Effectiveness and Safety of Oral Propranolol versus Other Treatments for Infantile Hemangiomas: A Meta-Analysis

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Abstract

Background
Epidemiological studies evaluating treatments for infantile hemangiomas have produced inconsistent results. A meta-analysis of published data was conducted to investigate the effectiveness and safety of oral propranolol versus other treatments for infantile hemangiomas.

Methods
A meta-analysis was conducted based on literature (published from 1960 to December 1, 2014) found on the PubMed, EMBASE, and OVID search engines. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the outcome measures. Heterogeneity, publication bias and subgroup analysis were performed.

Results
A total of 61 studies involving 5,130 participants met the inclusion criteria. Propranolol was found to be a more effective modality in treating IHs (ORs = 0.92; 95%CI, 0.89–0.95) and had fewer complications compared to the other treatments including systemic steroids (ORs = 0.68; 95% CI, 0.59–0.76); laser ablation (ORs = 0.55; 95% CI, 0.43–0.67); other beta-adrenergic blockers (ORs = 0.56; 95% CI, 0.50–0.61) and surgery (ORs = 0.55; 95% CI, 0.28–0.81). A subgroup analysis of propranolol showed that a dose of 2 mg/kg/day or more yielded better outcomes (ORs = 0.92; 95% CI, 0.88–0.95; ORs = 0.95; 95% CI, 0.89–1.00), and IHs that had not been previously treated had better responses to propranolol treatment (ORs = 0.95; 95% CI, 0.91–0.98).
Conclusions
The meta-analysis demonstrated that propranolol was more effective and safer than other therapies in treating IHs. It provides strong evidence for supporting the use of propranolol as a first-line therapy for IHs.

Introduction
Infantile hemangiomas (IHs) are the most common type of benign tumor, affecting approximately 10% of children [1]. Although, most IHs have a self-limiting course, some may result in residual telangiectasias or redundant skin. Therefore, early intervention is indicated for IHs [2].

Systemic corticosteroids used to be the first-line treatment for IHs. However, long term use tends to result in serious side effects such as hypertension, adrenal cortical insufficiency, and delayed of growth [3].

Other treatment modalities including laser ablation, interferon-α, vincristine and surgical excision are reserved as second- or third-line therapy for IHs because of their inconsistent efficacy, multiple complications and potential toxicity [4].

In 2008, propranolol, a nonselective beta-blocker, was serendipitously discovered to be effective for treating IHs. Leaute-Lamberer et al. successfully treated 11 children with oral propranolol and observed tumor color regression in all cases soon after the treatment. Since then, large clinical studies have confirmed the efficacy and safety of propranolol [5].

Recently, other nonselective beta-blockers such as atenolol and timolol have also been found to be useful in treating IHs [6].

The aim of this meta-analysis was to systematically review the existing published data regarding the treatment of IHs, and to compare the effectiveness and safety of propranolol with other therapies. A subgroup analysis was also performed to evaluate the relationship between the effectiveness of propranolol and factors including location, dosage and previous treatment.

Materials and Methods
The study protocol was in accordance with the PRISMA guidelines (S1 PRISMA Checklist) [7].

Search strategy
A literature search was performed by searching the PubMed, EMBASE, and OVID databases through December 2014. Combinations of the following terms were used in the search (1) outcome terms: hemangiomas, infantile hemangiomas and complicated hemangiomas; and (2) therapeutic terms: propranolol, systemic steroids, beta-blocker, laser ablation, vincristine, and surgical intervention. The review articles were assessed for relevant references.

Selection criteria
The studies were evaluated by two independent reviewers (XHL and XHQ). To avoid bias, discrepancies were resolved by a third reviewer (JWZ) through a discussion. To avoid the issue of missing data in certain studies, the respective authors were contacted and asked to provide relevant information.
Studies that met the following criteria were included in the meta-analysis: (1) infantile population; (2) study sample size ≥ 20 (the timolol/atenolol sample size was ≥ 10); (3) retrospective studies, prospective studies or RCT; (4) clear description of the therapy (propranolol, systemic steroids, laser ablation, etc.); and (5) well-reported outcome measures (including explicit reporting of the response rate). The studies that did not meet the inclusion criteria were excluded during the initial review.

Data extraction and quality assessment

Two reviewers (XHL and XHQ) independently extracted the data based on a standard data collection form. A third reviewer (JWZ) resolved any discrepancies by discussing and consulting on the original articles. For each identified study, the following data were collected: last name of the first author, publication year, country, study design, number of cases, participants’ sex and age, location of the IHs, previous treatments, dosage of treatment, response rate and complications.

Data synthesis and statistical analysis

Odds ratios (ORs) and 95% CIs that reflected a degree of control for potential confounders were extracted from the selected studies for analysis [8]. In this meta-analysis, either a random-effects model (DerSimonian-Laird method) or a fixed-effects model (Mantel-Haenszel method) was used for analysis. Heterogeneity among the studies was evaluated by using $I^2$ statistics. $I^2$ values of 25%, 50% and 75% were defined as low, moderate, and high, respectively [9]. A subgroup analysis was conducted to identify associations between the efficiency of propranolol and relevant study characteristics (location of IHs, geographical location of patients, mean dosage of treatment and prior therapy). Funnel plot asymmetry measured by Egger’s and Begg’s tests, was used to assess publication bias [10, 11]. Probability values < 0.05 were considered statistically significant [12]. Data analysis was performed using R software 2.13.0, package (meta package metaprop and forest functions).

