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A study of 95 infantile hemangiomas treated with propranolol: A potentially efficacious combination with laser therapy

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SUMMARY We studied 95 patients with infantile hemangioma (IH) treated with propranolol at the Department of Dermatology, Kumamoto University Hospital, from November 2016 to January 2022, based on sex, site, clinical classification, duration of treatment, and residual lesions after treatment. Four of the 95 patients discontinued propranolol due to side effects, and 55 completed follow-ups at our hospital. We observed that 30.1% showed complete resolution of the skin rash, while the remaining 69.8% had erythema or atrophic scarring. Complete resolution occurred in 70% of the cases with the subcutaneous type but only in 15% with the tumor type. Seventeen of the 55 patients who completed follow-ups were treated with propranolol combined with laser therapy. Combined use of propranolol and laser therapy significantly reduced severe erythema compared to the propranolol monotherapy. These results suggest that propranolol therapy in IH often leaves erythema except in the subcutaneous type and that an improvement in erythema can be expected when propranolol is combined with laser therapy.

Keywords combination therapy, infantile hemangioma, laser, propranolol, residual lesion

Infantile hemangioma (IH) is a benign tumor derived from vascular endothelial cells and characterized by neoplastic proliferation of vascular endothelial cells and resolution by apoptosis. In most cases, IH is not present at birth; it develops at 2-4 weeks and resolves spontaneously by 5-6 years of age (*1,2*). Léauté-Labrèze C *et al*. used propranolol in infants with IH complicated by hypertrophic obstructive cardiomyopathy and discovered by chance that the drug was remarkably effective in IH, which was reported in 2008 in a paper (*3*). In Japan, propranolol was approved for IH in September 2016 and is now used in many patients. In the past, IH was often treated by a wait-and-watch approach. However, the complete resolution of the hemangioma was surprisingly rare, and some residual lesions such as telangiectasia, atrophic scars, and sagging skin were often seen after resolution. With the advent of oral propranolol, the time seems ripe for aggressive therapeutic intervention to reduce residual lesions more lightly. In this study, we analyzed patients with IH who were treated with propranolol at our hospital and reported on the efficacy of the combination of propranolol and laser therapy.

Data from 95 patients with IH treated with oral propranolol therapy at the Department of Dermatology, Kumamoto University Hospital (Kumamoto, Japan) from November 2016 to January 2022 were analyzed retrospectively for sex, site, clinical classification (*4*), treatment duration, and residual lesions after treatment. In accordance with the Declaration of Helsinki, the institutional review board approval was obtained, and all patients provided written informed consent. The laser used was a 595-nm long-pulse dye laser (V-beam, Candela Corp. Wayland, USA). Categorical variables were expressed as frequencies and percentages and compared using the χ^2 test. All analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a p-value < 0.05 was regarded as statistically significant.

We introduced propranolol to 95 patients with IH at our hospital, and 55 completed follow-ups within the target period, 17 of whom were treated with propranolol combined with laser therapy (Figure S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*). The average age for initiation of propranolol was 4 months, and the

average duration of treatment was 1 year and 2 months, regardless of concurrent laser therapy. Four patients discontinued propranolol due to side effects, which included hypotension, diarrhea, asthma-like attacks, and hypoglycemia/convulsions (Table S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*).

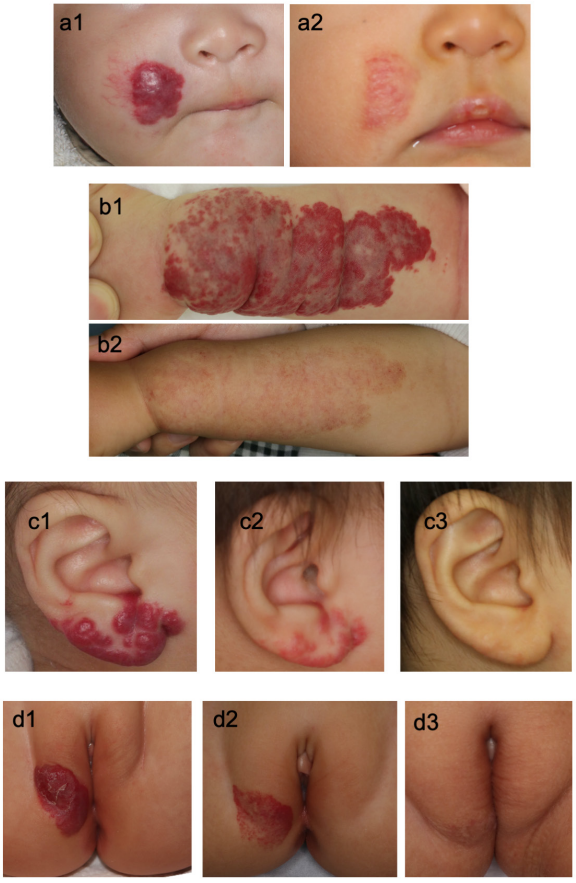

Figure 1. Residual erythema. (a, b) Cases of residual erythema after oral propranolol treatment. IH of tumor type in the right cheek: **(a1)** before treatment, **(a2)** after 6 months of oral propranolol therapy. IH of tumor type in the forearm: **(b1)** before treatment, **(b2)** after 2 years of oral propranolol therapy. **(c, d)** Cases of erythema improved by adding laser treatment to oral propranolol. IH of tumor type in the right auricular: **(c1)** before treatment, **(c2)** after 6 months of oral propranolol therapy, and **(c3)** additional laser treatment after 3 irradiations. IH of tumor type in the genitalia: **(d1)** before treatment, **(d2)** after 1 year and 2 months of oral propranolol therapy, and **(d3)** additional laser treatment, after 3 irradiations.

