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Pediatrics; originally published online May 6, 2013;

DOI: 10.1542/peds.2012-3828

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American Academy of Pediatrics

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RCT of Timolol Maleate Gel for Superficial Infantile Hemangiomas in 5- to 24-Week-Olds

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KEY WORDS

infantile hemangioma, timolol/adverse effects, randomized controlled trial

ABBREVIATIONS

CI—confidence interval
DBP—diastolic blood pressure
IH—infantile hemangioma
SBP—systolic blood pressure

Drs Chan and McKay participated in the acquisition of data, analysis and interpretation of data, drafting and revising the article for important intellectual content, and approval of the final manuscript as submitted; Dr Adams participated in the study concept and design, critical revision of the article, and approval of the final manuscript as submitted; and Dr Wargon participated in the study concept and design, analysis and interpretation of data, critical revision of the article for important intellectual content, and final approval of the final manuscript as submitted.

This trial has been registered with the Australian and New Zealand Clinical Trials Registry at www.anzctr.org.au (identifier ACTRN12610001069044).

www.pediatrics.org/cgi/doi/10.1542/peds.2012-3828

doi:10.1542/peds.2012-3828

Accepted for publication Feb 6, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: A Sydney Children's Hospital Foundation grant provided support for statistical analysis of the results. The Touched by Olivia Foundation funded the Vascular Birthmark Research Fellowship position.



WHAT'S KNOWN ON THIS SUBJECT: The systemic nonselective β -blocker propranolol hydrochloride is increasingly used as first-line management for infantile hemangiomas. Superficial nonulcerating lesions do not require systemic medications. Case series have suggested the efficacy of timolol; however, its safety has been questioned.



WHAT THIS STUDY ADDS: This randomized controlled trial indicates that timolol maleate 0.5% gel is a well-tolerated, safe, and effective treatment of superficial infantile hemangiomas.

abstract

OBJECTIVE: Timolol maleate 0.5% gel is a safe and effective medication for treating superficial infantile hemangiomas (IHs) in infants with a median age of 9 weeks.

METHODS: Forty-one infants who had superficial IHs without ulceration and not near mucosal surfaces were recruited and randomly assigned to placebo and treatment (timolol maleate 0.5% gel) groups. Efficacy was assessed by performing blinded volume measurements at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 and blinded investigator photograph scoring at weeks 0, 12, and 24. Safety was assessed by measuring heart rate and systolic and diastolic blood pressure at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24.

RESULTS: Fifteen of the 19 infants receiving treatment and 17 of the 22 infants receiving placebo completed the study. Significant color change on the blinded photographic scores was noted at week 24 of the study ($P = .003$). There was a significantly higher proportion of treated IHs that reduced in size by $>5\%$ at weeks 20 and 24 ($P < .02$). The predicted proportion of IH volume change was also significantly less for treated IHs from week 16 onward when compared with placebo ($P < .05$). There was no significant variation in blood pressure and heart rate between the groups.

CONCLUSIONS: Topical timolol maleate 0.5% gel with a maximum dose of 0.5 mg per day is a safe and effective option for small superficial IHs that have not ulcerated and are not on mucosal surfaces. *Pediatrics* 2013;131:1–9

Infantile hemangiomas (IHs) are among the most common tumors of infancy, with ~4% of infants affected.¹⁻³ Khan et al⁴ reported that IHs arise from CD133⁺ stem cells, which can differentiate into several cell lineages including adipocytes. The mechanisms that control the proliferation and involution of these lesions are not as yet fully understood. Focal IHs are rarely present at birth and exhibit a characteristic growth phase typically up to the age of 9 months.⁵ A gradual involution phase takes place over the subsequent 2 to 10 years^{1,5}; however, recently, Couto et al⁶ suggested that most IHs do not substantially further improve after 3.5 years of age. Increasingly, nonselective β -blockers, including propranolol hydrochloride, have replaced or been used in conjunction with previously recommended treatments such as systemic corticosteroids and vincristine for the treatment of IHs to prevent ulceration and disfigurement and for systemic involvement.^{7,8} The mechanism via which β -adrenergic receptor antagonists inhibit the growth of IHs remains to be fully elucidated. Whereas the side-effect profile of propranolol hydrochloride is favorable,^{8,9} the potential for hypoglycemia, bronchial hyperactivity, and hypotension makes it difficult to justify its use for less severe IHs.

For small, superficial focal lesions without features necessitating propranolol or other systemic agents, the use of topical imiquimod 0.5%¹⁰ and potent topical corticosteroids¹¹ has also been reported. Topical timolol solution is a nonselective β -adrenergic receptor inhibitor that was approved in 1978 for the treatment of glaucoma and has been safely used as first-line therapy for pediatric glaucoma for >30 years.^{12,14} A number of case reports and case series have observed the efficacy of timolol maleate 0.5% gel for the treatment of IHs¹⁵⁻²²; however, concern has been raised regarding its safety.¹²

This blinded, randomized, placebo-controlled study aims to begin to answer these questions relating to the safety and efficacy of topical timolol maleate 0.5% gel in the setting of small, superficial focal IHs in infants aged 5 to 24 weeks.