Results

Eligible studies and study characteristics

A total of 61 studies [13–73] were selected from 1097 potential articles for the meta-analysis (Fig 1). The characteristics of the selected articles are listed in Tables 1 and 2. The analysis included 5,130 IH cases from the 61 studies; of these cases, 3761 were located in the head and neck, 216 were located in the trunk, and 160 were located in the extremities. Of the included studies, 30 studies chose propranolol as the definitive treatment; 31 studies used other treatments (15 studies used systemic steroids, 7 studies used laser ablation, 2 studies used surgery, 3 studies used atenolol and 4 studies used timolol). The average age of the patients was 6.2 months. Evaluation of the outcomes was based on visual measurements, photograph scoring, Doppler ultrasonography or MRI.

Propranolol for treating IHs

A total of 30 studies [13–42], which included 1893 individuals reported the response and side-effects of propranolol for treating IHs. The pooled odd ratio (OR) for effectiveness was 0.92 (95% CI, 0.89–0.95), and a high heterogeneity was observed between the studies ($P_{\text{heterogeneity}} < 0.0001$; $I^2 = 87.1\%$) (Fig 2a). Of the included studies, 25 studies with 286 cases reported complications of propranolol treatment including hypotension ($n = 33$), hypoglycemia ($n = 10$), insomnia ($n = 75$), diarrhea ($n = 26$), and respiratory disorder ($n = 28$), among others.
Sensitivity analysis confirmed that excluding any of the studies from the pooled analysis did not influence the results.

**Subgroup analysis of propranolol for treating IHs**

In the subgroup analysis, possible sources of heterogeneity such as location of the IHs, geographical distribution of the patients, mean dosage of the treatment and previous therapy (or not) were examined (Table 4). The results showed that the mean treatment dosage and previous therapy (or not) influenced the effectiveness of propranolol in treating the IHs. A propranolol dosage of 2 mg/kg/day or more resulted in better outcomes. The OR was 0.92 (95% CI, 0.88–0.95; \( P_{\text{heterogeneity}} < 0.0001; I^2 = 86.8\% \)) for the 2mg/kg/day dose and 0.95 (95%CI, 0.88–1.00; \( P_{\text{heterogeneity}} < 0.0001; I^2 = 89\% \)) for doses that exceeded 2 mg/kg/day; in comparison, for doses that were less than 2 mg/kg/day, the OR was 0.90 (95% CI, 0.79–1.00; \( P_{\text{heterogeneity}} < 0.001; I^2 = 89\% \)). The patients with severe or intractable IHs, which did not respond to previous treatment, received subsequent oral propranolol. The effectiveness of propranolol therapy among these cases was inferior to that among the cases without previous treatment. The ORs was 0.88 (95%CI, 0.83–0.93; \( P_{\text{heterogeneity}} < 0.0001; I^2 = 86.5\% \)) for the 15 studies that used some other form of treatment prior to propranolol administration; this was much lower...
| Study (propranolol) | Study design | Number of patients /Sex (M:F) | Location/Previous therapy | Age(m)/Dose(mg/kg/day) | Number of response | Complications |
|---------------------|--------------|-----------------------------|---------------------------|-----------------------|-------------------|---------------|
| Sans et al.2009/ America [13] | RS | 32/11:21 | H&N21;Torso; Extremity2;Multiple6/ Yes | 4.2/2 | 32 | Agitation2;Asthma1;Cold-extremity1; Insomnia2;Others3 |
| Buckmiller et al.2010/America [14] | RS | 32/5:27 | H&N22;Multiple 10/ Yes | 4.9/2 | 16 | Allergy1;Asthma1;Gastroesophagealreflux2; Fatigue6 |
| Holmes et al.2010/ Britain [15] | RS | 31/NR | NR/No | NR/3 | 31 | None |
| Schupp et al.2011/ German [23] | RS | 55/15:40 | H&N42;Multiple 13/ Yes | 6.4/2 | 54 | Asthma2;Cold-extremity6; Gastroenteropathy2;Fatigue4;Others3 |
| Fuchsmann et al.2011/America [18] | RS | 39/12:27 | H&N39/Yes | 4.1/2 | 37 | Insomnia5 |
| Schiestl et al.2011/ Europe [22] | RS | 25/9:16 | H&N25/Yes | 3.6/2 | 25 | Hypotension6 |
| Hogeling et al.2011/ America [19] | RCT | 20/7:13 | H&N17;Torso1; Extremity1;Multiple1/ Yes | 2.25/2 | 16 | Bronchiolitis4;Cold-extremity1; Gastroenteropathy1;Infection2;Insomnia2; Ulceration1;Others2 |
| Zvulunov et al.2011/ Israel [25] | RS | 42/5:37 | NR/No | 28/2.1 | 42 | Dyspnea1;Insomnia2;Somnolence1 |
| Cushing et al.2011/ America [16] | RS | 44/9:35 | H&N44/Yes | 5.8/2 | 39 | None |
| Jin et al.2011/China [20] | RS | 78/NR | NR/No | 3.7/2 | 77 | Insomnia12 |
| Zaher et al.2011/ Europe [24] | RS | 30/NR | H&N30/No | NR/2 | 29 | None |
| Graaf et al.2011/ Netherlands [17] | RS | 28/7:21 | H&N28/Yes | 8.8/2.2 | 28 | Cold-extremity3;Constipation3; Hyperreactivity3;Hypoglycemia2; Hypotension16;Insomnia8 |
| Chai et al. 2014/ China [36] | RS | 27/6:21 | H&N22;Torso5/No | 4.1/2 | 27 | somnolence7 |
| Price et al. 2011/ America [21] | RS | 68/NR | NR/No | 4.5/2 | 56 | Hypoglycemia1;Skin rash2 |
| Rössler et al.2011/ German [29] | RS | 30/NR | NR/No | 4.5/2 | 25 | Diarrhea2;Hypotonia3;Reducedactivity3 |
| Meng et al.2012/ China [28] | RS | 22/9:13 | H&N22/Yes | 5.5/1.5 | 20 | Diarrhea2;Hypotension5 |
| Lv et al.2012/China [27] | RS | 37/10:27 | H&N37/Yes | 2.8/2 | 26 | Diarrhea9;Nausea1 |
| Laranjo et al.2014/ Portugal [38] | RS | 30/15:15 | H&N21;Torso5; Extremity4/No | 6/2.8 | 30 | None |
| Graaf et al.2013/ Portugal [30] | RS | 28/NR | NR/No | 6.8/2 | 28 | Bronchospasm4;Constipation3; Hypoglycaemia2;Hypotension1; Sleep-disturban11 |
| Ma et al.2013/ German [31] | RS | 89/37:52 | H&N51;Torso24; Extremity8; Perineum6/No | 3.56/0.75 | 65 | Cold-extremity1;Diarrhea3;Hypoglycemia4; Insomnia2;Nusea2 |
| Georgountzou et al.2012/Greece [26] | RS | 28/8:20 | H&N4;Multiple4/Yes | 5.59/2 | 21 | Hypotension4 |
| Mcsweiney et al.2014/German [39] | RS | 20/5:15 | H&N19;Torso1/No | 6/2 | 20 | Cold-extremity1 |

