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Original Article

Concurrent versus sequential combination of propranolol and dual-wavelength laser (585 nm and 1064 nm) to treat complicated infantile hemangiomas

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Abstract: Background: Complicated Infantile Hemangiomas (CIHs) clearance takes over 6 months or incomplete with propranolol treatment alone, and frequently relapses after drug discontinuation. In order to evaluate the efficacy of concurrent versus sequential combination therapy of systemic propranolol with dual-wavelength laser (585 nm and 1064 nm) in the treatment of CIH, sixty-one CIH patients were randomized into two groups. Patients in group A (sequential therapy, 30 cases) were treated with oral propranolol (1-2 mg/kg/d) until maximal reduction of tumor size was achieved, after which laser treatment was initiated. Patients in group B (concurrent therapy, 31 cases) were treated with oral propranolol (1-2 mg/kg/d) for one week before laser was applied concurrently. The size and color of tumors were observed and recorded to assess the treatment efficacy. As a result, the time to cure CIH in group A and B was 14.0±0.87 months and 9.0±1.21 months, respectively ($P<0.05$). No severe side effects were observed. In conclusions, combination of oral propranolol and dual-wavelength laser was safe and effective for CIH treatment and concurrent therapy was found to be superior to sequential therapy.

Keywords: Infantile hemangioma, laser, propranolol, combination therapy

Introduction

Infantile Hemangiomas (IHs) are the most common vascular tumors in childhood [1]. IHs can present at birth or within the first few weeks of life, and generally grow during the first 6 months of life, followed by gradual but spontaneous involution within 5 to 7 years [2, 3]. Although most IHs resolve without negative consequences, approximately one-fourth of cases persist and require early treatment due to potential complications such as ulceration, infection, discomfort or pain, permanent discoloration or scarring, visual obstruction with permanent disfiguring, auditory or airway obstruction, visceral involvement, cardiac insufficiency, or hypothyroidism [2, 4-10]. Approximately 10-15% of affected children have complicated infantile hemangiomas (CIHs) [11, 12]. These can be severe or even life threatening if they present in vital organs, grow rapidly, involve large areas, and/or resolve incompletely. Furthermore, if left untreated, CIHs can result in psychological and physiologic sequelae.

In 2008, when Léauté-Labrèze [13] discovered that propranolol has a significant effect on hemangioma involution, propranolol has become a preferred treatment option for CIH, because of its effectiveness, mild side effects, low cost, and the favorable outcomes for ulcerated hemangioma. Recent evidence suggests propranolol treatment is superior to traditional corticosteroids treatment for complicated IHs [14]. Nearly all published reports regarding propranolol treatment have described favorable outcomes. According to our previous studies [15, 16], low-dose propranolol (1-2 mg/kg/d) treatment of CIHs showed improved efficacy and decreased adverse effects compared to traditional treatment modalities. However, the course of oral propranolol treatment alone was usually over 6 months, and relapse occurred frequently after drug discontinuation. In addition, local discoloration and the formation of

Table 1. General characteristics of RIHs

Cases	61
Age at onset	0.75 week (range, 0-8 week)
Mean age at first consultation	3.55 month (range, 0.1-8.53 month)
Number of hemangiomas lesions	64
Mean (SD) number of hemangiomas	1.05 (1-3)
Ulceration	2
Size	1.5-42 cm^2
Type	
Mixed	54 (84.37%)
Superficial	10 (15.63%)
Location	
Eyelid	2 (3.12%)
Cheek	6 (9.38%)
Ear	2 (3.12%)
Lip	4 (6.25%)
Neck	4 (6.25%)
Trunk	24 (37.50%)
Extremities	19 (29.69%)
Perineum	3 (4.69%)

scar from the residual tissue were commonly seen in patients treated with propranolol only. Although it is controversial whether laser treatment is better than an active observational strategy, the development and wide range of earlier applications of laser technology led to excellent clearance rates and fewer adverse events in superficial hemangiomas have been reported [17-21]. For complicated IH, combination of oral propranolol with a different adjuvant treatment modality, such as laser therapy, has been used [15, 22]. We also found that early laser treatment could reduce the occurrence of scar and changes in skin texture, which leads to the beneficial effects on preventing the recurrence of CIHs [15]. Currently, there is no consensus on whether CIH can be treated with a combination of the propranolol and laser. To investigate this, we treated 61 infants with CIH using a combination of oral propranolol and laser sequentially or concurrently.

