.

Trial registration number

The trial is registered at the Japan Registry of Clinical Trials (jRCTs 041190041).

Full date of first registration: 11/06/2019

Web link: <https://jrct.niph.go.jp/en-latest-detail/jRCTs041190041>

1. Introduction

Infantile hemangioma (IH) is the most common soft-tissue tumor in infants, occurring in 4–5% of infants. Tumors of IH occurring within the first week of life grow rapidly over the first 3–6 months of life. By the age of 4 years, 90% of IHs regress spontaneously [1, 2]. Therefore, IH tumors are often followed up for observation [1, 2].

Most IHs occur in the periphery of the head and neck areas [3], which can seriously affect a child's appearance and psychology [4]. Even when associated vital, functional, and cosmetic problems are mild, parents are often concerned about the cosmetic aspects because most IHs form on the body surface, and thus, the parents request treatment for IH [4]. In 2008, a French patient with hypertrophic obstructive cardiomyopathy complicated by IH was treated with propranolol, a nonselective beta-blocker, which ameliorated the hemangioma [5]. This led to the recognition of oral propranolol therapy against IH [5]. Today, oral propranolol is approved worldwide and is the first-line treatment for IH in patients with a potential risk of dysfunction and serious condition [1, 2]. However, several side effects have been reported, including hypotension, bradycardia, sleep disturbance, hypoglycemia, hyperkalemia, and respiratory symptoms [1, 2]. These side effects occur because of the systemic effects of propranolol, as it

is an oral formulation, although the currently approved oral propranolol therapy is highly effective against IH [1].

Several reports are available on topical application of propranolol for IH [6]. However, to date, no clinical trials on topical propranolol have been conducted using standardized procedures. Previous studies only included patients with regressed IH, involved longer treatment periods to target the regressed period, were clinical trials with complex or subjective evaluation methods without standardized procedures, or were observational studies [6].

Therefore, this study was conducted to evaluate the efficacy and safety of 5% propranolol topical cream in Japanese patients with IH.

2. Results

2.1 Patients

A total of 8 patients participated in the study between July 2019 and July 2020. All patients received and completed 24 weeks of study treatment and were analyzed (Figure 1). The patient characteristics are summarized in Table 1. There were 2 males and 6 females. Among them, 2 patients had a gestational age of less than 37 weeks. The mean ($\pm$ SD) age at the start of propranolol therapy was 91.8 ($\pm$ 39.7) days. The IH was located on the scalp, back, upper and lower extremities, and genitalia. The clinical type of all patients was superficial. One patient with IH had ulcer.

2.2 Efficacy

The efficacy rate of propranolol at weeks 24 and 12 is summarized in Tables 2 and S1. According to the centralized assessments, the efficacy rate at week 24 from baseline was 68.8% (95%CI: 44.1–85.9%), and the lower limit of the 95%CI exceeded the efficacy criteria of 12%. In comparison, the efficacy rate at week 12 from baseline was 31.3% (95% CI: 14.1–55.9%). Two assessors showed a Cohen's Kappa coefficient of 0.714, which was virtually identical. As shown in Table 2, the mean surface area (3.6, 3.5, and 2.7 cm² at weeks 0, 12, and 24, respectively), mean maximum diameter (2.8, 2.5, and 2.2 cm at weeks 0, 12, and 24, respectively), and mean color intensity (21.3, 14.7, and 9.2 at weeks 0, 12, and 24, respectively) decreased over time. All cases of IH in patients treated with propranolol before treatment and at weeks 12 and 24 are shown in Figure 2.

2.3 Safety

AEs that occurred during the study treatment are summarized in Table 3. The incidence of any AEs and drug-related AEs were 87.5% (7 in 8 patients) and 0%, respectively. The AEs were mild elevation in liver enzymes, upper respiratory tract inflammation, abrasions, eczema, subcutaneous hematomas, urticarias,

and infectious dermatitis. Mild elevations in liver function enzymes observed during the study period resolved spontaneously. Upper respiratory tract inflammation was mild in all cases and resolved with expectorant oral treatment. Eczema, which occurred in a different area from the target IH, resolved with moisturizer treatment. Urticaria that occurred in a different place from the subject IH was cured with oral antihistamines. Abrasions and subcutaneous hematomas occurred in areas other than the target IH and were cured without treatment. Infectious dermatitis occurred at the target IH site and quickly healed with oral antimicrobial treatment. None of the reported risks associated with propranolol, such as hypotension, bradycardia, hypoglycemia, or bronchial asthma, were observed in the patients during the study treatment (Table S2).