(Continued)
than the OR for the 15 studies that used propranolol alone (0.95; 95%CI, 0.91–0.98; $P_{\text{heterogeneity}} < 0.0001; I^2 = 88\%$).

Systemic steroids for treating IHs

Fig 2b shows the results for the treatment of IHs with systemic steroids based on an analysis of 15 studies [43–57] with 2,620 participants. In the pooled analysis, the OR was 0.68 (95%CI, 0.59–0.76; $P_{\text{heterogeneity}} < 0.0001; I^2 = 95.8\%$) for effectiveness. Sensitivity analysis showed that excluding any study from the pooled analysis did not affect the results.

Other therapies for treating IHs

Seven studies [58–64] on laser ablation, with 278 patients, were examined (Fig 3). The pooled OR for effectiveness was 0.55 (95%CI, 0.43–0.67; $P_{\text{heterogeneity}} = 0.0001; I^2 = 77.8\%$). In addition, the OR was 0.56 (95%CI, 0.50–0.61; $P_{\text{heterogeneity}} < 0.0001; I^2 = 88.9\%$) for the effectiveness of other beta-adrenergic blockers [67–73] and 0.55 (95%CI, 0.28–0.81; $P_{\text{heterogeneity}} = 0.0159; I^2 = 82.8\%$) for the effectiveness of surgery [65, 66].

Discussion

Our analysis of the 61 studies demonstrates that propranolol was more effective and safer in treating IHs than the other therapies. A subgroup analysis showed that the preferred dose of propranolol treatment was 2 mg/kg/day or more. In addition, the patients who had received previous treatments did not respond as well to propranolol treatment.
Table 2. Characteristics of studies that used other therapies for treating IHs.

