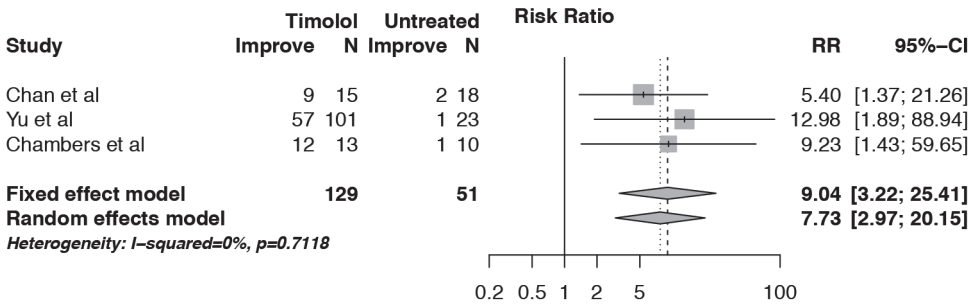

Fig. S1. Meta-analysis of the randomized clinical trial and two observational studies with untreated control groups. The fixed effects meta-analysis of the randomized clinical trial (Chan et al.) and two observational studies (Yu et al. and Chambers et al.) generated a pooled risk ratio (RR) of 9.04 (95% CI 3.22; 25.41) without evidence of heterogeneity ($p = 0.71$, $I^2 = 0\%$).

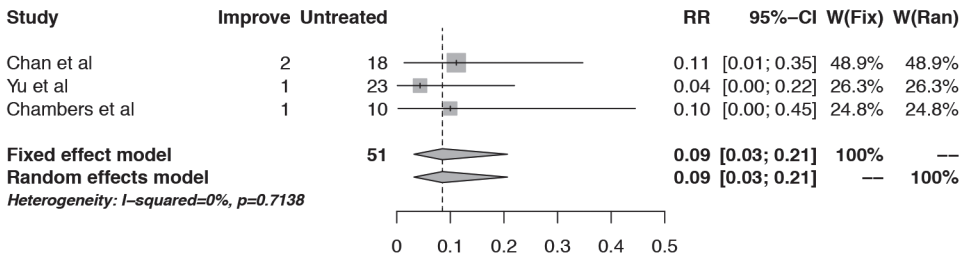

Fig. S2. Meta-analysis of the proportion of untreated patients that had some improvement in their infantile hemangioma. The mean (fixed effect) improvement relative risk (RR) rate was 0.09 (9%) with no evidence of heterogeneity ($p = 0.71$, $I^2 = 0\%$).

Table SI. Studies included in the meta-analysis

Study/year	Design, country	Patients	Intervention	Outcome	Adverse effects
Chan et al. (25), 2013	RCT, Australia	*n* = 32 (M: 5/F: 14) (Type of IH Sup: 15) Sites Head and neck: 12 Trunk: 3 Extremities: 4	0.5% timolol BD (15/32) Placebo (17/23) Mean at initiation: 2.25 months Mean duration of Tx: 6 months	Assessed by photography >5% decrease in volume in timolol: (9/15) >5% decrease in volume in placebo: (2/16)	No significant side effects, no rebound
Moehrle et al. (32), 2013	Prospective case series, Germany	*n* = 11 (M: 5/F: 6) (Type of IH >8 mm in size) Sites Head and neck: 4 Trunk: 2 Extremities: 5	0.5% timolol GFS under occlusion Mean at initiation: 3.89 months Mean duration of Tx: 3.64 months	Assessed by photography >80% decrease in size: (7/11) 50–80% decrease in size: (4/11)	No significant side effects, no rebound
Ni et al. (33), 2011	Prospective case series, USA	*n* = 7 (Type of IH Sup: 7)	0.5% timolol BD Mean at initiation: 3 months Mean duration of Tx: 3 months	Assessed by photography Complete resolution (7/7)	No significant side effects, no rebound
Pope et al. (36), 2010	Prospective case series, Canada	*n* = 6 (Type of IH Sup: 6) Site Head and neck: 6	0.5% timolol BD Mean at initiation: 11.7 months Mean duration of Tx: 3.3 months	Mean VAS: (43.8±23.2)	No significant side effects, no rebound
Oranje et al. (34), 2013	Prospective case series, Netherlands	*n* = 20 (Type of IH Sup: 8, Mix: 4, Deep: 8) Sites Periocular: 11 Head: 4 Nose: 2 Hand: 2 Arm: 1	0.5% timolol 3 to 4 times daily Mean at initiation: 3.65 months Mean duration of Tx: 3 months	Assessed by physician and caregivers Excellent: (7/20) Good: (9/20) Sufficient: (1/20) No response: (3/20)	No significant side effects, no rebound
Semkova et al. (39), 2013	Prospective case series, Bulgaria	*n* = 25 (M: 10/F: 15) (Type of IH Sup: 25) Sites Head and neck: 27 Trunk and Extremities: 12	0.1% timolol five times daily Mean at initiation: 3 months Mean duration of Tx: 2 months	Global assessment score (GAS) mean: 2.56 GAS-3 to 3, 0=no change, 3 complete resolution	No significant side effects, no rebound
Xu et al. (46), 2014	Prospective case series, China	*n* = 35 (M: 11/F: 24) (Type of IH Sup: 35) Sites Head and neck: 22 Trunk: 8 Extremities: 5	0.5% timolol BD Mean at initiation: 4.7 months Mean duration of Tx: 5.5 months	Assessed by photography Good: (18/35) Partial: (10/35) No response: (6/35)	No significant side effects, no rebound

