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Novel Combination Topical Timolol and Pulsed Dye Laser Therapy for Early Effective Safe Treatment of Infantile Hemangiomas

Chun-Shin Chang[1,2] **and Gavin Chun-Wui Kang**[1,3*]

[1]*Department of Plastic, Reconstructive and Craniofacial Surgery, Craniofacial Research Center, Chang Gung Memorial Hospital, Linkou, Taiwan*

[2]*Department of Chemical and Materials Engineering, College of Engineering, Chang Gung University, Taoyuan, Taiwan*

[3]*Department of Plastic, Reconstructive and Aesthetic Surgery, KK Women's and Children's Hospital, Singapore*

[*]**Corresponding author:** Gavin Chun-Wui Kang, Department of Plastic, Reconstructive and Aesthetic Surgery, KK Women's and Children's Hospital, Singapore, Tel: +6581231029; E-mail: gavinkangcw@yahoo.com

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Abstract

Introduction: Infantile Hemangiomas (IH) are the most common benign pediatric tumors and carry potential cosmetic and functional sequelae. Topical timolol and Pulsed Dye Laser (PDL) are effective IH therapies and previous studies have suggested the superiority of combination timolol-PDL therapy for IH over timolol alone. We present our experience using combination timolol and PDL therapy for IH, postulate a synergistic effect, and analyze the impact of age on outcomes.

Method: Sixteen consecutive children with superficial IH were treated with topical 0.5% timolol. Fourteen responded poorly to one month of timolol-alone treatment and were started on concurrent monthly 595 nm PDL treatment. Outcome was scored at 3 months using a Visual Analog Scale (VAS): 4 for excellent (76-100% improvement), 3 for good (51-75%), 2 for moderate (26-50%), 1 for poor (0-25%).

Result: Two patients on timolol alone had excellent response. The rest on combination timolol-PDL therapy were aged 9.6 months on average at initiation of treatment, with mean treatment duration of 4.9 months and a mean 14.3 months follow-up. Treatment was effective in all patients; mean VAS was respectively 3.69 and 3.58 for those younger than 7 months and those older at treatment initiation. Those started on combined treatment before 7 months and who achieved complete IH regression did so within an average 4.6 months and before turning one, compared with the average 11 months for patients started older (p=0.042). One had hyperpigmentation after IH regression. There were no other systemic or local complications.

Conclusion: Early first-line topical timolol treatment for superficial IH combined with 595 nm PDL when indicated, seems safe, simple, and appears to promote fast complete regression with high patient satisfaction making it a good active non-surgical treatment option as opposed to passive waiting. Treatment should ideally start before 7 months of age.

Keywords: Hemangioma clearance; Topical beta-blocker; 585 nm pulsed dye laser; Propanolol; Rapid hemangioma involution

Introduction

Infantile hemangiomas, with a 6 percent incidence, are the most common benign pediatric tumors [1]. Hemangiomas are predominantly seen in female and premature infants, and have a higher incidence among Caucasians (5 percent) compared to Asians (1 percent) [2]. Initially an erythematous macular patch or a blanched area, it grows rapidly for the first 4-8 months of life, reaches a plateau at 6-12 months, and begins to involute before 18 months [3]. Although most regress spontaneously, some hemangiomas cause serious cosmetic and functional problems necessitating medical or surgical intervention. The IH proliferate during the first or second year of life followed by spontaneous involution over months or years [3], making medical or surgical treatment mostly unnecessary.

Therapy is indicated for life-threatening or functional complications (obstruction of airway or vision, or oral, nasal, auditory orifices; bleeding), permanent disfigurement, ulceration, and to minimize psychosocial stress and avoid potentially scarring surgery [4]. Yet many parents of IH patients become frustrated with passive waiting and even go doctor-hopping searching for active cure. Some unfortunately received unwarranted surgery complicated by scarring and further disfigurement. Even with complete natural involution, there is - especially with larger lesions - often a tell-tale saggy fibrofatty residuum that may require surgical excision/contouring again with potential scarring (Figure 1). Clearly a safe effective simple non-surgical active treatment option that promotes faster and complete IH clearance would be highly-desired. Systemic beta-blocker propranolol was found to cause rapid regression of hemangiomas [5], and effective treatment has since been widely reported [6]. However propranolol risks significant adverse effects.

Timolol, a topical beta-blocker with less risk of systemic effect, was first used to treat periorbital hemangiomas [7,8], and subsequently found useful for hemangiomas elsewhere, but not all patients respond well to it. The 595 nm pulse dye laser (PDL) is another effective treatment for hemangiomas [9-12].