METHODS

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted in a single institution between March 2011 and September 2012. Approval was obtained from the institutional review board of the South Eastern Sydney and Illawarra Area Health Service, Northern Hospital Network Human Research Ethics Committee. Written informed consent was obtained from the children's parents after a discussion of the risks and benefits of participating.

Eligibility of Patients

Patients were recruited at a single tertiary center from neonatal, pediatric ophthalmology, general pediatric, and pediatric surgery clinics from March 2011 to April 2012 (Fig 1). Participation was offered to infants between the age

5 and 24 weeks with small, focal superficial IHs not requiring systemic therapy. Exclusion criteria included hypersensitivity to timolol maleate, wheezing, cardiac rhythm disturbances or congenital heart disease, or large, ulcerated, mucosal, or subcutaneous IHs. During the trial, proliferation of the lesion, ulceration, or parental desire to commence systemic therapy resulted in withdrawal from the trial and institution of systemic medications.

Study Design

Patients were enrolled in the trial by 1 of 2 study physicians and randomly assigned (by using a method of minimization)²³ by the clinical trials pharmacist into 4 groups: age between 5 and 15 weeks or between 16 and 24 weeks and size of lesion < or >25 mm. Participants, caregivers, and physicians were blinded to group status. Baseline screening comprised a cardiovascular examination, including blood pressure and heart rate, as well as clinical photography and 2 hemicircumference measurements of the IH, 90° apart. The

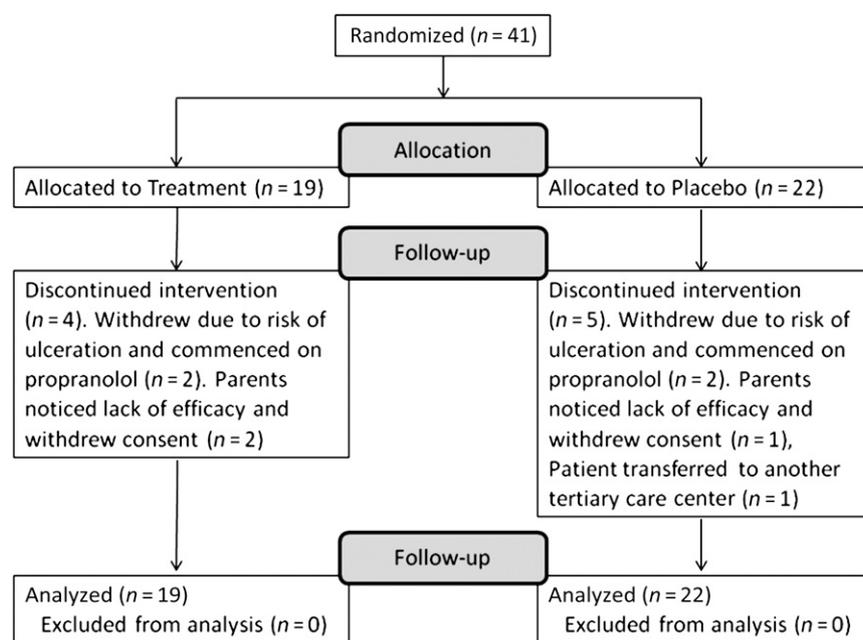


FIGURE 1
Flow diagram of trial participants.

study medication was dispensed in a ratio of 1:1 as placebo or timolol maleate 0.5% gel (5.0 mg of timolol/6.8 mg of timolol maleate in 1 mL; gellan gum, trometamol, mannitol, and water for injection; 0.0012% benzododecinium bromide added as a preservative.)¹³ The parents were instructed to apply with a fingertip part of 1 drop of the gel onto the surface of the IH (enough to just coat the lesion) twice a day, and to gently rub it in. One drop of timolol maleate 0.5% gel has been estimated to contain 0.25 mg of timolol.¹² The first application was conducted in the outpatient department, and blood pressure and heart rate were measured just before application and 1 hour after application of placebo or timolol maleate 0.5% gel. Heart rate and blood pressure measurements were compared with age-related reference ranges.²⁴ Two hemircumference measurements 90° apart were taken of the IH in question before the first application of placebo or timolol maleate 0.5% gel. Repeat hemircumference measurements, as well as blood pressure and heart rate, were taken at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 after commencement of study participation. In addition, photographs were taken by a clinical photographer at baseline, week 12, and week 24. After 24 weeks, participation in the trial ceased and subjects were given the option of off-label use of timolol maleate 0.5% gel for ongoing treatment of the IH. Interim blinded statistical analysis was carried out at the study midpoint to confirm whether the trial should be continued or ceased.

