Effect of combined low-dose oral prednisone with beta-adrenergic receptor antagonists for refractory infantile hemangiomas: retrospective cohort study in 76 patients

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Background: Beta-adrenergic receptor antagonists have been the first-line treatment for infantile hemangiomas (IHs); however, monotherapy may fail to achieve sufficient efficacy for certain patients, especially for refractory IHs. The aim of this study was to evaluate the efficacy and safety of the combination of prednisone and beta-adrenergic receptor antagonists for refractory IHs.

Methods: We studied 76 patients with refractory IHs. After more than one month of insufficient oral propranolol therapy, forty-four patients received additional treatment of prednisone, while thirty-two patients continued to receive beta-adrenergic receptor antagonists monotherapy. The response to treatment was assessed according to hemangioma score values.

Results: The outcomes of patients after combined treatment were significantly better than those with monotherapy of beta-adrenergic receptor antagonists. The age to initiate prednisone was significantly negatively correlated with the improvement in the combination treatment group. The age at initiate treatment showed significant correlation with score variation percentage in both groups. There was no significant difference in the treatment duration observed between the two groups. Multivariable logistic regression analysis for all patients showed prednisone administration was the most important factor to better overall outcomes.

Conclusions: Short-term addition of low-dose oral prednisone is an effective and safe adjunctive treatment for oral propranolol in contributing to refractory IH. Both early administration and long enough duration would be necessary.

Keywords: Infantile hemangioma (IH); refractory; combination of low dose oral prednisone with oral propranolol; effectiveness; beta-adrenergic receptor antagonists

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Introduction

Infantile hemangiomas (IHs) are the most common tumor of infancy, with a prevalence estimated at 1–10% of the infants worldwide. IHs most often appear on the head, neck, and trunk and some patients will experience complications, such as pain, ulceration and functional limitation (1). Previous studies indicate that decreasing gestational age, low birth weight, and female predominance are closely associated with higher IH incidence (2). In 2008, Léauté-Labrèze *et al.* reported the success to treat hemangioma with propranolol (3), which leads to a revolution of IH management, and the use of propranolol has come to the forefront because of its efficacy and minimal side effect. Since then, propranolol and other beta-adrenergic receptor antagonists have become the first-line treatment instead of corticosteroid therapy. For superficial IHs, topical beta-adrenergic receptor antagonists have been commonly used (4-6) and oral propranolol has become the standard treatment for high-risk and deep IH (7). However, the clinical response rate of the first-line treatment with propranolol is around 90% and there are still cases with large size or serious complications or low sensitivity to propranolol can not receive notable improvement after beta-adrenergic receptor antagonists (7,8). Therefore, a combination of prednisone and beta-adrenergic receptor antagonists is brought to the forefront (9-13) by several investigators. There were few studies in this filed, however, higher dose or longer duration of prednisone were used, or fewer cases were reported.

In this study, we summarized our experiences of treating refractory IH patients with a combination of low dose and short duration prednisone and beta-adrenergic receptor antagonists, which demonstrated a promising perspective for these cases.

Methods

Study design

We conducted the retrospective cohort study of refractory IH patients between June 2014 and June 2018 at our outpatient clinic at the Department of Oral and Maxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Patients that fulfilled our inclusion and exclusion criteria were consecutively enrolled. The inclusion criteria was: patients who received oral propranolol at least 1 month after treatment initiation; the hemangioma score value was evaluated before and after oral propranolol treatment, and the hemangioma score variations were defined as ≤1; parents or guardian of patients gave written informed consent. The exclusion criteria included hypersensitivity to propranolol, heart defects or arrhythmia. Patients were followed up through outpatients and by mobile application or phone call, if necessary.

This study was carried out in accordance with the recommendations of Declaration of Helsinki. The protocol was approved by the Institute Review Board of Shanghai Ninth People's Hospital (SH9H-2019-T272-1). All parents or guardian of participants of this study gave written informed consent in accordance with the Declaration of Helsinki for the participation in the study, and the publication of identifiable images at the initiate prescription.