Materials and methods

Clinical criteria

Patients: Sixty-one infants with CIHs treated at our hospital from 2009 to 2011 [median age 3.55 (1-6) months] were included in the study, with approval from local IRB and formal consent. General characteristics of the patients were presented in **Table 1**. The patients were randomized into two groups. Group A (sequential therapy) included a total of 30 cases (7 males and 23 females). Patients in Group A were given local dual-wavelength laser therapy after discontinuation of oral propranolol (1-2 mg/kg/d). Propranolol treatment was stopped when maximized treatment effect was achieved. Group B (concurrent therapy) included a total of 31 cases (8 males and 23 females). Patients in Group B were treated with oral propranolol (1-2 mg/kg/d) for one week before laser therapy was added concurrently. Demographic information was similar in both groups.

Inclusion criteria

The diagnosis for all patients was confirmed through history and clinical manifestations, combined with local hemangioma ultrasound, CT or MRI examination. The following characteristics were routinely considered as inclusion criteria: 1. The lesion in question had a distinct proliferative phase; 2. Physicians determined topical treatment alone could not control the progression of the disease; 3. The thickness of lesions was ≥1 cm and confirmed by ultrasound. Patients who had taken or were taking systemic corticosteroids were excluded. Before treatment, patients underwent the following tests: vascular ultrasound or MRI, ECG, chest X-ray, urinalysis, liver and kidney function, blood glucose, and blood electrolyte levels. Patients with bronchitis, pneumonia, sinus bradycardia, any degree of atrioventricular block, acute heart failure, or any other systemic disease were excluded. In addition, patients with a family history of asthma were also excluded.

Drug and equipment

Oral drug: propranolol hydrochloride tablets (Hubei Huazhong Pharmaceutical Co., Ltd. China), 10 mg/tablets, provided by The Third Xiangya Hospital of Central South University outpatient pharmacy. Equipment: dual-wavelength laser (Pulsed dye laser: 585 nm and long pulse infrared laser: YAG 1064 nm) (Cynergy, Cynosure, Westford, MA).

Treatment protocol

Medication preparation: Before treatment, informed consent was obtained from patients after discussion of risks and benefits. After consenting, lesions were digitally photographed and measurements of the lesion size and thickness were obtained. Ultrasounds evaluation was then performed. Finally, the patient's weight, heart rate, blood pressure, tests for liver function, kidney function and thyroid function, blood glucose, lipid panel, electrolyte level, and EKG, were obtained.

Treatment methods: Therapeutic doses of 1.0~2.0 mg/kg/d of oral propranolol divided into 2-3 doses were given postprandially. In our study, we used tablet propranolol which was consistently supplied by the same manufacturer, and the dosage of propranolol we used was half of the tablet-5 mg, qd, bid or tid. All infants were achieved or exceeded 2.5 kg at the start of medication. We applied 5mg/day propranolol tablet by grinding the medicine and mixed with water, which is ≤2 mg/kg/d, a typical starting dose for propranolol. On the first day of treatment, half of the target dose was given. If no adverse reaction was observed after 48 hours, the full therapeutic dose was given. The adverse effects were monitored and managed accordingly during the treatment. After 7-10 days, the infants who had no abnormal signs and symptoms were routinely managed as outpatients and given oral propranolol by their parents with monthly subsequent visit. All infants in our study did not use any general or local anesthesia. In order to protect the eyes of infants, goggles or appropriately positioned gauze was used routinely. For the laser treatment of CIHs, we commonly used 585 nm laser settings of 6-8 J/cm^2, 7 mm spot size, and 2 ms pulse width, 1064 nm laser settings of 30-45 J/cm^2, and 15-20 ms pulse width, with treatment intervals of 4 weeks. The optimal efficacy of instant reaction of lesions color was purplish red. Of note, the cooling system of the laser equipment and laser treatment-related care, such as locally appropriate ice cooling, played a significant role in reducing the side effects.

Subsequent visit

We recorded the changes of lesions appearance by digital photograph monthly, measured the dimensions and thickness of lesions when necessary, and compared the changes of lesions before and after treatment by vascular ultrasound. The heart rate and body weight were also measured, and according to the infants' weight and response of treatment, the dose of propranolol was adjusted.