Outcome Measures

Response to therapy was measured by (1) blinded predicted volume estimation²⁵ at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 and (2) blinded scoring of clinical photographs at 0, 12, and 24 weeks. For volume estimation, 2 measurements of the IH hemispheric diameter were taken 90° apart and the estimated hemispheric

volume was calculated by the formula $0.07 \times m^3$ where m is the mean of the 2 hemispheric measurements.²⁵ The photographs at 0, 12, and 24 weeks were scored by 1 blinded investigator as 0 if no redness was observable, 1 if the lesion was ~50% red, or 2 if the lesion was completely red.

With regard to safety data, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured before administering the first dose of placebo or drug, as well as 1 hour after the initial dose, and then at every visit.

Statistical Analysis

The data were analyzed by a statistician blinded to group status. Descriptive statistics are presented as percentages (%) of the group, means and SD, or medians and interquartile range.

The number of children with redness as indicated by the photo score at visits 1, 12, and 24 and the percentage with a categorized lesion size at each time point were investigated by using continuity corrected χ^2 or Pearson's χ^2 test. A linear mixed model with an autoregressive covariance structure was used to examine whether there were significant differences in volume and percentage change in volume, heart rate, SBP, or DBP between the groups over time. The autoregressive covariance structure was used to allow volumes close together in time to be more correlated than those farther apart. A time-by-group interaction was included to allow the groups to vary differently by time. Post hoc comparisons with a least significant difference were used to determine whether there was a significant difference between groups at each visit.

RESULTS

A total of 41 children were enrolled in the study; 19 were randomly assigned to treatment and 22 were randomly

assigned to placebo. There were no significant differences in gender ratios, age, and site of lesion between the groups (Table 1). Although we planned to recruit and analyze subjects in 2 age groups (5–15 weeks and 16–24 weeks old), only 3 of 41 individuals were in the older age group category and subjects were consequently not stratified on the basis of age in the results analysis. Similarly, subjects were also initially stratified on the basis of an IH mean diameter being < or >25 mm (vol = 1094 mm³). However, only 4 of 41 subjects had IH lesions with a mean diameter >25 mm. Thus, in the results analysis all subjects were considered in 1 group regardless of lesion size. Whereas all IH lesions analyzed commenced as macular lesions, volumetric approximation and analysis were required because a significant number of lesions developed a height of at least 5 mm, thus making mean diameter a less accurate measure of IH lesion size. Comparisons of predicted absolute volume of IH lesions between treatment and placebo groups were made at each time point (Table 2). To gauge whether there was a significant reduction in predicted absolute volume between

TABLE 1 Baseline Characteristics of Subjects

	Treatment	Placebo
<i>n</i>	19	22
Gender, %		
Male	26	33
Female	74	67
Age, mean (SD), mo	2.1 (0.8)	3 (0.9)
Site of lesion, %		
Face	47	50
Neck	16	14
Torso	11	—
Thigh	11	5
Upper limb	11	9
Back	5	14
Hand	—	9
Volume, median (IQR), mm ²	60 (180.4)	26.8 (179.5)
<10 mm ² , %	21	32
10–50 mm ² , %	21	32
50–1000, %	53	32
>1000 mm ² , %	5	5

IQR, interquartile range; —, indicates 0%.

treatment and placebo, a comparison was made with regard to the number of IH lesions that decreased in predicted absolute volume by $\geq 5\%$ in the treatment and placebo groups (Table 3). Because 5- to 24-week-old infants grow rapidly, most IH lesions also correspondingly increased in size. A comparison was thus made between relative change in predicted absolute volume of IH lesions between treatment and placebo (Fig 2). This comparison was additionally stratified on the basis of initial predicted absolute volume of IH lesions (Fig 3).

There was no significant difference in predicted absolute volume size between the treatment and placebo groups at baseline or at any of the individual time points. There was a marginally significant difference in the size of the IH lesions at weeks 12 and 16, with the lesions being smaller in the treatment group (Table 2; $P = .05$). In terms of relative reduction in size of IHs (Table 3), there was a significantly higher proportion of IH lesions with at least a 5% volume reduction in the treatment group compared with placebo at week 8 ($P = .04$), week 20 ($P = .02$), and week 24 ($P = .01$; Table 3). Because 5- to 24-week-old infants grow rapidly and hence their nonproliferating IHs increase in size relatively, a measurement of the proportional change in growth compared between groups was also analyzed (Fig 2). Before week 12

there was no significant difference between predicted percentage change in volume between treatment and placebo ($P > .05$). Subsequent to week 16, there was a significantly lower predicted percentage volume increase in the treatment group compared with the placebo group ($P < .01$).