Treatment regimen

All patients were given oral propranolol (Jiangsu Yabang Aipusen Pharmaceutical Industry Limited Company, China) at a dose of 2.0 mg/kg/day. For patients with superficial or compound IHs, topical 0.5% timolol maleate eye drops (Bausch Lomb Pharmaceutical Industry Limited Company, China) was used three times a day at an interval of 8 hours.

Patients were divided into two groups retrospectively depending on whether received additional oral prednisone. For patients in group 1, prednisone (Shanghai Sine Pharmaceutical Laboratories Company, China) was used only for one month at a dose of 1 mg/kg every other day and other drug administrations were as the same as the patients (group 2) who received monotherapy of beta-adrenergic receptor antagonists. The drug administrations were continued until objective goals were obtained or no further improvement was achieved.

All patients underwent a thorough physical examination prior to the treatment, including cardiovascular examination, ultrasound investigation, and clinical photography. During the treatment, cardiovascular examination (including heart rate and blood pressure) were carried out before and after the initiate treatment. Then cardiovascular examination was repeated every one month as a routine. Weight and height were also recorded before and after one month's prednisone in patients of group 1.

Outcome measurement

Until now, no standardized or validated method exists for outcome measurement of hemangiomas. Because

Table 1 Hemangioma score

Component	Quality	Score (0–17)
Color of the lesion	Bright red	2
	Pale	1
	Skin color	0
Surface consistency	Markedly raised	2
	Raised	1
	Flat	0
Firmness	Firm	2
	Softer	1
	Not firm or much softer	0
Depth (if ultrasound was performed; otherwise "0")	Maximal (90–100%)	2
	Less (50–89%)	1
	No depth or much less deep (<50%)	0
Size (maximum diameter)	>4 cm	2
	<4 & >2 cm	1
	<2 cm	0
Organ involvement	Functional limitation	7
	Impending functional limitation	4
	None	0

the goal of treatment was minimizing functional and cosmetic impairment, we modified the semi-quantitative hemangioma score system (6) to evaluate the therapeutic effects. The outcomes of each patient were evaluated based on the improvement of color, size, surface consistency, firmness, depth and functional disturbance (as shown in *Table 1*). Evaluation of the improvement was conducted twice by the other two independent physicians when the first visit, the diagnosis of refractory IH made, one month after oral prednisone and after the full course of treatment. Therapeutic response was assessed by the percentage of changes in score values as follows: excellent response (75–100%), good response (50–75%), fair response (25–50%) and poor response (0–25%).

Statistical analysis

Statistical analysis was performed using the SPSS software package (version 16.0; SPSS, Chicago, IL) and R program. Descriptive data were expressed as number, percentage, or means ± standard deviation. Wilcoxon test was used to compare the clinical response at different groups and based on the percentage of changes in score values. Spearman rank correlation was used to analyze the correlation between clinical characteristics and the percentage of changes in score values. Orient logistic regression analysis was used to determine the important factors to the treatment response. P value <0.01 were considered significant.

Results

Clinical and histological features

Eighty-six patients were identified as eligible for the study because their hemangioma score variations were defined as ≤1. Ten were excluded because of missing data. The remaining 76 made up the cohort. The mean age when the diagnosis of refractory IH was mad was 5.52 (±2.85) months, and 54 patients (71.05%) were female. The detailed histological features were in *Table 2*.