Criteria for discontinuing drug

In Group A, propranolol was weaned when the treatment effect was no longer obvious with regards to the lesion color, thickness, and size. In Group B, propranolol was weaned when the lesion had faded. To follow the principle of gradual reduction of medicine withdrawal, propranolol was reduced by 5 mg weekly until complete withdrawal. Of note, in situations where the patients were found to have heart abnormalities, liver and kidney dysfunction, severe cold induced asthma, or any other complications, propranolol would be discontinued or reduced. When the parameters monitored in patients returned to normal, we considered resuming the medications in select cases.

Evaluation criteria

We graded the lesions prior to treatment as 10 points (initial score), and the changes during treatment were recorded monthly. If lesion volume fades by 20%, we recorded it as 8 points, and if lesion volume fades by 50%, this was recorded as 5 points, and so on. 0 point was given for complete resolution of the lesion. Three researchers independently scored the treatment effect each times, and the average of three scores were reported. We considered complete resolution of the hemangioma if the lesion had achieved 1 or 0 point.

Statistical methods

Student's T test was used to assess statistical differences between two groups using SPSS17.0 software. Results were presented by mean (M) ± standard deviation (SD). Statistical significance was set at $P<0.05$.

Results

Efficacy evaluation

The treatment efficacy was statistically different when compared to their initial score after the first month of treatment in each group. The treatment efficacy rating between A and B

Table 2. Comparison of efficacy rating between two groups

Treatment time	Efficacy ratings (M ± SD)		T	P
	Group A (n=31)	Group B (n=30)		
1 month	8.77±0.43[a]	8.90±0.31[b]	-1.331	0.189
2 months	7.19±0.80	8.00±0.46	-4.894	<0.001
3 months	6.23±0.99	7.00±0.46	-3.944	<0.001

Note: [a,b], the treatment efficacy ratings of group A and group B were statistically different compared to each respective initial score, after one month of treatment. *p* value was obtained by comparing the treatment efficacy rating of each month between group A and group B.

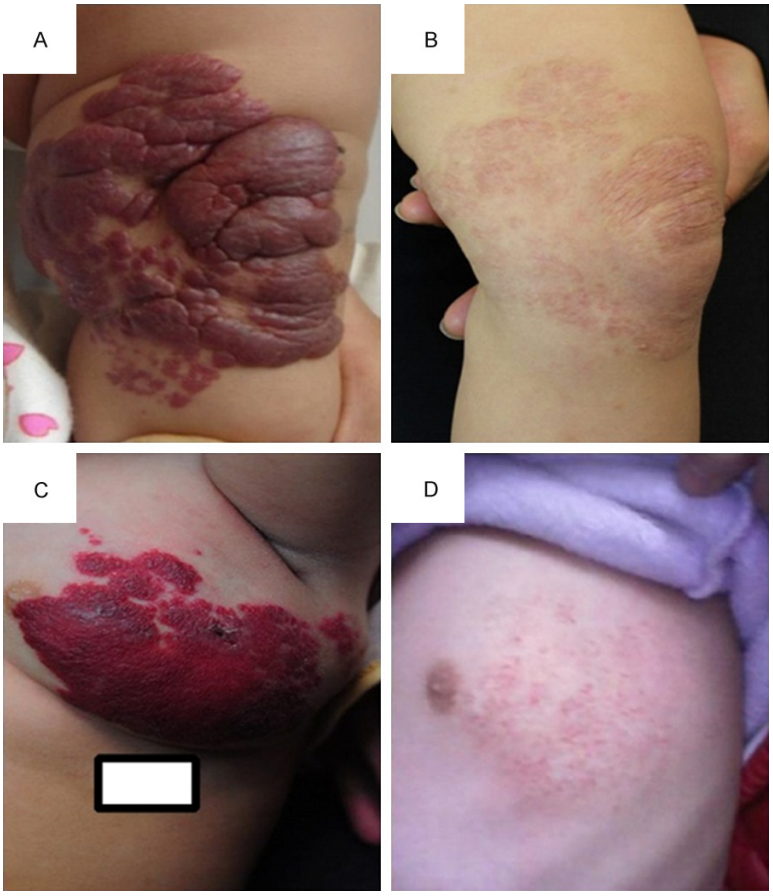

Figure 1. Representative images of 61 infants at ages of 1-6-month old when treatments were initiated shown before (A, C) and after (B, D) the combination treatments of propranolol and laser sequentially (A, C) and concurrently (B, D) for 11-15-month demonstrating complete (100%) clearance. (A) Left lower limb hemangioma in an infant at 3 months of age before treatment and (B) at 18 months of age after receiving sequential combination treatment with propranolol for 8 months followed by 7 laser sessions. (C) Left chest hemangioma in an infant at 3 months of age before treatment and (D) at 9 months of age after receiving concurrent combination treatment with propranolol for 6 months and 6 laser sessions.