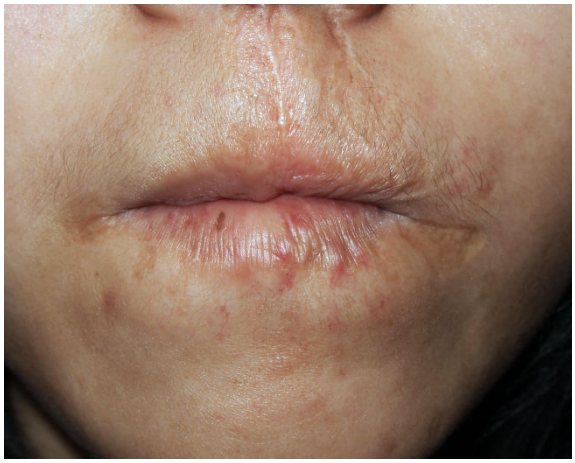

Figure 1: Limited involution of a lip hemangioma resulted in remnant fibrofatty tissue causing abnormal distorted lip contours that required two upper lip contour revisions causing visible surgical scars in this 23-year-old male patient. Early intervention in life might have brought about faster and more complete involution and possibly reduce the amount of fibrofatty residuum, avoiding this suboptimal aesthetic result.

Patients treated with PDL have evidence of wound healing demonstrable by electron microscopy [13]. Damage of the skin surface caused by PDL, however minimal, could theoretically enhance transdermal timolol delivery [14]. Previous studies have suggested superiority of combination timolol and PDL therapy for IH over timolol alone but with a paucity of detail [15,16]. We present our series of pediatric superficial IH treated with a protocol combining topical timolol and PDL.

Materials and Methods

In this retrospective study 16 consecutive patients with superficial infantile hemangiomas were treated at our pediatric plastic and reconstructive center from Sept 2011 to March 2014. All hemangiomas were uncomplicated and discrete, and ultrasonographically determined to be superficial without any deep dermal or subcutaneous component.

Only patients with normal physical examination without cardiorespiratory problems were included. Parents were informed regarding off-label use of timolol and instructed to apply 2 drops of 0.5% timolol solution twice daily onto and gently rub over the entire hemangioma with a finger for several seconds. The first application of timolol solution was done at the clinic under medical supervision and patients were then observed for more than 30 min before discharge.

Evaluation of treatment response was performed at 1-month follow-up. If there was little or no decreased pigmentation and/or size of the hemangioma, the patient would be started on monthly 595 nm PDL (Vbeam Perfecta, Candela Corp, Wayland, MA) with concurrent timolol treatment using these laser parameters: 7 mm spot size, 10 to 15 J/cm^2, 1.5 to 10 ms pulse duration, and dynamic cooling spray duration of 30 ms with a 10 to 30 ms delay. Timolol, or timolol with concurrent monthly PDL, was continued for as long as there was persistent improvement.

Standardized pre-treatment and post-treatment photographs (3 months after treatment initiation) of the hemangioma were evaluated with a visual analogue scale (VAS) independently by two plastic surgeons and two dermatologists who were blinded to the timeline of the photos. The VAS uses a 4 point-scale where reviewers score the degree of improvement giving 4 points for excellent (76-100%), 3 points for good (51-75%), 2 points for moderate (26-50%), or 1 point for poor (0-25%). Such complications as scarring, atrophy, hyperpigmentation, hypopigmentation, ulceration, infection were assessed.

Statistical analysis

Inter-rater reliability was analyzed using Cronbach's α. Using both a Mann-Whitney U test and a t-test, the difference in time to complete hemangioma regression was compared between the early combined treatment group (started treatment before 7 months of age) and the late combined treatment group (started after 7 months). Kolmogogrov-Smirnov testing checked for data normality. Statistical analysis was performed using SPSS software (version 17.0; IBM Corporation, NY, USA).

Results

There were five male and 11 female patients whose clinical characteristics are shown in Table 1. Those two treated with timolol alone had excellent response. For the rest on combined topical timolol and 595-nm PDL, the mean age at treatment initiation was 9.6 months (range, 1.9 to 27 months) with a mean 14.3 months (range, 6 to 29.6 months) follow-up, and treatment was effective in all. The average duration of treatment for those on combination treatment was 4.9 months (range, 2 to 10 months). Reliability of VAS assessment was analyzed showing good inter-observer reliability (Cronbach α=0.855). All evaluators correctly identified pretreatment and posttreatment photographs.

Three months after treatment initiation, the mean VAS for the 14 patients on combined timolol and laser treatment was 3.64. The two on timolol alone each had a VAS of 4. Every patient received a VAS of 3 or better.

Analyzing by age at which treatment was initiated for the combined approach patients, those (n=8) who were started on combined treatment at or before 7 months of age (early treatment group) had a mean 3-month VAS of 3.69, and those (n=6) who started older (late treatment group) had a mean 3-month VAS of 3.58.