Based on the treatment regimen, the cohort was divided into 2 groups, forty-four patients who received combined

Table 2 Clinical characteristics of patients

Clinical characteristics	With prednisone (group 1) (N=44), n (%)	With prednisone (group 2) (N=32), n (%)	Total (N=76), n (%)
Gender			
Male	11 (25.00)	11 (34.38)	22 (28.95)
Female	33 (75.00)	21 (65.63)	54 (71.05)
Pregnancy			
Premature	8 (18.18)	4 (12.50)	12 (15.79)
Progesterone	13 (29.55)	12 (37.50)	25 (32.89)
Location			
Head and neck	39 (88.64)	21 (65.63)	60 (78.95)
Torso and extremities	3 (6.82)	10 (31.25)	13 (17.11)
Both	2 (4.55)	1(3.13)	3 (3.95)
Type			
Superficial	21 (47.73)	18 (56.25)	39 (51.32)
Compound	13 (29.55)	13 (40.63)	26 (34.21)
Deep	10 (22.73)	1 (3.13)	11 (14.47)
Feature			
Multi	7 (15.91)	4 (12.50)	11 (14.47)
Ulceration	1 (2.27)	0 (0.00)	1 (1.32)
Mucous	0 (0.00)	2 (6.25)	2 (2.63)
Extra agents			
Eye drop	34 (77.27)	29 (90.63)	63 (82.89)

treatment of propranolol and prednisone were assigned to group 1, and thirty-two patients who received monotherapy of propranolol were assigned to group 2 as control. Patients with superficial, compound but no mucosa IHs (n=63) received extra topical 0.5% timolol maleate eye drops, among them, thirty-four were in group 1 and twenty-nine were in group 2.

Therapeutic outcomes

The therapeutic outcomes were accessed by the average score variation percentage, which was the proportion of the score variation in the initial hemangioma score.

(I) The average score variation percentage after combined treatment in group 1 was 66.41% (23.03%), and 44.97% (17.57%) after monotherapy in group 2. The significant difference was observed between the two groups (P=0.000).

(II) In group 1, 35 (79.55%) patients showed immediate improvement after one month's prednisone, and the mean score variation percentage was 26.12% (±11.53%).

(III) The average entire treatment duration was 9 (±2.06) months in group 1 and 8.81 (±5.54) months in group 2. No significant difference was observed between the two groups (P=0.320).

(IV) For patients with superficial, compound, multiple IHs who received extra topical 0.5% timolol maleate eye drops (n=63), there was also significant difference between average score variation percentage in group 1 (n=34, 62.81%±22.47%) and those in group 2 (n=29, 44.38%±17.73%), with 0.002 as the P value.

(V) Analysis of other different clinical characteristics in group 1 and group 2 also performed and for patients with IHs on head and neck, a significant

Table 3 The therapeutic outcomes of patients with different clinical characteristics

Clinical characteristics	With prednisone (group 1), mean ± SD (%)	With prednisone (group 2), mean ± SD (%)	P value
Gender			
Male	67.62±27.37	42.14±18.04	0.034
Female	62.37±22.94	45.90±16.94	0.018
Pregnancy			
Premature	–	–	–
Progesterone	62.30±25.05	37.70±16.15	0.022
Feature			
Multi	–	–	–
Ulceration	–	–	–
Location			
Head and neck	63.91±23.66	44.93±17.47	0.004*
Torso and extremities	–	–	–
Both	–	–	–
Type			
Superficial	64.51±21.27	50.30±16.37	0.028
Compound	60.05±24.93	37.27±16.34	0.026
Deep	–	–	–
Total	63.69±23.90	44.61±17.13	0.001*

*, P<0.01 was considered as significant. The therapeutic outcomes were accessed by the average score variation percentage, which was the proportion of the score variation in the initial hemangioma score. –, the numbers of patients with one kind of characteristics is less than 10.

difference was found between with or without prednisone (*Table 3*).

Correlation analysis

We performed the correlation analysis between the score variation percentage and the entire treatment duration, the age at initiate treatment in both groups; between the score variation percentage and the age at initiate prednisone, the duration of treatment before and after prednisone in group 1 (*Table 4*).

(I) The age at initiate prednisone showed significant correlation with score variation percentage (r=–0.436, P=0.003) in group 1.