The plasma concentrations of propranolol in all patients are shown in Table 4. At weeks 4 and 24 of the study treatment, 37.5% (3 of 8 patients) and 87.5% (7 of 8 patients) of patients, respectively, showed propranolol in the plasma. The highest plasma propranolol concentration was 4.42 ng/mL at week 4 and 5.31 ng/mL at week 24.

3. Discussion

The present clinical trial demonstrated the efficacy and safety of 5% propranolol topical cream in Japanese patients with IH. The method for evaluating efficacy was similar to that used in previous clinical trials [7, 8]. In the current clinical trial, the efficacy rate of 5% propranolol topical cream against IH after 24 weeks of treatment was 68.8%, which was higher than that of the placebo group in the phase II/III clinical trial [8]. Regarding safety, no severe AEs, which are often associated with propranolol, were observed during the study.

Efficacy was demonstrated by the success rate at week 24 and decrease in surface area, maximum diameter, and color intensity. We used a placebo value of 12% as our estimate, which was the placebo value for the oral drug in the reported clinical trial [8]. This value was used because there was no valid estimate that could be used for topical agents. The efficacy rate at week 12 was low (31.2%), suggesting some time is required for the drug to produce an effect. Moreover, the surface area, maximum diameter, and color intensity exhibited a decreasing trend over time. The CIE 2000 color difference formula used to calculate the color difference is characterized by its high correlation with visual inspection and is used for efficacy assessment of treatment of IH [7, 8].

The cream was shown to be safe with no serious side effects such as hypotension, bradycardia, or hypoglycemia, unlike the oral formulation. In a clinical study of an oral liquid formulation in Japanese subjects, the median simulated trough concentrations in the plasma after repeated oral administration of 3 mg/kg/day propranolol twice daily for 168 h were 16.7, 20.8, and 26.4 ng/mL at 6, 9, and 12 h, respectively [9]. In the present study, plasma concentrations were measured at weeks 4 and 24; both of the highest values were considerably lower than the simulated trough concentration, suggesting that the drug had little systemic effect and was only locally effective. Generally, a higher plasma concentration of a drug is associated with a higher incidence of side effects. Therefore, the low plasma concentration of

propranolol in this study may have resulted in the low incidence of adverse drug reactions compared with oral drug administration. These results support the safety of topical propranolol cream.

The efficacy and safety of topical timolol or propranolol have been described in several uncontrolled case reports and case series; however, only one randomized, controlled trial comparing timolol with placebo has been reported [1, 10]. Currently, no topical beta blockers are available for IH. A cream formulation was chosen in this study because a previous study comparing the effects of ointment, cream, and gel formulations of propranolol hydrochloride on porcine skin showed that creams exhibited higher retention of the drug effect on the skin surface, whereas peripheral vascular penetration was lower [11]. Topical beta blockers are expected to have a local effect because they are not subjected to the first-pass effects of the liver, once safety and efficacy are confirmed [1, 12].

4. Methods

4.1 Ethics

This study protocol was approved by the ethics committee of the Hamamatsu University School of Medicine in Japan. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and other applicable regulations. Written informed consent was obtained from the legal guardians of all patients prior to the study. This trial was registered at the Japan Registry of Clinical Trials (jRCTs 041190041).

4.2. Participants

The study included 35–150-day-old patients who were diagnosed with infant hemangioma of the superficial type with a diameter of 1.5 cm or more. Patients were recruited from the Department of Pediatrics, Hamamatsu Medical Center, and Chutoen General Medical Center in Shizuoka, Japan. Patients were excluded if they had the following conditions: 1. IH affecting life or function, 2. Kasabach–Merritt syndrome, 3. receiving treatment for IH (e.g., laser therapy and propranolol oral therapy), 4. poorly controlled heart failure, 5. a history of bronchial asthma or bronchospasm, 6. hypoglycemia (blood glucose <40 mg/dL), 7. hypotension (systolic blood pressure <50 mmHg, diastolic blood pressure <30 mmHg), and 8. bradycardia (pulse <80 beats per min).