Analyzing by time needed after initiation of treatment to obtain complete regression, among those who received early combined treatment before 7 months - one had incomplete regression at latest follow-up, and seven obtained complete regression at a mean 4.6 months (range, 2 to 8 months) after starting combined treatment. Of these seven subjects with complete regression, six attained complete regression before turning one. In the late treatment group (older than 7 months) two had incomplete regression at latest follow-up, and four obtained complete regression at a mean 11 months (range, 4 to 18 months) after starting treatment.

No	Sex	Location	Size (mm)	Age at First Treatment With Timolol (Months)	Number of PDL Treatments	Treatment Duration (Months)	Visual Analog Scale Rating at 3 months after treatment initiation	Complications	Follow-up (Months)	Number of months after treatment initiation at which complete regression was attained
1	M	Right thigh	40 x 40	5.1	2	2	4	None	6	2
2	F	Left cheek	50 x 30	6.5	6	6	3.25	None	26.1	18
3	F	Nose	20 x 20	0.9	5	5	3.5	None	22.4	8
4	F	Right upper lid	20 x 12	3.5	0	4	4	None	11.6	6
5	F	Left neck	6 x 6	7.0	0	3	4	None	6	2
6	F	Right ear	20 x 20	2.8	6	6	3.5	None	16	5
7	F	Right hand	20 x 30	17.2	5	5	3.25	None	6	Regression incomplete at latest follow-up
8	F	Right nasal dorsum	25 x 20	2.5	8	8	3.75	None	29.6	7
9	F	Right neck	20 x 15	8.1	6	6	4	None	24.5	12
10	M	Right buttock	4 x 4	5.4	1	1	4	None	6	3
11	F	Left scalp	16 x 16	4.5	6	6	3.5	None	17.6	4
12	F	Left upper lip	20 x 15	5.8	4	4	3.5	None	6	Regression incomplete at latest follow-up
13	M	Right scalp	18 x 18	1.3	2	2	3.75	None	6	3
14	F	Right chest	35 x 35	26	10	10	4	Hyper pigmentation	12	10
15	M	Right cheek	30 x 30	22	4	4	4	None	6	4
16	M	Right posterior back	30 x 30	12	4	4	3	None	6	Regression incomplete at latest follow-up

Table 1: Patient details and treatment outcomes.

Considering the small sample sizes, this difference in time to complete hemangioma regression between the early and late group was statistically significant using both the Mann-Whitney U test (p=0.042) and an independent t-test (p=0.024). Kolmogogrov-Smirnov test revealed normal distribution of data (p=0.114).

One had hyperpigmentation after hemangioma regression. At latest follow-up, there was no rebound recurrence in any patient. Further, none had scarring, atrophy, and hypopigmentation, and there were no instances of local burning, stinging, irritation, or peri-hemangioma erythema.

Case 1

A 3-month-old female presented with a protruding rapidly growing 25 mm x 20 mm superficial hemangioma at the nasal dorsum. At birth the hemangioma had initially presented as a small macula. Topical timolol 5% was applied twice daily to the lesion. There was no effect after one month of timolol treatment, thus combined monthly 595-nm PDL was started. Complete regression was achieved within 7 months after initiating combined treatment (Figure 2).

Case 2

A 3.5-month-old female presented with a superficial 20 mm x 12 mm right upper lid hemangioma. Topical timolol 5% twice daily for one month produced significant lightening. Complete regression was achieved within 6 months of initiating timolol (Figure 3).

Figure 2: Hemangioma over nose. After birth there was a red patch over nasal dorsum (photograph by parents) (Above, left). At initial presentation at three months of age, there was rapid growth of the 25 mm x 20 mm hemangioma with no subsequent response to one month of twice daily topical timolol (Above, right). Two months after combination therapy with topical timolol and 595-nm pulsed dye laser, regression was induced (Below, left). Complete regression achieved at 11 months of age after 7 months of combined treatment (Below, right).

Figure 3: Right upper lid hemangioma. A 3.5-month-old female presented with a superficial 20 mm x 12 mm right upper lid hemangioma (Left). Topical timolol 5% twice daily for one month produced significant lightening (Centre). Complete regression was achieved within 6 months of initiating treatment (Right).

Case 3

A 4.5-month-old female presented with a superficial 16 mm x 16 mm left scalp hemangioma. Topical timolol 5% twice daily for one month produced little effect. Complete regression was achieved after 4 months of combined topical timolol and 595-nm PDL treatment (Figure 4).

Discussion

Tollefson and Frieden suggested that for optimal outcomes IH treatment should be initiated before or early in the course of most rapid growth (from 8 weeks of age on), rather than later [17]. Based on the above, for best results in terms of rapid and complete aesthetic clearance, time is of the essence and safe efficacious IH treatment should be initiated as early as possible in infancy.