With regard to which IHs may be more amenable to topical timolol maleate 0.5% gel treatment, the impact of IH volume on treatment efficacy was considered. There were 12 IHs that were $< 100 \text{ mm}^3$ (mean diameter = 11.3 mm) in volume at baseline in the treatment group and 16 in the placebo group. For IHs with a baseline volume of $< 100 \text{ mm}^3$ (Fig 3), the predicted percentage increase in mean IH volume was significantly less in the treatment group from week 8 onward ($P < .003$). For IHs with a baseline volume $> 100 \text{ mm}^3$, there was no significant difference in predicted percentage change in IH volume between treatment and placebo at any time point (weeks 1–16, $P > .2$; week 20, $P = .09$; week 24, $P = .06$). In addition, a receiver operating characteristic curve plotted for IH lesions in the treatment group indicated that a cutoff of 65 mm^3 for baseline volume predicts whether volume will decrease by $\geq 5\%$ (area under the curve = 0.88, $P = .02$).

The clinical appearance of IH lesions as determined by blinded photo score was also compared between treatment and placebo groups at baseline, week 12,

and week 24. Representative photos of IHs treated successfully with topical timolol maleate 0.5% gel are shown along with images of IHs in the placebo group in Fig 4. A score of 0 indicated no redness, a score of 1 indicated the lesion was 50% red, and a score of 2 indicated the lesion was completely red. As shown in Table 4, no significant difference in score distribution was seen at baseline or at 12 weeks. At 24 weeks, there was a significant difference in blinded photo score distribution between treatment and placebo groups. The proportion of photo scores of 0 (no redness) was significantly greater in the treatment group (47%) than in the placebo group (6%). Conversely, the proportion of photo scores of 2 (completely red) was significantly less in the treatment group (6%) compared with the placebo group (55%; Pearson's χ^2 , $P = .003$).

With regard to side effects of topical timolol maleate gel, there were no cases of bradycardia or hypotensive episodes. Comparisons of mean heart rate (treatment mean heart rate = 147 beats per minute; 95% confidence interval [CI]: 140–154; placebo mean heart rate = 147 beats per minute; 95% CI: 140–154; $P = .81$), mean SBP (treatment mean SBP = 89 mm Hg; 95% CI: 86–93; placebo mean SBP = 84 mm Hg; 95% CI: 80–89; $P = .28$), and mean DBP (treatment mean DBP = 43 mm Hg; 95% CI: 36–51; placebo mean DBP = 38 mm Hg; 95% CI: 33–43; $P = .40$) indicated no

TABLE 2 Volume in Categories by Time

Week	Treatment					Placebo					P
	n	<10 mm ²	10–50 mm ²	50–1000 mm ²	>1000 mm ²	n	<10 mm ²	10–50 mm ²	50–1000 mm ²	>1000 mm ²	
1	19	21	21	53	5	22	32	32	32	5	.58
2	17	24	18	53	6	22	32	32	32	5	.56
3	17	18	18	59	6	22	36	27	32	5	.36
4	19	21	21	53	5	21	33	24	38	5	.79
8	19	37	5	53	5	19	21	32	42	5	.20
12	18	33	11	50	6	18	11	50	28	11	.05
16	15	40	7	47	7	18	11	44	33	11	.05
20	14	36	7	50	7	18	11	39	39	11	.13
24	15	33	7	53	7	18	17	33	39	11	.24

Data are percentages (%) of the group or n. There was a borderline significant difference at weeks 12 and 16 with more small lesions in the treatment group.

significant difference between treatment and placebo groups (Table 5).

In total, there were 9 dropouts from the study (4 in the treatment group and 5 in the placebo group) (Fig 1). Reasons for withdrawal are summarized in Table 6.

DISCUSSION

Efficacy

IH growth cessation occurring as early as 48 hours after commencement of oral propranolol hydrochloride has

been described previously.^{7,26–29} This relatively rapid onset of action for systemic therapy most likely encourages compliance.³⁰ In comparison, topical timolol maleate gel has been associated with growth arrest and a slower reduction in redness and thickness within the first 2 to 4 weeks of use as seen in 2 noncontrolled studies of the use of topical timolol maleate gel for IHS.^{20,21} Chambers et al²² reported a significant improvement with topical 0.25% timolol maleate gel compared with placebo for periorcular IHS after 8 weeks of treatment. The results presented from this study indicate a therapeutic onset of action after 12 to 16 weeks of therapy, with a significant increase in the number of IH lesions decreasing in size by >5% and a significant decrease in proportional growth rate noted in the treatment group compared with the placebo group. This later onset of action compared with oral propranolol hydrochloride may be related to a lower dose being used in this study

and may explain withdrawals due to subject-observed lack of efficacy. Withdrawal may also be attributed to parental anxiety as well as the inability to predict the appropriateness of the lesion to topical treatment and the risk of ulceration. Despite the withdrawal of 9 subjects from a relatively small sample size, intention-to-treat analysis still revealed a significant difference in measured outcomes as described above. From a practical perspective, it would be suggested that any lesion considered being at risk of ulceration or developing signs of early ulceration would be more suitable for systemic therapy.