4.3 Study Design and Treatments

This was a multicenter, phase II, open-label, single-arm study conducted in Japan from June 2019 to December 2020. Patients with IH were treated with 5% propranolol cream twice daily for 24 weeks. The study medication was prepared as follows. Propranolol hydrochloride powder (Tokyo Chemical Industry, Tokyo, Japan), polyethylene glycol 400 (PEG 400, Fujifilm Wako Pure Chemical Corporation, Osaka, Japan), and purified water were mixed by inversion and further placed in a warm water bath at 50°C for

15 min. The hydrophilic cream was added to this aqueous solution and mixed using a self-rotating mixer at $100 \times g$ for 1 min. The parents were instructed to apply the cream using a fingertip onto the surface of the IH (sufficient to just coat the tumor) twice per day and to gently rub it in. The condition of IH in participants was observed 8 times: at screening; baseline; and weeks 4, 8, 12, 16, 20, and 24.

4.4 Efficacy and Safety Assessments

Efficacy was assessed by two independent and trained assessors using standardized photographs with a defined procedure. The assessors evaluated all photos; the date of visit and patient number were masked. To measure efficacy parameters, we performed intrareader variability assessment in a previous clinical study [7]. Photographs of the target IH were taken according to a standardized procedure by an investigator assigned on day 1 and weeks 12 and 24 of treatment. A color chart for image correction, Casmatch (Bear Medic Corporation, Tokyo, Japan), was placed next to the tumor to adjust the brightness of all photographs. Casmatch, a diagnostic and evaluation method in the field of dentistry, was used for image analysis of the efficacy evaluation [13, 14]. Photographs were taken at least twice for each tumor with the tumor subject identification code, and color chart in focus. To determine the area, diameter, and color difference of the hemangioma from the photographs, image analysis was performed. First, color tone and size correction were performed using Casmatch in the images using Adobe Photoshop CC (Adobe Corporation, San Jose, CA, USA) and ImageJ (National Institutes of Health, Bethesda, MD, USA). Second, the tumor of interest was surrounded by a dot, and the area, length, diameter, and hues of red, green, and blue (RGB) were measured. The boundary between the tumor area and normal skin was determined by three investigators. In addition, four points of normal skin were selected to evenly surround the tumor followed by measurement of the RGB, and the average value of the four points was calculated. The color difference (dE^*_{2000}) was calculated for the RGB of the tumor and normal skin.

Safety was assessed by analyzing adverse events (AEs, i.e., any adverse change in condition between the time of informed consent and the end of the trial), laboratory investigations (measurement of glucose levels from finger-prick blood samples and serum propranolol concentrations), physical examination, assessment of vital signs and neurodevelopment, and electrocardiography. The plasma concentrations of propranolol were determined using liquid chromatography coupled with tandem mass spectrometry.

4.5 Outcome Measures

The primary and secondary outcomes were the rate of efficacy of treatment based on central evaluation (complete or near-complete healing of the target hemangioma) at weeks 24 and 12, respectively, compared with baseline. The other secondary endpoints were changes in the area, maximum diameter, and color intensity of the target IH at weeks 12 and 24.

4.6 Power Calculation

The sample size was calculated using the minimax method for a phase II study [15]. The sample size is 6 when the minimum effective rate is 0.12, expected effective rate is 0.6, alpha error is 0.05, and power is 0.8. We considered 12% as our estimate for minimum effective rate, as the efficacy rate [95% confidence interval (CI)] of the placebo group in a phase II/III clinical trial was 3.6% [0.44–12.53] in a previous study [8]. Assuming an incidence of dropout and data rejection of 25%, 8 cases were required. For efficacy assessment, propranolol cream was considered as effective if the lower limit of the 95% CI for efficacy at week 24 was greater than 12%.