(II) The age at initiate treatment showed significant correlation with score variation percentage both in group 1 (r=–0.462, P=0.002) and group 2 (r=–0.466, P=0.007).

(III) The entire treatment duration showed significant correlation with score variation percentage in group 1 (r=0.437, P=0.003) but not in group 2 (r=0.173, P=0.345).

(IV) In group 1 the duration of treatment after prednisone was significantly correlated with the improvement (r=0.525, P=0.000) but that before prednisone showed no correlation with the score variation percentage (r=0.196, P=0.203).

Addition of prednisone and the age at drug initiation were the most important factors

We performed ordinal logistic regression analysis on the overall outcomes in all patients with all clinical characteristics and different treatment regimens (gender, location, premature or not, with or without progesterone, type, feature, the age at drug initiation, the entire duration

Table 4 Correlation between clinical characteristics and clinical response

Clinical characteristics	Group 1		Group 2	
	Correlation coefficient	P value	Correlation coefficient	P value
Age at drug initiation	–0.462	0.002*	–0.466	0.007*
Age at initiate prednisone	–0.436	0.003*	–	–
Entire duration	0.437	0.003*	0.255	0.159
Duration before prednisone	0.196	0.203	–	–
Duration after prednisone	0.525	0.000*	–	–

*, P<0.01 was considered as significant.

of propranolol, addition of prednisone). The results showed that addition of prednisone (coefficient: –1.795, P=0.005) and the age at drug initiation (coefficient: –1.592, P=0.001) were the most important factors to the overall outcomes (*Table 5*).

Complications

No systemic adverse effects were noted during treatment. No significant increase in weight or height was recorded after one month's low dose prednisone in group 1. Local side effects were observed in 3 patients who used topical timolol, two patients experienced pruritus and 1 patient developed excoriations. These minor side effects resolved within 10 days without specific treatment.

Follow-up

The follow-up period after treatment ranged from 10 months to 2.5 years. No patient experienced recurrence or rebound growth of the lesion at the last follow-up. Typical images with excellent response were shown in *Figures 1-4*.

Discussion

Prednisone used to be the first-line therapy for IHs until numerous studies support the efficacy and reduced side effects of propranolol. Since 2008 beta-adrenergic receptor antagonists have become the first choice instead of corticosteroid therapy. However, monotherapy of propranolol can not always achieve notable improvement for the refractory IHs with large size or serious complications or low sensitivity to propranolol, as reported by other investigators (7,8).

In this study, we retrospectively analyzed the refractory IH treatment cohort, divided the cohort into 2 groups depending on the treatment regimens and compared the therapeutic outcomes between the combined additional prednisone group and monotherapy group. As shown in the result section, patients in combined treatment received significant improvement than those in the monotherapy group. Besides, 79.55% of patients showed immediate improvement after one month's prednisone. Patients with superficial, compound IHs were given extra topical 0.5% timolol maleate eye drops as the regular treatment. Our results showed that for those patients, treatment of oral propranolol and topical 0.5% timolol maleate eye drops with additional prednisone also achieved better outcomes than those without prednisone. This finding is in agreement with our hypothesis and consistent with other studies (9,11,13).

Correlation analysis showed that the age to initiate prednisone was significantly negatively correlated with the improvement in the combination treatment group, which suggested that additional prednisone should be given in the early stage when no notable improvement was achieved after the beta-adrenergic receptor antagonists treatment. Meanwhile, the age at initiate treatment showed significant correlation with score variation percentage both in group 1 and group 2, which indicated that refractory IHs should be treated as early as possible even though the combination therapy was not chosen.