IH was more prevalent among girls, with a male-to-female ratio of 1:3.3 (boys: 23.2%, girls: 76.8%) (Table S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*). About half of the patients (45.6%) had facial lesions, which are an indication for propranolol therapy due to possible subsequent functional and cosmetic problems. Most had tumor type (72.0%). Of the 55 patients who completed the follow-ups at our institution, only 30.1% had complete resolution of the skin rash, and the remaining 69.8% had erythema and atrophic scarring despite propranolol treatment (Figure 1a and 1b, Figure S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*). We observed that 70% of the patients with the subcutaneous type had complete resolution with propranolol monotherapy alone. In contrast, in the non-subcutaneous type, erythema often remained, and complete resolution of the tumor type was seen in only 15 % of cases (Figure S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*).

In the propranolol combined with the laser therapy group, all patients showed a reduction or disappearance of erythema (Figure 1c, d). Therefore, we performed a statistical analysis on the efficacy of the combination of propranolol and laser therapy. Regarding baseline characteristics, compared with the propranolol monotherapy group, the combined laser group was more likely to have the tumor type (85.7% *vs*. 52.4%, p = 0.010). No patients with the subcutaneous type received laser therapy due to lack of laser indications. There were no other differences in sex, number of lesions, or location between the two groups (Table S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=136*). To determine the effect of laser therapy on residual erythema, we compared the therapeutic outcomes of the two groups by dividing the degree of residual erythema into mild and severe. The subcutaneous type was excluded from this analysis as it was not indicated for laser treatment (Table 1). No cases of severe residual erythema remained in the combined laser treatment group. Severe erythema was significantly reduced in the propranolol combined with the laser therapy group compared to the propranolol monotherapy

Table 1. Relationship between residual erythema and laser therapy

Type of hemangioma	Degree of erythema	Propranolol monotherapy	Propranolol combined with laser	p-value
Plaque + Tumor		n = 32 IH	n = 21 IH	
(n = 53 IH)	mild	13 (40.6%)	9 (42.9%)	0.872
	severe	7 (21.9%)	0 (0%)	0.022
Plaque		n = 10 IH	n = 3 IH	
(n = 13 IH)	mild	5 (50.0%)	1 (33.3%)	0.563
	severe	0 (0%)	0 (0%)	-
Tumor		n = 22 IH	n = 18 IH	
(n = 40 IH)	mild	8 (36.4%)	8 (44.4%)	0.604
	severe	7 (31.8%)	0 (0%)	0.009

IH, infantile hemangioma.

group (21.9% *vs*. 0%, $p = 0.022$). This reduction was the most prominent for the tumor type (31.8% *vs*. 0%, $p = 0.009$).

In this study, we presented two novel findings. First, IH, except for the subcutaneous type lesions, treated with oral propranolol monotherapy often left residual lesions such as erythema. The cause of residual erythema after propranolol treatment is not yet understood. Factors contributing to erythema include simple residual lesions, nutrient vessels, and normal blood vessels that have become more prominent due to skin stretching. Future studies using Glut-1 staining of skin biopsy from the erythematous area may help to determine the cause. Second, we found that combined use of propranolol and laser therapy significantly reduced severe residual erythema compared to the propranolol monotherapy, especially in the tumor type. Almost all cases of tumor type IH that resolved completely were treated with propranolol combined with laser therapy. Laser therapy was more reliably and rapidly effective for erythema than oral propranolol, however due to the small number of patients in this study, there was no significant difference in the plaque type or residual mild erythema. Further case studies are needed.

Recently, several papers have reported on the combination of oral propranolol and laser therapy for IH (*5,6*). Reddy KK *et al*. reported that patients with segmental IH of the face had earlier remission in the propranolol plus laser therapy group than in the propranolol monotherapy group (*7*). In the present study, there was no difference in the mean durations of propranolol treatment with or without laser therapy. We observed several patients in which the tumor had flattened and only erythema remained, was continued propranolol for a long period of time despite laser therapy. When the tumor flattens, it may be better to discontinue propranolol, to prevent its side effects, and continue with only laser treatment.

To summarize this study, propranolol therapy effectively reduced the tumor size; however, erythema persisted for a longer time than expected, while laser therapy effectively eliminated the surface erythema. We believe that a regimen that extracts the advantages of each method is recommended; initiating laser therapy as soon as an IH is detected, adding oral propranolol when a tumor forms, and discontinuing oral propranolol and continuing laser therapy alone when the tumor flattens and only erythema is present. We hope that with the accumulation of data from future cases, the combination of propranolol and laser therapy can become the standard therapy for IH and that IH can be treated promptly with fewer residual lesions.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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