4.7 Statistical Analysis

The full analysis set or all patients administered the study treatment were the primary analysis set for all planned efficacy and safety analyses. All statistical results were descriptive [qualitative variables: number, percentage, and 95% CI; continuous data: number, mean, and standard deviation (SD)]. No statistical tests were performed.

5. Limitations

This study had some limitations. First, because of the small size, a control arm could be not set up, and patients with IH at all sites on the body could not be included. Second, the study was conducted only in Japanese patients. Third, the observation period was short (up to 24 weeks). Finally, unlike clinical trials [7, 8], we used the easier and more portable Casmach as a color scale. In this study, standardized procedures were used to evaluate color intensity and size with Casmach.

6. Conclusions

In summary, we conducted an open-label, single-arm study of 5% propranolol topical cream in Japanese patients with IH. The efficacy of the cream was found to be similar to that of the oral formulation. Additionally, the safety of the cream was found to be superior to that of the oral formulation, with no observed AEs. Topical propranolol may be considered a first-line treatment for small and superficial IHs in cosmetically problematic areas that do not require systemic treatment. Large, placebo-controlled trials of topical propranolol in multiracial patients with infantile hemangioma are warranted.

Declarations

Acknowledgements

We are grateful to all patients, physicians, and clinical research coordinators who participated in this study. We thank Yumi Kiyama, Yuki Matsushita, Kumiko Makino (Hamamatsu University School of Medicine), and Masao Fujiwara (Hamamatsu Rosai Hospital) for supporting this project; Kasumi Yamakawa, Chika Kawaguchi, Shinji Watanabe (Hamamatsu Medical Center) and Kisaki Minamida, Shinzo Kitajima, Masaharu Ito (Chutoen General Medical Center) for preparing the propranolol cream;

Riku Setogawa and Marina Mogi (University of Shizuoka) for technical assistance; and Professors Tsutomu Ogata (Hamamatsu University School of Medicine) and Noriyuki Namiki (University of Shizuoka) for their helpful insight. This study was funded by Japan Research Foundation for Clinical Pharmacology and Japan Foundation for Pediatric Research. Japan Research Foundation for Clinical Pharmacology and Japan Foundation for Pediatric Research had no role in the design and conduct of the study.

Authors' Contributions

EN and SU conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

YK, EO, and ST designed the data collection instruments, performed the initial analyses, and reviewed and revised the manuscript.

SS, MN, SH, and SI collected data and critically reviewed the manuscript.

AH, KO, NI, HW, and KU performed the investigations and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest:

The authors declare that they have no conflict of interest.

Availability of data and material:

Deidentified individual participant data will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to ngt815@gmail.com.

References

1. Léauté-Labrèze, C., Harper, J. I. & Hoeger, P. H. Infantile haemangioma. *Lancet*, **390** (10089), 85–94 (2017).
2. Tiemann, L. & Hein, S. Infantile hemangioma: A review of current pharmacotherapy treatment and practice pearls. *J. Pediatr. Pharmacol. Ther*, **25** (7), 586–599 (2020).