Previous studies have suggested that superficial^{19,22} and plaque-like IHS are more amenable than nodular and deep lesions²⁰ to topical timolol maleate gel treatment; hence, this study excluded deep lesions. By using a receiver operating characteristic analysis and stratifying the data on the basis of IH volume, a significant difference was noted in drug efficacy for lesions <100 mm³ in volume (mean hemispheric diameter <11.3 mm) from week 8 onward. Lesions >100 mm³ treated with topical timolol maleate gel appeared to have no significant difference in growth compared with lesions of a similar volume in the placebo group at any time point. Because a fixed dose of topical timolol maleate gel (1 drop twice a day) regardless of lesion size was applied, one might predict that smaller lesions, due to their higher surface area to volume ratio, are more amenable to topical therapies. The lack of different dosages used and the small number of large lesions in the present study make it difficult to predict the optimal management of large IH lesions with topical timolol maleate gel. With regard to the influence of site of IH lesion on topical timolol maleate gel efficacy, whereas it is predicted that IHS in areas in which the epidermis is thinner (eg, the eyelids) would be more responsive to

TABLE 3 Infants With IH Volume Reduced by $\geq 5\%$

Week	Treatment		Placebo		P
	n	Percentage of Group	n	Percentage of Group	
2	19	32	22	18	.53
3	19	26	22	5	.13
4	19	26	21	5	.14
8	19	37	20	5	.04*
12	18	39	19	16	.23
16	16	38	18	22	.55
20	15	47	18	6	.02*
24	15	60	18	11	.01*

* Significant difference at weeks 8, 20, and 24 with more lesions reduced by $\geq 5\%$ in the treatment group.

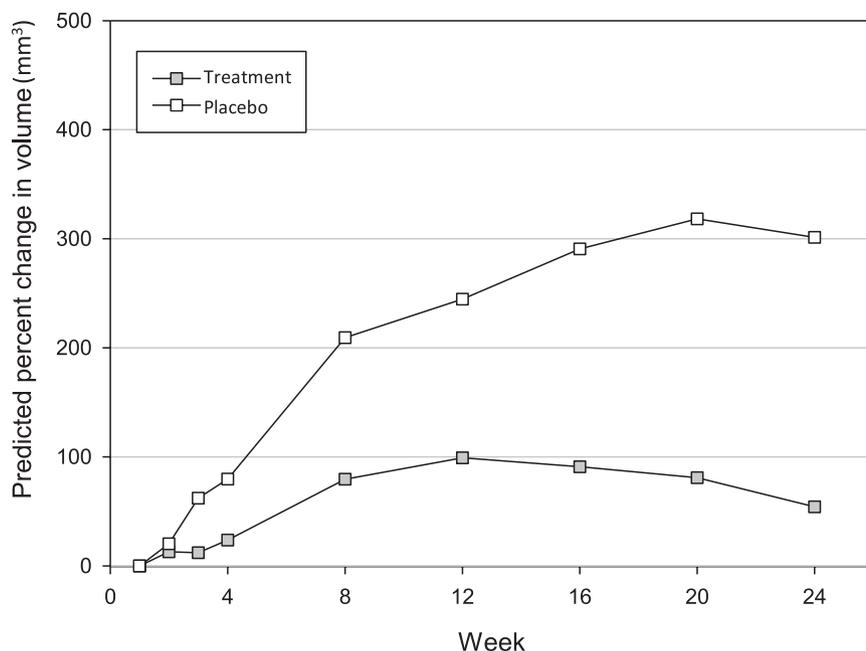


FIGURE 2

Percentage change in predicted volume for all IHS in treatment and placebo groups. *P* for group = .050. Post hoc group comparisons at each time point: weeks 0–4, *P* > .20; week 8, *P* = .07; week 12, *P* = .05; week 16, *P* = .01; week 20, *P* = .002; week 24, *P* = .002.