The entire treatment duration showed a significant correlation with the score variation percentage in group 1 but not in group 2. In group 1 the duration of treatment after prednisone was significantly correlated with the improvement but that before prednisone showed no correlation with outcomes. Considering the natural involution process, the treatment of our patients usually

Table 5 Logistic regression of clinical response

Clinical characteristics	Regression coefficient	P value	95% confidence interval
Gender			
Female	–	–	–
Male	0.481	0.406	–0.654–1.165
Pregnancy			
Premature	–0.877	0.229	–2.306–0.552
Normal birth	–	–	–
Progesterone			
Yes	–0.186	0.736	–1.266–0.894
No	–	–	–
Location			
Head and neck	0.102	0.941	–2.593–2.796
Torso and Extremities	–1.410	0.347	–4.351–1.531
Both	–	–	–
Type			
Superficial	–1.507E-5	1.000	–1.604–1.604
Compound	–0.766	0.351	–2.375–0.844
Deep	–	–	–
Feature			
Multi	0.696	0.398	–0.916–2.308
Ulceration	1.339	0.525	–2.787–5.464
Mucous	–0.233	0.887	–3.434–2.968
Age at drug initiation	–0.592	0.001*	–0.930–0.255
Entire duration	–0.006	0.912	–0.109–0.097
Addition of prednisone			
Yes	–	–	–
No	–1.795	0.005*	–3.047–-0.544

*, P<0.01 was considered as significant.

continued after the patient was one year's old. The earlier the patient began the treatment, the longer the entire duration and duration after the prednisone would be. Besides, since there was no significant difference on the treatment duration observed between the two groups, we believe that the additional prednisone would not shorten the entire treatment duration and administration of beta-adrenergic receptor antagonists until one year old would be necessary for all the patients.

Considering the confounding factors, we performed ordinal logistic regression analysis on the overall outcomes in all patients with all clinical characteristics and different treatment regimens. The results also suggested that addition of prednisone and early treatment were the most two important factors to the overall outcomes.

As a non-selective β blocker, the effect of propranolol on IHs have been attributed to vasoconstriction, angiogenesis inhibition, and apoptosis induction on many types of cell, especially hemangioma endothelial cells (HemECs) (14,15). It is reported that the sensitivity to β blockers

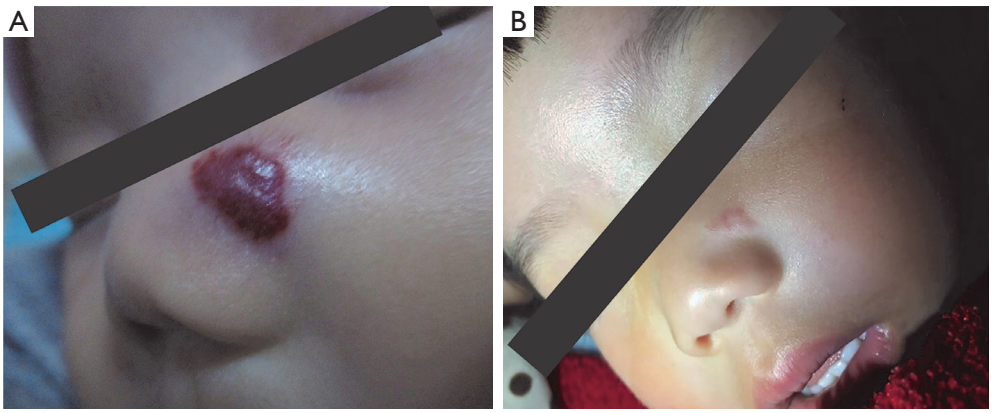

Figure 1 Case 1. The response of compound IH on the left paranasal region to combined prednisone, oral propranolol, and topical timolol solution. (A) Before starting prednisone therapy at 3-month; (B) at 12-month after prednisone therapy for 1 month and continuing oral propranolol and topical timolol solution.