RCT: randomised controlled trial; IH: infantile hemangioma; Sup: superficial; BD: twice daily; Tx: treatment; VAS: Visual Analogue Scale.

Table SII. Case reports included in the meta-analysis

Study/year/country	Patients	Intervention	Outcome	Adverse effects
Ambika et al. (19), 2013/India	*n* = 1, (M: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 3 months, Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Beal et al. (20), 2014/USA	*n* = 1, (M: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 3 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Calvo et al. (21), 2013/Spain	*n* = 1, (M: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 3 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Chang et al. (26), 2014/USA	*n* = 1, (F: 1) (Type: Sup: 1)	0.25% timolol BD then 0.5% timolol BD Age at initiation: 3 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Cante et al. (22), 2012/France	*n* = 2, (M: 1,F: 1) (Type: Sup: 2)	0.5% timolol BD in 1/2 and OD in 1/2 Age at initiation: 4.5 months Duration: 7.5 months	Assessed by photography Complete resolution	No side effects, no rebound
Chu et al. (27), 2013/USA	*n* = 3, (M: 1,F: 2) (Type: Sup: 3)	0.5% timolol-brimondine BD Age at initiation: 4 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, rebound reported 1/3
Ciudad et al. (28), 2015/Spain	*n* = 1, (F: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 5 months Duration: 5 months	Assessed by photography Complete resolution	No side effects, no rebound
Fernandez et al. (29), 2012/ Spain	*n* = 1, (M: 1) (Type: Sup: 1)	0.1% timolol BD Age at initiation: 2 months Duration: 4 months	Assessed by photography Complete resolution	No side effects, no rebound
Guo et al. (15), 2010/USA	*n* = 1, (F: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 4 months Duration: 1.75 months	Assessed by photography Complete resolution	No side effects, no rebound
Jha et al. (30), 2012/India	*n* = 1, (M: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 6 months Duration: 1.25 months	Assessed by photography Complete resolution	No side effects, no rebound
Matuszczak et al. (31), 2013/ Poland	*n* = 1, (F: 1) (Type: Sup: 1)	timolol BD Age at initiation: 13 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Rizvi et al. (38), 2015/India	*n* = 2, (M: 1,F;1) (Type: Sup: 2)	0.5% timolol BD Age at initiation: 1.5 months Duration: 12 months	Assessed by photography Complete resolution	No side effects, no rebound
Semkova et al. (40), 2014/ Bulgaria	*n* = 1, (M: 1) (Type: Sup: 1)	0.1% timolol 4 times daily Age at initiation: 3 months Duration: 2 months	Assessed by photography Complete resolution	No side effects, no rebound
Sorrell et al. (41), 2013/USA	*n* = 3, (M: 2, F: 1)(Type: Deep: 3)	0.5% timolol BD Age at initiation: 2.58 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Thomas et al. (43), 2013/India	*n* = 1, (F: 1) (Type: Sup: 1)	0.5% timolol BD Age at initiation: 0.57 months Duration: 3 months	Assessed by photography Complete resolution	No side effects, no rebound
Weissenstein et al. (44), 2012/ Germany	*n* = 1, (Type: Sup: 1)	0.1% timolol BD Age at initiation: 5.5 months Duration: 0.5 months	Assessed by photography Complete resolution	No side effects, no rebound
Weissenstein et al. (45), 2012/ Germany	*n* = 1, (Type: Sup: 1)	0.5% timolol BD Duration: 4 months	Assessed by photography Complete resolution	No side effects, no rebound
Xue et al. (47), 2013/UK	*n* = 2, (Deep: 2)	0.5% timolol BD Age at initiation: 3.8 months Duration: 10.5 months	Assessed by photography Complete resolution	No side effects, no rebound