3. Püttgen, K. B. Diagnosis and management of infantile hemangiomas. *Pediatr. Clin. North Am*, **61** (2), 383–402 (2014).
4. Zweegers, J., van der Vleuten, C.J. & The psychosocial impact of an infantile haemangioma on children and their parents. *Arch. Dis. Child*, **97** (10), 922–926 (2012).
5. Léauté-Labrèze, C. *et al.* Propranolol for severe hemangiomas of infancy. *N. Engl. J. Med*, **358** (24), 2649–2651 (2008).
6. Price, A., Rai, S., Mcleod, R. W. J., Birchall, J. C. & Elhassan, H. A. Topical propranolol for infantile haemangiomas: A systematic review. *J. Eur. Acad. Dermatol. Venereol*, **32** (12), 2083–2089 (2018).
7. Kaneko, T. *et al.* Efficacy and safety of oral propranolol for infantile hemangioma in Japan. *Pediatr. Int*, **59**, 869–877 (2017).
8. Léauté-Labrèze, C. *et al.* A randomized, controlled trial of oral propranolol in infantile hemangioma. *N. Engl. J. Med*, **372** (8), 735–746 (2015).
9. Takechi, T. *et al.* Population pharmacokinetics and pharmacodynamics of oral propranolol in pediatric patients with infantile hemangioma. *J. Clin. Pharmacol*, **58** (10), 1361–1370 (2018).
10. Chan, H., McKay, C., Adams, S. & Wargon, O. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. *Pediatrics*, **131**, e1739–e1747 (2013).
11. Padula, C., Nicoli, S., Pescina, S. & Santi, P. The Influence of formulation and excipients on propranolol skin permeation and retention. *BioMed. Res. Int*.1281673 (2018).
12. McMahon, P., Oza, V. & Frieden, I. J. Topical timolol for infantile hemangiomas: Putting a note of caution in “cautiously optimistic”. *Pediatr. Dermatol*, **29** (1), 127–130 (2012).
13. Cochrane, N. J., Walker, G. D., Manton, D. J. & Reynolds, E. C. Comparison of quantitative light-induced fluorescence, digital photography and transverse microradiography for quantification of enamel remineralization. *Aust. Dent. J*, **57** (3), 271–276 (2012).
14. Wang, S. *et al.* A colourimetric evaluation of the effect of bacterial contamination on teeth stained with blood in vitro: Evaluation of the efficacy of two different bleaching regimes. *Aust. Dent. J*, **63** (2), 253–260 (2018).
15. Kanda, Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*, **48**, 452–458 (2013).

Tables

Table 1

Baseline patient characteristics

Total number of patients	8
Sex; Number of patients	
Male	2
Female	6
Gestational age; Number of patients	
Term born (>37 weeks)	6
Born prematurely (<37 weeks)	2
Age at the treatment	
Days; mean ($\pm$ SD)	91.8 ($\pm$ 39.7)
35–90 days; Number of patients	5
<90 days; Number of patients	3
Hemangiomas; Number of patients	
Location	
Scalp	1
Back	1
Upper extremity	3
Lower extremity	2
Genitalia	1
Clinical type	
Superficial	8
Ulcer	
Yes	1
No	7

Table 2

Primary and secondary efficacy outcomes

	Before treatment	Week 12	Week 24
Primary efficacy evaluation			
Efficacy rate at week 24; % (95% CI)	-	-	68.8 (44.1– 85.9)
Secondary efficacy evaluation			
Efficacy rate at week 12; % (95% CI)	-	31.3 (14.1– 55.9)	-
Change in surface area, maximum diameter, and color intensity of target IH; mean (±SD)			
Surface area (cm ²)	3.6 (±1.7)	3.5 (±1.7)	2.7 (±1.5)
Maximum diameter (cm)	2.8 (±0.7)	2.5 (±0.7)	2.2 (±0.9)
Color intensity (dE* 2000)	21.3 (±4.2)	14.7 (±3.2)	9.2 (±3.0)

Table 3

Treatment-emergent adverse events in the safety population^a

	Number of patients
Hepatobiliary disorders	
Hepatic enzyme increased	1
Infections and infestations	
Upper respiratory inflammation	6
Skin and subcutaneous tissue disorders	
Abrasion	2
Dermatitis	1
Eczema	3
Subcutaneous hematoma	1
Urticarias	1
^a Safety population included all patients. Adverse events were any events that occurred or worsened during trial treatment; they were tabulated according to the terms from the Medical Dictionary for Regulatory Activities (MedDRA).	

Table 4

Plasma propranolol concentrations^a

Plasma concentrations (ng/mL)	Week 4	Week 24
Patient 1	N.D. ^b	0.59
Patient 2	1.16	0.60
Patient 3	N.D.	0.75
Patient 4	N.D.	5.31
Patient 5	4.42	2.89
Patient 6	N.D.	N.D.
Patient 7	4.00	2.27
Patient 8	N.D.	0.79
^a The detection limit was set at 0.50 ng/mL. Values below 0.50 ng/mL were considered N.D. ^b N.D., not detectable.		

Figures

Figure 1

CONSORT diagram

Figure 2

Photographs of target IH in all patients at day 0 and weeks 12 and 24

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplement.docx](#)