groups was statistically different after the second month of treatment and the differences persisted throughout the study (P<0.05, **Table 2**). Although both sequential and concurrent combination of propranolol and laser treatments led to completely CIH clearance (**Figure 1**), concurrent therapy required significant less time than sequential therapy (**Figure 2**).

Total treatment time

Group A took significantly longer time than Group B to lead CIH resolution. The mean time to complete resolution of IH lesions in Group A was 14.0±0.87 months, compared to 9.0±1.21 months in Group B (P<0.05, **Table 3**).

Medication time

The treatment time for group A was 7-9 months with a mean of 8.17±0.54, and the treatment time for group B was 5-9 months with a mean of 6.45±1.0 (P<0.05, **Table 4**).

Laser treatment times

There was no statistical significance in the differences of laser treatment times between the two groups. The mean times of laser treatment were 6.87±0.97 months for group A and 7.39±1.17 months for group B, respectively (P=0.065, **Table 5**).

Side effects

All the patient's heart rate declined but more than 100 times per minute after propranolol treatment. There were 2 cases with upper respiratory tract infection, 3 cases with mild hyperkalemia, and 1 case with decreased appetite. All these side effects gradually improved after treatment was reduced, or with symptomatic therapy. All patients were able to complete the entire treatment course.

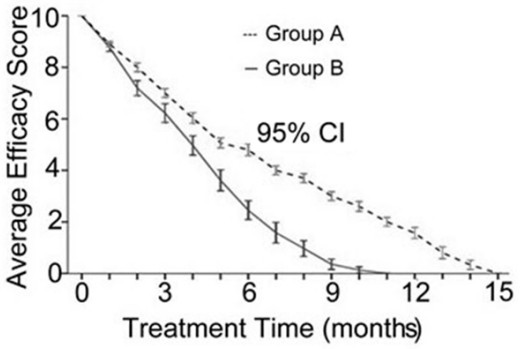

Figure 2. The efficacy-rating trend of the two groups. Lesions prior to treatment were graded as 10 points (initial score), and the changes during treatment were recorded monthly. If lesion volume fades by 20%, 8 points were graded and if lesion volume fades by 50%, 5 points were graded, and so on. 0 point was given for complete resolution of the lesion. The averages of scores determined by 3 researchers independently were presented.

Table 3. Comparison of total treatment time between two groups

Group	n	M ± SD (Healing time/month)	t	P
A	30	14.0±0.87	-18.459	<0.001
B	31	9.00±1.21		

Table 4. Comparison of medication time between two groups

Group	N	M ± SD (Healing time/month)	t	P
A	30	8.17±0.54	-7.849	<0.001
B	*31*	6.45±1.09		

Table 5. Comparison of laser treatment times between two groups

Group	n	M ± SD (Laser treatment/time)	t	P
A	30	7.39±1.17	1.881	0.065
B	31	6.87±0.97		

Discussion

Treatment of CIHs by propranolol is well documented, but the treatment outcome can be slow or incomplete, and there are potential risks with prolonged treatment. Moreover, relapse of CIHs frequently occurs after discontinuation of propranolol, partly with textural changes (**Figure 3**). Although propranolol

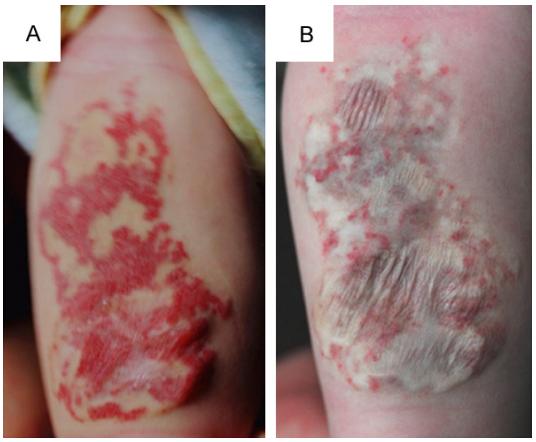

Figure 3. A. The flexor side of right forearm hemangioma in an infant at 3.5 months of age before treatment during a period of rapidly proliferating, who has been receiving treatment with one laser sessions at 0.5 months of age and follow up by 3 months. B. When at 8.5 months of age after receiving oral propranolol for 5 months, tumor controls and reduces, but significant residual tissue is still visible.