IH: infantile hemangioma; Sup: superficial hemangioma; Tx: treatment; VAS: visual analogue scale; BD: twice daily. GFS: Gel forming solution; TDS: thrice daily.

Table SIII. Case-control studies with risk of bias

Study, year/ country	Patients	Intervention	Outcome	Adverse effects	Risk of bias
Chakkitta-kandiyil et al. (23), 2012/ Canada	*n* = 73 (M: 17/F: 56) (Type of IH Sup: 46, Mix: 14, Deep: 2) Sites Head and neck: 62 Trunk: 8 Extremities: 7	0.5% timolol GFS BD (62/73) 0.1% timolol GFS BD (11/73) Avg. at initiation: 4.27 months Avg duration of Tx: 3.4 months	Mean VAS in 0.5% timolol BD: (48±28) Mean VAS in 0.1% timolol BD: (24±29) 1 patient with mix IH had no response	1 patient had sleep disturbances, no rebound growth in 3–6 months of follow-up after discontinuation of treatment	1. Confounding: serious risk 2. Selection of participants: moderate risk 3. Measurement of intervention: low risk 4. Departure from intended intervention: moderate risk 5. Missing data: low risk 6. Measurement of outcome: moderate risk 7. Selection of reported result: low risk Overall bias: serious risk
Chambers et al. (24), 2012/ USA	*n* = 23 (Type of IH Sup: 5, Mix: 7, Deep: 1) Sites: 13 periocular	0.25% BD (13/23) Observation (10/23) Avg. at initiation: 4.8 months Avg duration of Tx: 2 months	Assessed by photography >50% decrease: (8/13) 0–50% decrease: (4/13) 1 grew in size	No side-effects, no rebound in 3–41 months of follow-up after discontinuation of treatment	1. Confounding: critical risk 2. Selection of participants: serious risk 3. Measurement of intervention: serious risk 4. Departure from intended intervention: serious risk 5. Missing data: low risk 6. Measurement of outcome: serious risk 7. Selection of reported result: low risk Overall bias: critical risk
Park et al. (35), 2014/ Korea	*n* = 102 (M: 23/F: 79) (Type of IH Sup: 102) Sites Head and neck: 47 Trunk: 26 Extremities: 32 Perineum: 6	0.5% timolol BD (61/102) PDL + 0.5% timolol (41/102) Avg duration of Tx: 12 months	Assessed by photography >75–100% decrease: (14/61) 50–74% decrease: (14/61) 25–49% decrease: (11/61) 0–24% decrease: (19/61) No improvement: (3/61)	No side-effects, no rebound (follow-up period not clearly defined)	1. Confounding: serious risk 2. Selection of participants: serious risk 3. Measurement of intervention: moderate risk 4. Departure from intended intervention: low risk 5. Missing data: serious risk 6. Measurement of outcome: low risk 7. Selection of reported result: moderate risk Overall bias: serious risk
Qiu et al. (37), 2013/USA	*n* = 145 (M: 24/F: 27) (Type of IH Sup: 51) Sites Head and neck: 12 Trunk: 4 Extremities: 4	0.5% timolol TDS (51/145) Imiquimod (94/145) Avg. at initiation: 3.07 months Avg duration of Tx: 4.43 months	Mean VAS in 0.5% timolol TDS: (78.5±20.43) Mean VAS in Imiquimod: (67.38±26.01)	No side-effects with timolol, Crusting in imiquimod during treatment, no rebound growth documented	1. Confounding: serious risk 2. Selection of participants: moderate risk 3. Measurement of intervention: low risk 4. Departure from intended intervention: serious risk 5. Missing data: low risk 6. Measurement of outcome: low risk 7. Selection of reported result: low risk Overall bias: moderate risk
Tawfik et al. (42), 2015/ Egypt	*n* = 60 (M: 7/F: 23) (Type of IH Sup: 24, Mix: 6) Sites Head and neck: 19 Trunk: 4 Extremities: 7	0.5% timolol BD (30/60) PDL Nd: Yag (30/60) Avg. at initiation: 6 months Avg duration of Tx: 4 months	Assessed by photography >76–100% decrease: (9/30) 51–75% decrease: (9/30) 26–50% decrease: (4/30) <25% decrease: (4/30) No improvement (4/30)	1 patient had sleep disturbances, no rebound growth in 3 months of follow-up after discontinuation of treatment	1. Confounding: low risk 2. Selection of participants: low risk 3. Measurement of intervention: moderate risk 4. Departure from intended intervention: low risk 5. Missing data: low risk 6. Measurement of outcome: low risk 7. Selection of reported result: low risk Overall bias: moderate risk
Yu et al. (48), 2013/China	*n* = 123 (M: 47/F: 77) (Type of IH Sup: 101) Sites Head and neck: 65 Trunk: 27 Extremities: 32	0.5% timolol TDS (101/123) Observation (23/123) Avg. at initiation: 6 months Avg duration of Tx: 4 months	Assessed by photography Promoted regression: (57/101) Controlled growth: (36/101) Ineffective: (8/101)	No side-effects reported during 4 months of treatment, no rebound growth documented	1. Confounding: serious risk 2. Selection of participants: moderate risk 3. Measurement of intervention: serious risk 4. Departure from intended intervention: serious risk 5. Missing data: low risk 6. Measurement of outcome: moderate risk 7. Selection of reported result: low risk Overall bias: serious risk