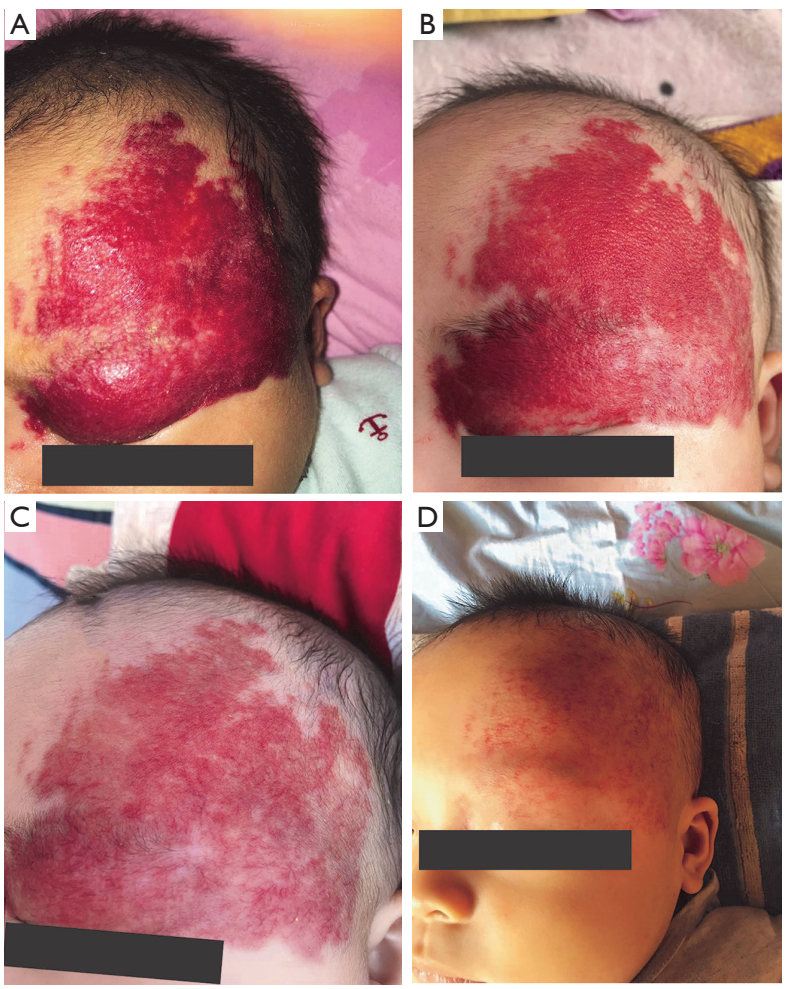

Figure 2 Case 2. The response of large compound IH on the left forehead region to combined prednisone, oral propranolol, and topical timolol solution. (A) Before starting propranolol therapy at 1-month; (B) before starting prednisone therapy at 5-month; (C) after prednisone therapy for 1 month; (D) at 12-month after the end of propranolol therapy.