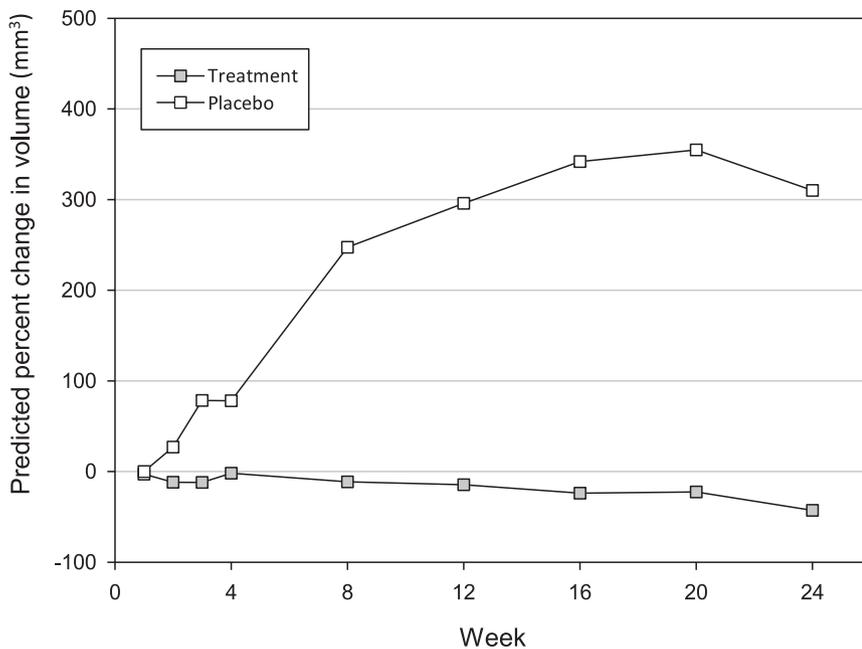


FIGURE 3 Percentage change in predicted volume for small lesions only (<100 mm³ at baseline). *P* for group = .003. Post hoc group comparisons at each time point: weeks 0–4, *P* > .20; week 8, *P* = .003; week 12, *P* = .001; weeks 16–24, *P* < .0001.

topical timolol maleate gel, the safety concern and paucity of existing data of systemic absorption at these sites prevented a direct analysis of this prediction.

Although it was anticipated that subjects in 2 age groups (5–15 weeks and 16–24 weeks old) would be recruited, only 3 individuals were in the 16- to 24-week-old age group category. The overall mean age of participants was 9 to 10 weeks. Other studies of topical timolol maleate gel for the treatment of IH have involved subjects between the ages of 5 and 30 weeks²¹ and 12 and 68 weeks²⁰ and cohorts with mean ages of 19 weeks²² and 32 weeks.¹⁹ The efficacy of topical timolol maleate gel in the relatively young age group of the present study supports previously noted observations that timolol maleate gel may be more effective during the early proliferation stage.²⁰ The safety data from this study indicate that even in this younger cohort, a limited volume of topical timolol maleate gel has a favorable side-effect profile.

The sustained effect of the 24-week course of topical timolol maleate gel has not directly been considered in this study. Posttrial follow-up of the majority of study candidates, however, has provided the investigators with the impression that no significant rebound of IHs occurred in those successfully treated with topical timolol maleate gel once the medication ceased. This finding is supported in other studies in which no significant IH rebound at 4 weeks after 8 to 30 weeks of treatment,²¹ at 4 months after 6 months of treatment,²⁰ and at 3 to 6 months after a mean treatment duration of 3.4 ± 2.7 months¹⁹ was described.

Safety

The specific pharmacokinetics of timolol maleate gel are not well defined; however, 1 study of the systemic absorption of topically applied 5% timolol via 0.2-mg/cm² transdermal patches indicated that plasma concentrations were undetectable in 3 of 4 patients 48 hours after application.³¹ This finding

is mirrored by the fact that safety data from studies of the use of topical timolol maleate to treat IH have generally been favorable.^{19,20,22} However, concern has been voiced regarding the potential systemic absorption and side effects that may arise from topical timolol maleate gel and what specific monitoring requirements are needed while receiving therapy. McMahon et al¹² estimated that 1 drop of 0.5% timolol gel-forming solution may equate to 2 to 8 mg of oral propranolol hydrochloride. As a comparison, oral propranolol hydrochloride is generally used at a dose of 1 mg/kg 2 to 3 times a day. In the pediatric ophthalmology literature, systemic bioavailability of timolol solution applied to mucosal surfaces has been estimated to be as high as 60% to 80%³² and has been attributed to cases of apnea, asthma, bradycardia, dizziness, and dissociated behavior.¹² In the studies of timolol maleate solution for the treatment of IHs, a case report of a 4-month-old girl developing blepharoptosis after treatment of a thin-plaque IH on the upper eyelid with 0.5% timolol solution has been described.¹⁶ The systemic absorption of timolol maleate gel formulation is considered to be significantly less than that of timolol maleate solution and hence has been favored in more recent studies.³³ With regard to the gel formulation, in a study in 73 individuals treated with timolol maleate 0.1% or 0.5% gel, 1 case of significant sleep disturbance necessitating treatment cessation has been reported as well as local site-of-application side effects such as burning, stinging, and irritant reactions.¹⁹ In a study in 25 individuals aged 12 to 68 weeks using topical timolol 1% gel, no adverse events were noted.²⁰ Similarly, no adverse effects were described in a retrospective, consecutive, nonrandomized cohort study of twice-daily timolol maleate 0.25% gel for the treatment of periorcular IHs.²² In the present study, which used timolol



FIGURE 4

Clinical photos of IHs at baseline (left), 12 weeks (middle), and 24 weeks (right) after commencement of placebo or treatment. A, subject no. 131 (treatment); B, subject no. 104 (treatment); C, subject no. 111 (treatment); D, subject no. 202 (placebo); E, subject no. 125 (placebo); F, subject no. 102 (placebo).

maleate 0.5% gel on intact skin, no adverse events were noted and there were no significant differences in mean heart rate and mean SBP and DBP. Review of the use of topical timolol maleate for ophthalmologic purposes also indicates no significant differences in heart rate and blood pressure; however a reduction in exercise-induced increases in heart rate during the daytime has been

TABLE 4 Redness as Indicated by Blinded Photo Score

Time and Group	n	Score 0	Score 1	Score 2	P
Week 1					
Treatment	19	—	21	79	.17
Placebo	21	—	41	59	
Week 12					
Treatment	16	13	56	31	.49
Placebo	17	6	44	50	
Week 24					
Treatment	15	47	47	6	.003*
Placebo	18	6	39	55	

Data are percentages (%) or n of the group with photo score as indicated. 2, completely red; 1, half red; 0, no redness. P values were determined by Pearson's χ^2 test. —, indicates 0%.