| Study (Systemic Steroids) | Study design | Number of patients /Sex (M:F) | Location/Previous therapy | Age(m)/Dose(mg/kg/day) | Number of response | Complications |
|---------------------------|--------------|-------------------------------|----------------------------|------------------------|--------------------|---------------|
| Kushner et al.1979/Japan [43] | RS           | 25/ NR                        | H&N25/No                   | 4.2/2                  | 21 NR              |               |
| Narcy et al.1985/America [44] | RS           | 21/ NR                        | H&N21/No                   | NR/2                   | 7 NR               |               |
| Chowdri et al.1994/America [45] | RS           | 74/ NR                        | H&N48;Torso11; Extremity15/No | 36/10                  | 32 NR              | Cushingoid-appearance2 |
| Sadan et al.1996/Israel [46] | RS           | 60/15:45                      | H&N60/No                   | 5.5/3.5                | 56                 | Growth-retardation1;Moon-face32;Osteoporosis1 |
| Blei et al.1999/Europe [47]  | RS           | 30/ NR                        | H&N27;Extremity3/No        | NR/3.5                 | 8                  | Endocrine-disorder4;Growth-retardation3;Moon-face7 |
| Chen et al.2000/China [48]   | RS           | 155/ NR                       | H&N155/No                  | 3.8/10                 | 93                 | Cushingoid-appearance2;Cutaneous-diseases5 |
| Jalil et al.2006/America [49] | RCT          | 50/ NR                        | NR/No                      | NR/2                   | 19                 | Overall,22% |
| Pope et al.2007/America [50] | RCT          | 20/3:17                       | H&N20/No                   | 3/2                    | 8                  | Endocrine-disorder16;Hypertensions4 |
| Chantharatanapiboon et al.2008/Thailand [51] | RS       | 160/49:111                  | H&N134;Extremity26/No      | 5.5/1.5                | 144                | NR |
| Rössler et al.2008/German [52] | RS           | 38/11:27                     | H&N30;Torso4; Extremity3; Perineum1/Yes | 4.2/2                  | 33                 | Growth-retardation3;Hypertensionn2;Others6 |
| Pandey et al.2009/Britain [53] | RS           | 1127/342:785                 | H&N1058;Torso 69/No        | NR/1.5                 | 1003               | Growth-retardation58;Hypertension50;Moon-face58 |
| Zhou et al.2010/China [54]   | RS           | 23/2:21                      | NR/No                      | 6/3.5                  | 20                 | Cushingoid-appearance8;Poor-appetite5 |
| Prasetyono et al.2011/Indonesia [55] | RS       | 749/178:571                  | H&N749/Yes                 | 4.17/1.5                | 532                | Fatigue13;Ulceration10 |
| Greene et al.2011/America [55] | RS           | 67/16:51                     | H&N67/No                   | 3/2.5                  | 56                 | NR |
| Nieuwenhuis et al.2013/Netherlands [57] | RS       | 21/5:16                      | H&N19;Torso2/No            | 2.5/3                  | 13                 | Cushingoid-appearance8;Others4 |

| Study (Laser ablation) | Study design | Number of patients /Sex (M:F) | Location/Previous therapy | Age(m)/Dose(mg/kg/day) | Number of response | Complications |
|------------------------|--------------|-------------------------------|----------------------------|------------------------|--------------------|---------------|
| Scheepert et al.1995/Scotland [58] | RS           | 50/8:42                       | H&N50/No                   | 5.5/NR                 | 30                 | Scarring1 |
| Chatrath et al.2002/Britain [59] | RS           | 36/10:26                     | H&N36/No                   | 3/NR                   | 16                 | Tracheocutaneous-fistula19;Scarring1 |
| Hunzeker et al.2010/America [60] | RS           | 22/7:15                       | H&N21/No                   | 3.45/NR                | 17                 | Hyperpigmentation2 |
| Li et al.2010/China [61] | RS           | 62/23:39                     | NR/No                      | 5/20J                  | 38                 | Blister3;Hyperpigmentation9;Hypopigmentation3 |
| Kaune et al.2014/German [63] | RS           | 38/14:24                     | NR/No                      | 5/NR                   | 25                 | Blister17 |
| Su et al.2014/China [64] | RS           | 48/11:37                     | H&N20;Torso14; Extremity11; Perineum3/No | 24/50J                | 14                 | Blister9;Hypopigmentation1;Scarring1 |
| Alcántara et al.2013/Span [62] | RS           | 22/2:20                       | H&N20;Torso1; Extremity1/No | 6/NR                   | 11                 | Atrophy2;Hyperpigmentation1;Ulceration1 |

| Study (Surgery) | Study design | Number of patients /Sex (M:F) | Location/Previous therapy | Age(m)/Dose(mg/kg/day) | Number of response | Complications |
|----------------|--------------|-------------------------------|----------------------------|------------------------|--------------------|---------------|
| Watanabe et al.2009/Japan [65] | RS           | 32/3:29                       | H&N26;Multiple6/Yes        | 15.9/NR                | 13                 | None |
| Kulbersh et al.2011/America [66] | RS           | 46/ NR                        | H&N46/Yes                  | 4/NR                   | 31                 | Wound dehiscence1;Wound infection6 |

(Continued)
Steroids used to be the first-line treatment for IHs over the past several decades. It could be administered either locally or systemically and had a response rate of 78.05% [43–57]. Long-term steroid usage, however, tended to cause serious side effects [3]. Laser ablation, vincristine and surgical intervention have also been used to treat IHs but with varied efficiency and safety concerns [74].

Propranolol was first reported as a treatment for IHs by Lèautè-Labrère et al. in 2008 [5]. In this meta-analysis, propranolol showed a better effectiveness, with a response rate as high as 88.75%, which is 1.19 times higher than other treatments [13–42]. It is also a safer therapy, with fewer side effects [75, 76]. According to Labrèze et al., diarrhea (28/101), sleep-disorder (22/101), bronchitis (17/101) and cold hands and feet (10/101) were the common events [77]. The present study showed that propranolol treatment was more effective at a doses of 2 mg/kg/day or more [13]. However, because there is a lack in dose response studies, the optimal dose of propranolol remains to be investigated.