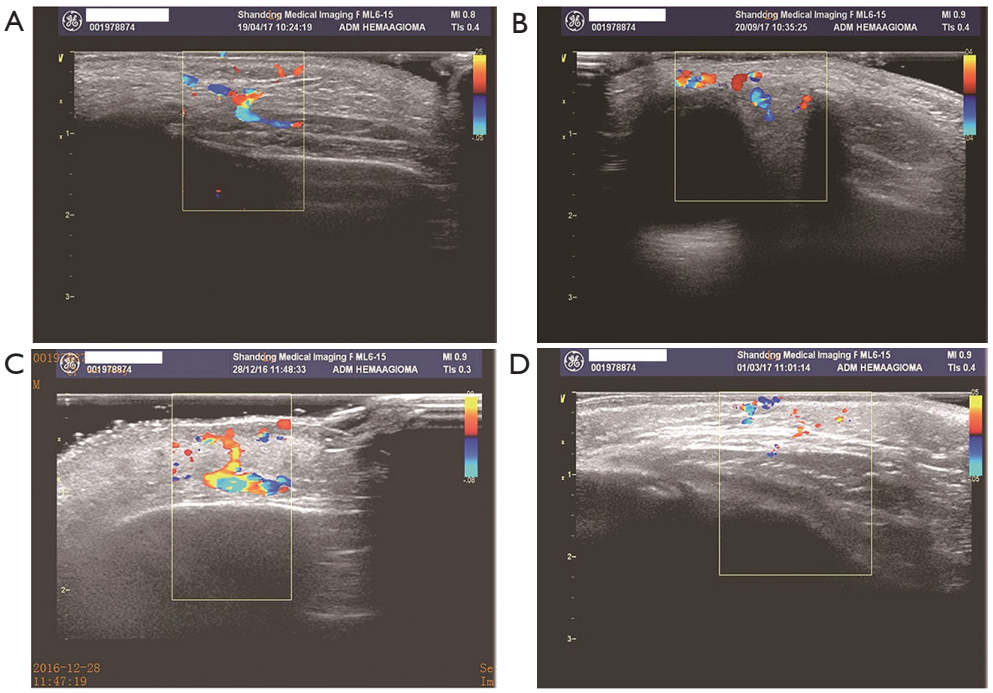

Figure 3 Ultrasonic examination results of case 2. (A) Before starting propranolol therapy, at 1-month, IH was about 0.91 cm thick on the left forehead region, and the blood flow signals accounted for 30% of the whole mass area. The size of lower echoic area was about 1.9 cm × 0.9 cm on the left orbital region and the blood flow signals accounted for 30% of the whole mass area; (B) before starting prednisone therapy, at 5-month, IH was about 0.53 cm thick on the left forehead region, and the blood flow signals accounted for 15–20% of the whole mass area. The size of lower echoic area was about 1.4 cm × 0.57 cm on the left orbital region, and the blood flow signals accounted for 20% of the whole mass area; (C) at 6-month after prednisone therapy for 1 month and continuing oral propranolol and topical timolol solution, IH was about 0.53 cm thick on the left forehead region, and the blood flow signals accounted for 10% of the whole mass area. IH was about 0.53 cm thick on the left eye region, and the blood flow signals accounted for 10–20% of the whole mass area; (D) at 12-month after the end of propranolol therapy, on the left forehead region, the blood flow signals accounted for 10% of the whole mass area. The size of the lower echoic area was about 0.82 cm × 0.67 cm on the left orbital region, and the blood flow signals accounted for 10–15% of the whole mass area.

differed from races and the quantity of propranolol bound to plasma protein resulted in different pharmacological activities (16). The different subtypes of β-adrenoceptor (β-AR) also contributed to the different sensitivity of propranolol (17-19). These may explain some of the fair or poor response to propranolol and the better outcomes for patients receiving a combination of propranolol and prednisone in our study. As the previous first-line therapy, prednisone was reported to be effective for IHs based on the ability to suppress angiogenesis and macrophages and downregulate vascular endothelial growth factor and basic fibroblast growth factor (20). When the current first-line medicine, beta-adrenergic receptor antagonists, cannot receive notable improvement, the addition of prednisone may have a synergistic inhibitory effect for refractory IHs.

In recent years, there were few case reports suggesting the efficiency of the combination treatment with oral corticosteroids and propranolol in the complicated, ulcerated IH (9,10). To the best of our knowledge, this is most cases work that reports combined medication of oral prednisone with propranolol for refractory infantile hemangiomas. Some studies also revealed the promising effects of the additional oral prednisone; however, higher dose or longer duration were used, or fewer cases were reported. Nieuwenhuis *et al.* reported 21 cases in whom propranolol failed or was contraindicated but oral prednisone received good responses in 62% patients, with a dose of 3 mg/kg/day (13). In 2015, Aly *et al.* suggested that combining propranolol with corticosteroids gives a faster response and should be considered in treating life- or function-threatening hemangiomas, with a dose of 2 mg/kg/day (11). Oral prednisolone with a low dose of