* $P < .05$.

TABLE 5 Safety Data for Comparison of Mean Heart Rate, SBP, and DBP Between Treatment and Placebo Groups

	Treatment (95% CI)	Placebo (95% CI)	P
Mean heart rate, beats per minute	147 (140–154)	147 (140–154)	.81
Mean SBP, mm Hg	89 (86–93)	84 (80–89)	.28
Mean DBP, mm Hg	43 (36–51)	38 (33–43)	.40

TABLE 6 Subjects Withdrawn From the Study

Subject Number	Treatment or Placebo	Study Week Withdrawn	Reason for Withdrawal From Trial
109	Placebo	4	Development of new subcutaneous periorbital IH; commenced receiving propranolol
115	Placebo	4	At risk of ulceration; commenced receiving propranolol
121	Placebo	8	Withdrawn because of transfer to another tertiary center
128	Placebo	12	At risk of ulceration; commenced receiving propranolol
135	Placebo	16	Voluntarily withdrawn
124	Treatment	8	Voluntarily withdrawn; subsequently commenced receiving propranolol
201	Treatment	12	Developed small ulcer; commenced receiving propranolol
108	Treatment	16	At risk of ulceration; commenced receiving propranolol
119	Treatment	16	Small nonproliferating lesion; strong parental desire to commence propranolol

reported.^{34,35} Similarly, we would suggest that the likelihood of bradycardia and hypotension due to the use of topical timolol maleate gel for intact IHs is very low. Exercise-induced differences would be less pronounced in the younger age distribution of our present study due to relatively low levels of exercise, although continuous measurement of blood pressure and heart rate would provide a more accurate assessment of this possibility. The safety of topical timolol maleate gel for ulcerated, mucosal, or periorbital IHs also requires additional study.

Limitations

Although numbers were sufficient to compare blood pressure and heart rate between the groups, there were insufficient numbers to exclude rare and idiosyncratic adverse events. Continual blood pressure and heart rate monitoring would provide additional insights with regard to safety. Neither this study

nor previous studies showed significant comparisons of efficacy on the basis of the IH site.¹⁹ A more sensitive scoring system incorporating other variables such as height/depth of IH with or without ultrasound imaging and a more comprehensive photographic scale would have improved the study.

CONCLUSIONS

This randomized placebo-controlled trial in infants aged 5 to 24 weeks indicates that up to 2 drops per day of topical timolol maleate 0.5% gel for 24 weeks' duration is a safe and effective therapy for the treatment of IH not requiring systemic treatment. The onset of action appears to be slower than oral propranolol chloride with significant improvements in absolute volume reduction, proportional growth, and clinical appearance noted after only 12 to 16 weeks. The efficacy of topical timolol maleate 0.5% gel appears to be more pronounced for lesions with a mean diameter of <11.3 mm (ie, <100 mm³ in vol). The side-effect profile of topical timolol maleate 0.5% gel in the 5- to 24-week age group is favorable, with no significant differences in heart rate, SBP, or DBP. Larger multicenter trials may provide insight into factors such as site-dependent efficacy as well as additional safety, monitoring, dosing, duration-of-treatment, and age-group-specific data.

ACKNOWLEDGMENTS

The Vascular Birthmark Research Fellowship is funded by the Touched by Olivia Foundation. We thank Dr Jenny Peat, Honorary Professor of Statistics, Australian Catholic University, for her assistance in the statistical analysis of the data; Ms Sarah Hill, Clinical Nurse Consultant, Department of Dermatology, Sydney Children's Hospital, for assistance in the collection of subject data; and Ms Shelley Wang, University of New South Wales medical student, for her assistance in collection of subject data.