Recently, other beta-adrenergic blocker agents such as timolol and atenolol were reported to treating IHs. They appeared to be as effective as propranolol but with fewer side effects. Given the small number of cases reported in the literature, conclusions cannot be reached at present.

This meta-analysis is advantageous in two respects. First, a substantial number of participants were included. A meta-analysis by Peridis et al. included 13 studies, but none of them included more than 20 participants [78]. Lou et al. examined included 35 studies, but only 6 of them included more than 20 participants [79]. In this meta-analysis, 61 studies were included, and 59 of the studies had more than 20 participants. Second, data extraction, data analysis, and quality assessment were performed independently by two investigators, and consistency was achieved by a third reviewer, which enhanced the accuracy and reliability of the findings.

However, there are several limitations that should be addressed. First, the outcome measures varied across the studies, which weakened the strength of the identified association. Some of the studies used visual methods alone, while others used objective methods such as Doppler

| Study (Timolol/Atenolol) | Study design | Number of patients /Sex (M:F) | Location/Previous therapy | Age(m)/Dose(mg/kg/day) | Number of response | Complications |
|--------------------------|-------------|--------------------------------|---------------------------|------------------------|-------------------|--------------|
| Semkova et al.2012/Bulgaria [69] | RS          | 25/10:15                       | NR/No                     | 7.5/NR                 | 4                 | NR           |
| Yu et al.2013/China [71]     | RS          | 101/NR                         | H&N;Torso;Extremity       | NR/NR                  | 57                | NR           |
| Oranje et al.2011/Netherlands [67] | RS          | 20/NR                         | H&N20/Yes                 | 3.7/0.5                | 17                | NR           |
| Chan et al.2013/Sydney [68]  | RCT         | 19/5:14                        | H&N12;Torso               | 2.1/0.5                | 15                | None         |
| Alvaro et al.2014/Chile [72] | RCT         | 13/6.7                         | NR/No                     | 5.3/1                  | 7                 | NR           |
| Sharma et al.2013/Canada [70] | RS          | 22/NR                         | NR/Yes                    | 3.3/NR                 | 16                | Hypotension1 |
| Park et al.2014/Korea [73]   | RS          | 61/NR                         | NR/No                     | NR/NR                  | 29                | None         |

NR, not reported; RS, retrospective study; PS, prospective study; H&N, head and neck

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Fig 2. The effectiveness of propranolol (a) and systemic steroids (b) for treating IHs.

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ultrasonography, MRI and endoscopy to evaluate the treatment outcomes. This discrepancy may lead to inevitable bias in the estimated ORs. Second, methodological differences among the studies may have also resulted in heterogeneity, as high $I^2$ values were observed in this meta-analysis. A subgroup analysis was performed to explore the possible heterogeneity of the studies.

Based on the findings of this analysis, a few questions remain to be answered. First, the patients with previous treatments did not respond as well to propranolol treatment. Thus, do previous IH treatments influence the effectiveness of propranolol? Second, due to the lack of dose response studies, the optimal dose of propranolol and other treatment modalities for treating IHs remains unknown. To answer these questions, further well-designed RCT studies are need to be performed.

In conclusion, propranolol is a more effective and safer treatment for IHs, and can be used as the first-line therapy for complicated IHs cases.

### Table 3. Complications and adverse events of propranolol (N. = 1893).

| Adverse Event       | No.(%)     | No./N.(%) |
|---------------------|------------|-----------|
| Hypotension         | 33(11.54)  | 1.74      |
| Hypoglycemia        | 10(3.50)   | 0.53      |
| Insomnia            | 75(26.22)  | 3.96      |
| Diarrhea            | 26(9.09)   | 1.37      |
| Cold extremity      | 17(5.94)   | 0.90      |
| Fatigue             | 13(4.55)   | 0.69      |
| Constipation        | 10(3.50)   | 0.53      |
| Respiratory disorder| 28(9.79)   | 1.48      |
| Gastrointestinal disorder | 9(3.15)   | 0.48      |
| Others              | 65(22.72)  | 3.43      |
| **Total**           | 286(100%)  | 15.11%    |

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### Table 4. Stratified analysis of propranolol for treating IHs.