IH: infantile hemangioma; Sup: superficial hemangioma; Avg: average; Tx: treatment; months: months; VAS: visual analogue scale; BD: twice daily. GFS: Gel forming solution; TDS: thrice daily.

Table SIV. Summary of findings

Participants (studies), n	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Comments
							With control	With timolol	
Treatment effect[a] *– critical outcome*									
329 (6 observational studies)[b]	Serious	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE		277/329 (84.2%)	
15 (1 RCT)[c]	Serious	Not serious	Not serious	Serious	Undetected	⨁⨁◯◯ LOW		9/15 (60.0%)	
Resolution >50 % baseline – important outcome									
155 (4 observational studies)[d]	Serious	Not serious	Not serious	Serious	Undetected	⨁⨁◯◯ LOW		73/155 (47.1%)	
Complete resolution (100%) – important outcome									
243 (4 observational studies)[e]	Serious	Not serious	Not serious	Serious	Undetected	⨁⨁◯◯ LOW		36/243 (14.8%)	
Documented adverse effects – critical outcome									
329 (6 observational studies)[b]	Serious	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE		2/329 (0.6%)	
15 (1 RCT)[c]	Serious	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE		0/15 (0.0%)	
Rebound growth – less important outcome									
329 (6 observational studies)[b]	Serious	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE		0/329 (0.0%)	The follow-up period to document rebound growth varied for each study.
15 (1 RCT)[c]	Serious	Not serious	Not serious	Serious	Undetected	⨁⨁◯◯ LOW		0/15 (0.0%)	
Parents assessed improvement with topical Timolol – less important outcome									
61 (1 observational study)[f]	Serious	Not serious	Not serious	Serious	Undetected	⨁⨁◯◯ LOW		58/61 (95.1%)	

[a]Treatment effect is defined as any improvement in the infantile hemangioma from baseline. [b]Chakkittakandiyil 2012, Chambers 2012, Park 2014, Qiu 2013, Tawfik 2015, Yu 2013. [c]Chan 2013. [d]Chambers 2012, Park 2014, Qiu 2013, Tawfik 2015. [e]Park 2014, Qiu 2013, Tawfik 2015, Yu 2013. [f]Park 2014.
RCT: randomised control trial.