REFERENCES

- Jacobs AH. Strawberry hemangiomas; the natural history of the untreated lesion. *Calif Med*. 1957;86(1):8–10
- Dickison P, Christou E, Wargon O. A prospective study of infantile hemangiomas with a focus on incidence and risk factors. *Pediatr Dermatol*. 2011;28(6):663–669
- Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol*. 2008;25(2):168–173
- Khan ZA, Boscolo E, Picard A, et al. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. *J Clin Invest*. 2008;118(7):2592–2599
- Chang LC, Haggstrom AN, Drolet BA, et al; Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics*. 2008;122(2):360–367
- Couto RA, Maclellan RA, Zurakowski D, Greene AK. Infantile hemangioma: clinical assessment of the involuting phase and implications for management. *Plast Reconstr Surg*. 2012;130(3):619–624
- Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo J-B, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358(24):2649–2651
- de Graaf M, Breur JMPJ, Raphaël MF, Vos M, Breugem CC, Pasmans SGMA. Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. *J Am Acad Dermatol*. 2011;65(2):320–327
- Janmohamed SR, de Laat PCJ, Madern GC, Dorresteijn EM, Jan Danser AH, Oranje AP. Treating hemangioma of infancy with beta-blockers: is there really a risk of hypotension? *J Am Acad Dermatol*. 2012;67(2):315–316, author reply 316–318
- Ho NTC, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol*. 2007;56(1):63–68
- Garzon MC, Lucky AW, Hawrot A, Frieden IJ. Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. *J Am Acad Dermatol*. 2005;52(2):281–286
- McMahon P, Oza V, Frieden IJ. Topical timolol for infantile hemangiomas: putting a note of caution in “cautiously optimistic”. *Pediatr Dermatol*. 2012;29(1):127–130
- Timoptol-XE Product Information Merck Sharp & Dohme (Australia) Pty Ltd:1–11. Available at: <http://secure.healthlinks.net.au/content/msd/pi.cfm?product=mkptimxe>. Accessed March 22, 2013
- Coppens G, Stalmans I, Zeyen T, Casteels I. The safety and efficacy of glaucoma medication in the pediatric population. *J Pediatr Ophthalmol Strabismus*. 2009;46(1):12–18
- Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. *Arch Dermatol*. 2010;146(5):564–565
- Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using beta-blocker solution. *Arch Ophthalmol*. 2010;128(2):255–256
- Kunzi-Rapp K. Topical propranolol therapy for infantile hemangiomas. *Pediatr Dermatol*. 2012;29(2):154–159
- Khunger N, Pahwa M. Dramatic response to topical timolol lotion of a large hemifacial infantile haemangioma associated with PHACE syndrome. *Br J Dermatol*. 2011;164(4):886–888
- Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. *Pediatr Dermatol*. 2012;29(1):28–31
- Semkova K, Kazandjieva J. Topical timolol maleate for treatment of infantile haemangiomas: preliminary results of a prospective study [published online ahead of print]. *Clin Exp Dermatol*. 2012; Mar;38(2):143–146
- Moehrl M, Léauté-Labrèze C, Schmidt V, Röcken M, Poets C-F, Goelz R. Topical timolol for small hemangiomas of infancy [published online ahead of print]. *Pediatr Dermatol*. 2012; Mar;30(2):245–249
- Chambers CB, Katowitz WR, Katowitz JA, Binenbaum G. A controlled study of topical 0.25% timolol maleate gel for the treatment of cutaneous infantile capillary hemangiomas. *Ophthalm Plast Reconstr Surg*. 2012;28(2):103–106
- Wade A, Pan H, Eaton S, Pierro A, Ong E. An investigation of minimisation criteria. *BMC Med Res Methodol*. 2006;6:11
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004; 114(suppl 2):555–576
- Tsang MW, Garzon MC, Frieden IJ. How to measure a growing hemangioma and assess response to therapy. *Pediatr Dermatol*. 2006;23(2):187–190
- Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics*. 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e423
- Manunza F, Syed S, Laguda B, et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. *Br J Dermatol*. 2010;162(2):466–468
- Schiestl C, Neuhaus K, Zoller S, et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. *Eur J Pediatr*. 2011;170(4):493–501
- Holmes WJM, Mishra A, Gorst C, Liew SH. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. *J Plast Reconstr Aesthet Surg*. 2011;64(4):445–451
- Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. *Pediatrics*. 2011;128(2). Available at: www.pediatrics.org/cgi/content/full/128/2/e259
- Kubota K, Yamada T, Kikuchi K, Koyama E, Ishizaki T. Pharmacokinetics and beta-blocking effects of transdermal timolol. *Eur J Clin Pharmacol*. 1993;44(5):493–495
- Urtti A. Delivery of antiglaucoma drugs: ocular vs systemic absorption. *J Ocul Pharmacol*. 1994;10(1):349–357
- Shedden AH, Laurence J, Barrish A, Olah TV. Plasma timolol concentrations of timolol maleate: timolol gel-forming solution (TIMOPTIC-XE) once daily versus timolol maleate ophthalmic solution twice daily. *Doc Ophthalmol*. 2001;103(1):73–79
- Dickstein K, Hapnes R, Aarsland T. Comparison of aqueous and gellan ophthalmic timolol with placebo on the 24-hour heart rate response in patients on treatment for glaucoma. *Am J Ophthalmol*. 2001;132(5):626–632
- Nieminen T, Lehtimäki T, Mäenpää J, Ropo A, Uusitalo H, Kähönen M. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. *Scand J Clin Lab Invest*. 2007;67(2):237–245

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Pediatrics; originally published online May 6, 2013;

DOI: 10.1542/peds.2012-3828

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