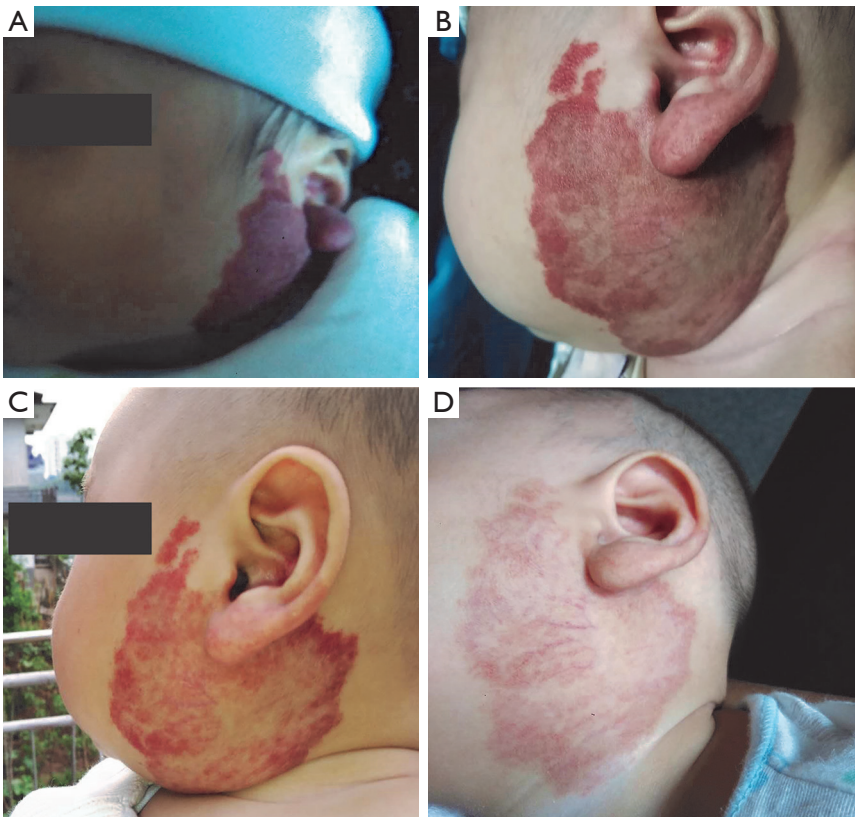

Figure 4 Case 3. The response of large compound IH on the left parotid region to combined prednisone, oral propranolol, and topical timolol solution. (A) Before starting propranolol therapy at 1-month; (B) sfter propranolol therapy for 2 months; (C) at 4-month after prednisone therapy; (D) at 8-month after the end of propranolol therapy.

1 mg/kg/day was given to the IH patients and received better outcomes in Anjum's research, while the duration was 3 months (12).

Compared to the previous studies, our research explored the effective theory in a larger cohort and with a lower dose (1 mg/kg/qod) and shorter duration (one month) of corticosteroids. No significant increase in weight or height was observed after one month's low dose prednisone, and neither severe adverse events were noted among all patients. All these results demonstrated that adjuvant prednisone therapy is safe for pediatric patients.

The retrospective observational design is subject to selection bias and limits the generalizability of the results. A further randomized controlled study of multimodal therapy for refractory IHs is worthwhile based on larger series.

In conclusion, the brief addition of low-dose oral prednisone is an effective and safe adjunctive treatment to beta-adrenergic receptor antagonists treatment in contributing to refractory IHs. The addition prednisone would not shorten the entire treatment duration. Both early administration and long enough duration would be necessary.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was carried out in accordance with the recommendations of Declaration of Helsinki. The protocol was approved by the Institute Review Board of Shanghai Ninth People's Hospital (SH9H-2019-T272-1). The study outcomes will not affect the future management of the patients. All parents or guardian of participants of this study gave written informed consent in accordance with the Declaration of Helsinki for the participation in the study, and the publication of identifiable images.

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