Previously the mainstay of nonsurgical treatment for IH, systemic corticosteroids risk the adverse effects of adrenal suppression, growth retardation, and gastritis. Intralesional and topical corticosteroids, with less risk of systemic effects, are more suited for small IH and may cause skin depigmentation, skin and fat atrophy and necrosis. Propranolol - shown to be rapidly efficacious for IH in the proliferative phase has supplanted corticosteroids as first choice treatment [6]; it arrests IH growth through increased endothelial apoptosis, microvascular vasoconstriction, and downregulation of angiogenic pathways [18-20]. Propranolol has undesirable potential effects: bradycardia, hypotension, hypoglycemia, rash, gastrointestinal discomfort/reflux, fatigue and bronchospasm [21-23]. Complete cardiovascular workup is recommended before initiating propranolol. Intralesional propranolol is also effective but like intralesional corticosteroid requires pediatric general anesthesia; moreover such vascular tumors risk systemic absorption.

Timolol is a topical beta-blocker working *via* the same mechanism as propranolol, making it ideal for cutaneous IH since topical application risks less systemic effects. Effective treatment has been reported with 0.1%, 0.25% and 0.5% timolol maleate. Its major advantages are its availability, low cost, ease of use, minimal risk of adverse events, especially when applied to the face [24]. Peak plasma concentrations after ocular administration of 0.5% timolol is very low making cutaneous application safe.

As the leading effective laser treatment for IH, PDL works through selective photothermolysis to prevent enlargement and promote involution of IH [25,26]. Instead of waiting passively for natural regression that may take a long time and even lead to suboptimal cosmetic results and psychosocial distress despite later intervention, the high safety profile of topical timolol and/or PDL presents a splendid opportunity to actively intervene early, safely, and non-systemically with a higher likelihood of earlier and complete regression [10,12,27-29].

Reddy et al. reported that IH treated with combined propranolol and PDL displayed more rapid and complete clearance requiring an overall lower propranolol dose [30]. Fractional carbon dioxide laser per se is not a treatment for IH but has been used as pretreatment creating “ablated laser holes” in the skin to increase timolol drug uptake for IH treatment [31]. In contrast not only does PDL have a direct therapeutic effect on the hemangioma, it also causes microdamage – however minimal - to the tumor epidermal surface, thereby facilitating transdermal penetration and absorption of topical timolol, delivering a one-two combo knockout. While Park et al. and others have supported combination treatment of IH with timolol and PDL [15,32,33], we are first to present a detailed treatment protocol combining specifically timolol and 595-nm PDL, and to conceptualize a synergistic mechanism of action as well as elucidate effect of age on outcomes. Park et al. showed retrospectively that combination topical timolol and PDL treatment of IH achieved a better clinical response than timolol alone, but did not detail patient age, clinical characteristics, and laser parameters [15].

Based on the VAS result at 3 after months of treatment, the clinical response to combination therapy was good or excellent regardless of age at treatment initiation. Those started on combination treatment before 7 months of age and who achieved complete IH regression did so within about 5 months and before turning one. In comparison, those who started older and achieved complete regression did so taking twice the time (11 months). It appeared that early combination therapy before 7 months in the period of sustained rapid IH proliferation - when the lesion was smaller, incipient, and more superficial - stops progression and promotes earlier faster more complete clearance.

Our chief indication for combined timolol and PDL treatment was superficial IH. Most reported that deep IH with a subcutaneous component respond less optimally to either topical timolol or PDL treatment, although combined timolol and fractional laser treatment is said to be effective for deeper lesions [31]. The absence of systemic and adverse skin effects made this a largely pleasant experience for the patients and their parents. Notably all parents in our study expressed great satisfaction about being empowered to actively, safely, and easily intervene with conscientious medication and laser sessions to rid their children of a potentially unsightly vascular tumor. All indicated that given the choice again, they would choose topical timolol and PDL over watchful waiting.

Although our study was limited by the small number of subjects and absence of controls (ideally adding on a timolol-only arm, a laser-only arm, and a non-treatment arm), we have demonstrated the efficacy and safety of combination topical timolol and PDL in the early treatment of superficial IH. Moreover it should be emphasized again that for many frustrated parents and proactive clinicians, active simple treatment with safe effective non-systemic modalities trumps the uncertainty of passive non-treatment. Also as early intervention is essential for best results, we believe in stepping up a gear early by switching from timolol-alone to combination timolol and laser – previously shown to be superior [15] - when there was no improvement after a month.

Barring any contraindications, we advocate considering early use of topical timolol 0.5% as first-line treatment for superficial infantile hemangiomas, adding on combined 595-nm PDL treatment for greater enhanced therapeutic effect should the lesion not timely respond to timolol alone. Assessing the aesthetic outcome and satisfaction rate by a randomized controlled trial on a larger population would be the next goal.

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