| Stratified          | No. of studies | Heterogeneity within subgroup |
|---------------------|----------------|------------------------------|
|                     |                | OR (95%CI) | $I^2$ (%) | P for heterogeneity |
| **Location:**       |                |             |           |                    |
| Head and Neck       | 8              | 0.89 (0.81, 0.97) | 88.1     | <0.001 |
| Head, Neck and others | 17          | 0.88 (0.84, 0.93) | 90.4     | <0.001 |
| **Geographical location:** |          |             |           |                    |
| United States       | 7              | 0.86 (0.77, 0.95) | 86.1     | <0.001 |
| Europe              | 14             | 0.91 (0.86, 0.96) | 89.3     | <0.001 |
| Asian               | 9              | 0.96 (0.93, 0.99) | 85.4     | <0.001 |
| **Mean dose(mg/kg/day):** |          |             |           |                    |
| < 2                 | 4              | 0.90 (0.79, 1.00) | 89       | <0.001 |
| = 2                 | 21             | 0.92 (0.88, 0.95) | 86.8     | <0.001 |
| > 2                 | 5              | 0.95 (0.89, 1.00) | 89       | <0.001 |
| **Prior therapy:**  |                |             |           |                    |
| Yes                 | 15             | 0.88 (0.83, 0.93) | 86.5     | <0.001 |
| No                  | 15             | 0.95 (0.91, 0.98) | 88       | <0.001 |

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Fig 3. The effectiveness of other therapies for treating IHs.

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Supporting Information
S1 PRISMA Checklist. PRISMA 2009 Checklist.

Author Contributions
Conceived and designed the experiments: JZ XQ. Performed the experiments: XL XQ. Analyzed the data: XL XQ. Contributed reagents/materials/analysis tools: XL XQ LZ. Wrote the paper: XL. Reviewed the manuscript: XL XQ JZ LZ.

References
1. Frieden IJ, Haggstrom AN, Drolet BA, Mancini AJ, Friedlander SF, Boon L, et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7–9, 2005, Bethesda, Maryland, USA. Pediatric dermatology. 2005; 22(5):383–406. PMID: 16190987
2. Buckmiller L, Dyamenahalli U, Richter GT. Propranolol for airway hemangiomas: case report of novel treatment. The Laryngoscope. 2009; 119(10):2051–4. doi:10.1002/lary.20633 PMID: 19650125
3. Maturo S, Hartnick C. Initial experience using propranolol as the sole treatment for infantile airway hemangiomas. International journal of pediatric otorhinolaryngology. 2010; 74(3):323–5. doi: 10.1016/j.ijporl.2009.12.008 PMID: 20071038
4. Nguyen J, Fay A. Pharmacologic therapy for periocular infantile hemangiomas: a review of the literature. Seminars in ophthalmology. 2009; 24(3):178–84. doi: 10.1080/08820530902805602 PMID: 19437355
5. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. The New England journal of medicine. 2008; 358(24):2649–51. doi: 10.1056/NEJMoa0708819 PMID: 18550886
6. Moehrle M, Leaute-Labreze C, Schmidt V, Rocken M, Poets CF, Goelz R. Topical timolol for small hemangiomas of infancy. Pediatric dermatology. 2013; 30(2):245–9. doi: 10.1111/j.1525-1470.2012.01723.x PMID: 22471694
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Goøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine. 2009; 6(7):e1000100. doi:10.1371/journal.pmed.1000100 PMID: 19621070
8. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. American journal of epidemiology. 2003; 157(10):940–3. PMID: 12746247
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003; 327(7414):557–60. PMID: 12958120
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315(7109):629–34. PMID: 9310563
11. Qu X, Huang X, Jin F, Wang H, Hao Y, Tang T, et al. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. International journal of cardiology. 2013; 166(2):385–93. doi: 10.1016/j.ijcard.2011.10.114 PMID: 22112679
12. Qu X, Zhang X, Zhai Z, Li H, Liu X, Li H, et al. Association between physical activity and risk of fracture. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 2014; 29(1):202–11.
13. Sans V, de la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics. 2009; 124(3):e423–31. doi: 10.1542/peds.2008-3458 PMID: 19706583
14. Buckmiller LM, Munson PD, Dyamenahalli U, Dai Y, Richter GT. Propranolol for infantile hemangiomas: early experience at a tertiary vascular anomalies center. The Laryngoscope. 2010; 120(4):676–81. doi: 10.1002/lary.20807 PMID: 20112413
15. Mishra A, Holmes WJ, Gorst C, Liew SH. Role of propranolol in the management of periocular hemangiomas. Plastic and reconstructive surgery. 2010; 126(2):671.
16. Cushing SL, Boucek RJ, Manning SC, Sidbury R, Perkins JA. Initial experience with a multidisciplinary strategy for initiation of propranolol therapy for infantile hemangiomas. Otolaryngology—head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011; 144(1):78–84.
17. de Graaf M, Breur JM, Raphael MF, Vos M, Breugem CC, Pasmans SG. Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. Journal of the American Academy of Dermatology. 2011; 65(2):320–7. doi: 10.1016/j.jaad.2010.06.048 PMID: 21601311

18. Fuchsman C, Quintal MC, Giguere C, Ayari-Khalfallah S, Guibaud L, Powell J, et al. Propranolol as first-line treatment of head and neck hemangiomas. Archives of otolaryngology—head & neck surgery. 2011; 137(5):471–8.

19. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011; 128(2):e259–66. doi: 10.1542/peds.2010-0029 PMID: 21788220

20. Jin YB, Lin XX, Ye XX, Chen H, Ma G, Jiang CH, et al. [A prospective study of propranolol as first-line treatment for problematic infantile hemangioma in China]. Zhonghua zheng xing wai ke za zhi = Chinese journal of plastic surgery. 2011; 27(3):170–3. PMID: 21837993

21. Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. Archives of dermatology. 2011; 147(12):1371–6. doi: 10.1001/archdermatol.2011.203 PMID: 21844428

22. Schiestl C, Neuhaus K, Zoller S, Subotic U, Forster-Kuebler I, Michels R, et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. European journal of pediatrics. 2011; 170(4):493–501. doi: 10.1007/s00431-010-1324-2 PMID: 20936146

23. Schupp CJ, Kleber JB, Gunther P, Holland-Cunz S. Propranolol therapy in 55 infants with infantile hemangioma: dosage, duration, adverse effects, and outcome. Pediatric dermatology. 2011; 28(6):640–4. doi: 10.1111/j.1525-1470.2011.01569.x PMID: 21995836

24. Zaher H, Rasheed H, Hegazy RA, Hegazy RA, Abdelhalim DM, Gawdat HI. Oral propranolol: an effective, safe treatment for infantile hemangiomas. European journal of dermatology: EJD. 2011; 21(4):558–63. doi: 10.1684/ejd.2011.1372 PMID: 21697036

25. Zvulunov A, McCuaig C, Frieden UJ, Mancini AJ, Puttgen KB, Dohil M, et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. Pediatric dermatology. 2011; 28(2):94–8. doi: 10.1111/j.1525-1470.2010.01379.x PMID: 21362031

26. Georgountzou A, Karavitakis E, Klimentopoulou A, Xaidara A, Kakourou T. Propranolol treatment for severe infantile hemangiomas: a single-centre 3-year experience. Acta paediatrica (Oslo, Norway: 1992). 2012; 101(10):e469–74.

27. Lv MM, Fan XD, Su LX. Propranolol for problematic head and neck hemangiomas: an analysis of 37 consecutive patients. International journal of pediatric otorhinolaryngology. 2012; 76(4):574–8. doi: 10.1016/j.ijporl.2012.01.020 PMID: 22326207

28. Meng J, Li Z, Gu Q, Zhang J, Zhuang Q, Si Y, et al. Propranolol intervention therapy for infants with facial hemangioma. Contemporary oncology (Poznan, Poland). 2012; 16(5):432–4.

29. Rossler J, Schill T, Bahr A, Truckenmüller W, Noellke P, Niemeyer CM. Propranolol for proliferating infantile haemangioma is superior to corticosteroid therapy—a retrospective, single centre study. Journal of the European Academy of Dermatology and Venereology: JEADV. 2012; 26(9):1173–5.

30. de Graaf M, Raphael MF, Breugem CC, Knol MJ, Bruijnzeel-Koomen CA, Kon M, et al. Treatment of infantile hemangiomas with atenolol: comparison with a historical propranolol group. Journal of plastic, reconstructive & aesthetic surgery: JPRAS. 2013; 66(12):1732–40.

31. Ma X, Zhao T, Xiao Y, Yu J, Chen H, Huang Y, et al. Preliminary experience on treatment of infantile hemangioma with low-dose propranolol in China. European journal of pediatrics. 2013; 172(5):653–9. doi: 10.1007/s00431-012-1928-9 PMID: 23829783

32. Sadykov RR, Podmelle F, Sadykov RA, Kasimova KR, Metellmann HR. Use of propranolol for the treatment infantile hemangiomas in the maxillofacial region. International journal of oral and maxillofacial surgery. 2013; 42(7):863. doi: 10.1016/j.ijom.2013.03.015 PMID: 23618833

33. Sondhi V, Patnaik SK. Propranolol for infantile hemangioma (PINCH): an open-label trial to assess the efficacy of propranolol for treating infantile hemangiomas and for determining the decline in heart rate to predict response to propranolol. Journal of pediatric dermatology/oncology. 2013; 35(7):493–9. PMID: 23929318

34. Vercellino N, Romanini MV, Pelegrini M, Rimini A, Occella C, Dalmonte P. The use of propranolol for complicated infantile hemangiomas. International journal of dermatology. 2013; 52(9):1140–6. doi: 10.1111/j.1365-4632.2012.05795.x PMID: 23829783

35. Xiao Q, Li Q, Zhang B, Yu W. Propranolol therapy of infantile hemangiomas: efficacy, adverse effects, and recurrence. Pediatric surgery international. 2013; 29(6):575–81. doi: 10.1007/s00383-013-3283-y PMID: 23519547

36. Chai Q, Chen WL, Huang ZQ, Zhang DM, Fan S, Wang L. Preliminary experiences in treating infantile hemangioma with propranolol. Annals of plastic surgery. 2014; 72(2):169–72. PMID: 21629056
37. Hassan BA, Shreef KS. Propranolol in treatment of huge and complicated infantile hemangiomas in Egyptian children. Dermatology research and practice. 2014; 2014:541810. doi: 10.1155/2014/541810 PMID: 24899888

38. Laranjo S, Costa G, Parames F, Freitas I, Martins JD, Trigo C, et al. The role of propranolol in the treatment of infantile hemangioma. Revista portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology: an official journal of the Portuguese Society of Cardiology. 2014; 33(5):289–95.