monotherapy treatment has achieved significant treatment effect with fewer side effects, it is common for CIH to leave residual tissues and to recur after drug discontinuation by this monotherapy treatment. In addition, increasing the doses of propranolol is unlikely to improve the treatment efficacy significantly [23, 24]. Dual-wavelength laser, using MultiPlex technology with two wavelengths, which combines the pulsed dye laser (585 nm) and YAG (1064 nm) laser, pulsed dye laser allows oxygenated hemoglobin transformed into methemoglobin, which increases the Nd: YAG laser absorption rate by 3-5 fold, thereby increasing its safety. Meanwhile, deeper penetrating optimizes its efficacy. Its unique cooling system can instantly cool to -4°C at the treatment site, thus reducing local heat caused by laser burning, by which to reduce damage, prevent the formation of scar and enhance the safety of the treatment. Witman and his colleagues [25] reported that PDL treatment of superficial hemangiomas may rarely lead to significant complications including atrophic scarring and severe ulceration. It is worth noting that, nearly all of infants treated with the similar fluency compared with the our parameters, but without dynamic cooling.

In this report, we present our study of combining oral propranolol with dual-wavelength laser therapy to treat CIHs, and evaluate the efficacy

of sequential and concurrent combination therapies. Our data indicate a favorable response of CIHs to propranolol-laser combination treatment. CIHs treated with concurrent propranolol-laser therapy responded more completely and quickly than those treated with propranolol followed by sequentially laser application. The patients from the concurrent therapy group achieved near-complete clearance within 11 months (mean 9.0±1.21 months), whereas patients from the sequential therapy group achieved near-complete clearance by about 15 months (mean 14.0±0.87 months). In both groups, CIHs treated with propranolol combined with laser all showed significant improvement within one month of treatment, although the significant difference between the two treatment strategies was achieved after two months. Greater clearance was achieved by the end of the treatment course, and concurrent therapy displayed more rapid and complete clearance than sequential therapy: propranolol treatment time in group A (mean=8.17 months) is longer than that in group B (mean=6.4 months) before reaching to the maximal improvement. The differences are clinically and statistically significant. For infants with large superficial IH, achieving near-complete clearance for 3 to 7 months sooner would have important benefits, including the possibility to reduce the risk of IH complications and/or to reduce the associated family burden. The difference in the numbers of laser treatment session associated with these improved outcomes between the two groups was relatively small, averaging to 7. Reddy and his colleagues [20] reported that IHs need to be continuously treated with propranolol for nearly 12 months per standard therapy. They also noticed that, for IHs at the growth phase, propranolol discontinuation would lead to the recurrence or rebound of IHs. They found that IHs treated concurrently with propranolol and pulsed dye laser (PDL) achieved complete clearance more often than IH treated with propranolol followed by PDL or IH treated with propranolol alone. The remaining question was whether the combination treatment reduces the course of propranolol treatment without impairing the outcome. Results from our studies showed that complete clearance of CIHs is possible within 9 months by concurrent propranolol-laser therapy. Geronemus [26] acknowledged that pulsed dye laser (PDL) therapy was a safe and effective method and the synergistic benefit of PDL and propranolol for IHs will also be an area of significant interest. However, due to the potential appearance of aesthetic complications, functional impairments, and life-threatening events is hard to predict, the debating for whether early application of laser therapy or simply wait and see remains [18, 27]. Currently, there is no formal guideline in the treatment of CIHs. This study has demonstrated remarkable efficacy of the concurrent propranolol-dual-wavelength laser combination treatment. However, further studies are demanded to elucidate the mechanism of propranolol and/or laser therapy in the treatment of CIHs, in hopes of making treatment even more effective.

Conclusion

Treatment of CIHs using a combination of oral propranolol and dual-wavelength laser is effective and safe. Moreover concurrent therapy is superior to sequential therapy.

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Disclosure of conflict of interest

None.

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