Supplemental Online Content

Muñoz-Garza FZ, Ríos M, Roé-Crespo E, et al. Efficacy and safety of topical timolol for the treatment of infantile hemangioma in the early proliferative stage: a randomized clinical trial. *JAMA Dermatol*. Published online April 7, 2021. doi:10.1001/jamadermatol.2021.0596

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Inclusion and exclusion criteria

Patients aged 10–60 days, with focal or segmental IH (lesion size 0.3–5 cm) of any morphology (superficial, deep, mixed, precursor or abortive), were enrolled in the trial. Main exclusion criteria were: IH patients with an indication for systemic therapy (ulcerated, mucosal surface or disfiguring IH) or receiving another IH treatment modality (β-blockers, corticosteroids, interferon, cyclophosphamide, vincristine); hemangiomas associated with PHACE or PELVIS/SACRAL/LUMBAR syndromes, or affecting any internal organ or airway; patients with an underlying disease

including bronchial asthma, severe pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, overt heart failure or cardiogenic shock; patients with congenital defects including chromosomal syndromes or congenital heart disease (tetralogy of Fallot, transposition of large vessels, ventricular septal defect, atrial septal defect, patent ductus arteriosus); patients with malignancies (e.g. leukemia, sarcoma, neuroblastoma, retinoblastoma); and hypersensitivity to the active substance or excipients.

Statistical analyses

Quantitative data were described by percentages, arithmetic mean, median, interquartile range (IQR) and standard deviation (SD). Fisher's test was used to evaluate the possible change in response to treatment, with calculation of odds ratio (OR) and confidence intervals (CIs). Changes in lesion volume, thickness and

colour were analysed by a Wilcoxon test for paired data. Analysis of variance (ANOVA) and the non-parametric Friedman test were used for comparisons of the time courses between treatment groups. Statistical significance was set at the 5% level. SPSS v25.0 (IBM) was used for all statistical analyses.

Patients withdrawn from the study were considered as treatment failures for the primary endpoint and as missing data for the other endpoints.

eTable 1. Baseline characteristics of patients with infantile hemangiomas

Characteristic	No. (%)		
	Timolol (n = 33)	Placebo (n = 37)	Total (n = 70)
Sex			
Female	29 (41)	27 (39)	56 (80)
Male	4 (6)	10 (14)	14 (20)
Age at inclusion, mean (SD), d	50.9 (8.3)	43.3 (11.4)	48.4 (10.6)
Gestational age, wk			
<37	9 (27)	8 (22)	17 (25)
>37	24 (73)	28 (78)	52 (75)
Infantile hemangioma			
Localization			
Head/face	7 (21)	17 (46)	24 (34)
Other body sites	26 (79)	20 (54)	46 (66)
Form			
Segmented	4 (12)	3 (8)	7 (10)
Localized	29 (88)	32 (86)	61 (87)
Indeterminate	0	2 (5)	2 (3)
Subtype			
Superficial	22 (67)	30 (81)	52 (74)
Mixed	6 (18)	5 (14)	11 (16)
Minimal or arrested growth	4 (12)	2 (5)	6 (9)
Deep	1 (3)	0	1 (1)
Lesion volume, mm^3			
Median (IQR)	136.71 (29.53-344.79)	106.46 (35.80-315.31)	121.58 (35.80-321.80)
<10	3 (9)	3 (8)	6 (9)
11-100	9 (27)	12 (32)	21 (30)
101-1000	16 (48)	17 (46)	33 (47)
>1000	5 (5)	5 (14)	10 (14)
Lesion thickness, mm^3			
Mean (SD)	1.91 (0.35)	1.86 (0.35)	1.31 (0.90)
<1	4 (12)	5 (14)	9 (13)
1-3	28 (85)	32 (86)	50 (86)
>3	1 (3)	0	1 (1)

Abbreviation: IQR, interquartile range.

eTable 2. Blood pressure and heart rate measurements at baseline and 1-hour post initial treatment

	Timolol						Placebo					
	Baseline SBP	1hr SBP	Baseline DBP	1hr DBP	Baseline HR	1hr HR	Baseline SBP	1hr SBP	Baseline DBP	1hr DBP	Baseline HR	1hr HR
Mean (SD)	103.97 (17.64)	102.70 (11.34)	55.73 (14.41)	54.30 (10.32)	142.82 (15.91)	138.91 (16.45)	98.84 (20.12)	94.14 (15.34)	52.11 (14.26)	94.14 (15.34)	144.78 (13.97)	140.84 (14.08)
P	.3014		.2458		.0564		.0932		.2275		.0533	

DBP, diastolic blood pressure; HR, heart rate; SBP systolic blood pressure; SD, standard deviation.

eFigure. Lesion thickness, by category, in IH patients treated with timolol or placebo for 24 weeks. The 36-week time point includes 12-week post-treatment surveillance.