39. McSwiney E, Murray D, Murphy M. Propranolol therapy for cutaneous infantile haemangiomas initiated safely as a day-case procedure. European journal of pediatrics. 2014; 173(1):63–8. doi: 10.1007/s00431-013-2105-5 PMID: 23933667

40. Sagi L, Zvulunov A, Lapidoth M, Ben Amitai D. Efficacy and safety of propranolol for the treatment of infantile hemangioma: a presentation of ninety-nine cases. Dermatology (Basel, Switzerland). 2014; 228(2):136–44.

41. Szycyna P, Stewart K, Anderson W. Treatment of infantile hemangiomas with propranolol: clinical guidelines. Plastic and reconstructive surgery. 2014; 133(4):852–62. PMID: 24352207

42. Luo Y, Zeng Y, Zhou B, Tang J. A retrospective study of propranolol therapy in 635 infants with infantile hemangioma. Pediatric dermatology. 2015; 32(1):151–2. doi: 10.1111/pde.12308 PMID: 24602103

43. Kushner BJ. Local steroid therapy in adnexal hemangioma. Annals of ophthalmology. 1979; 11(7):1005–9. PMID: 484996

44. Narcy P, Contencin P, Bobin S, Manach Y. Treatment of infantile subglottic hemangioma. A report of 49 cases. International journal of pediatric otorhinolaryngology. 1985; 9(2):157–64. PMID: 4030237

45. Chowdri NA, Darzi MA, Fazili Z, Iqbal S. Intralesional corticosteroid therapy for childhood cutaneous hemangiomas. A report of 62 cases. Journal of plastic surgery. 1994; 33(1):46–51. PMID: 7944196

46. Sadan N, Wocla B. Treatment of hemangiomas of infants with high doses of prednisone. The Journal of Pediatrics. 1996; 128(1):141–6. PMID: 8551406

47. Blei F, Chianese J. Corticosteroid toxicity in infants treated for endangering hemangiomas: experience and guidelines for monitoring. International Pediatrics. 1999; 14:146–53.

48. Chen MT, Yeong EK, Homg SY. Intranasal corticosteroid therapy in proliferating head and neck hemangiomas: a review of 155 cases. Journal of pediatric surgery. 2000; 35(3):420–3. PMID: 10726680

49. Jafari S, Akhtar J, Ahmed S. Corticosteroids therapy in the management of infantile cutaneous hemangiomas. Journal of the College of Physicians and Surgeons—Pakistan: JCPSP. 2006; 16(10):662–5. PMID: 17007757

50. Pope E, Krachik BR, Macarthur C, Stempak D, Stephens D, Weinstein M, et al. Oral versus high-dose pulse corticosteroids for problematic infantile hemangiomas: a randomized, controlled trial. Pediatrics. 2007; 119(6):e1239–47. PMID: 17485449

51. Chantharatanapiboon W. Intranasal corticosteroid therapy in hemangiomas: clinical outcome in 160 cases. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2008; 91 Suppl 3: S90–6. PMID: 19253502

52. Rossler J, Wehl G, Niemeyer CM. Evaluating systemic prednisone therapy for proliferating haemangiomas in infancy. European journal of pediatrics. 2008; 167(7):813–5. PMID: 17676341

53. Pandey A, Gangopadhyay AN, Gopal SC, Kumar V, Sharma SP, Gupta DK, et al. Twenty years’ experience of steroids in infantile hemangioma—a developing country’s perspective. Journal of pediatric surgery. 2009; 44(4):688–94. doi: 10.1016/j.jpedsurg.2008.10.038 PMID: 19361627

54. Zhou Q, Yang XJ, Zheng JW, Wang YA, Zhang ZY. Short-term high-dose oral prednisone on alternate days is safe and effective for treatment of infantile hemangiomas. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2010; 109(2):166–7. doi: 10.1016/j.tripleo.2009.10.026 PMID: 20123404

55. Greene AK, Couto RA. Oral prednisolone for infantile hemangioma: efficacy and safety using a standardized treatment protocol. Plastic and reconstructive surgery. 2011; 128(3):743–52. PMID: 21572374

56. Prasetyono TO, Djoenaedi I. Efficacy of intravenous steroid injection in head and neck hemangioma: a systematic review. Annals of plastic surgery. 2011; 66(1):98–106. PMID: 21042190

57. Nieuwenhuis K, de Laat PC, Jannmohamed SR, Mader GC, Oranje AP. Infantile hemangioma: treatment with short course systemic corticosteroid therapy as an alternative for propranolol. Pediatric dermatology. 2013; 30(1):64–70. doi: 10.1111/j.1525-1470.2012.01846.x PMID: 22958179

58. Scheepers JH, Quaba AA. Does the pulsed tunable dye laser have a role in the management of infantile hemangiomas? Observations based on 3 years’ experience. Plastic and reconstructive surgery. 1995; 95(2):305–12. PMID: 7824610
59. Chatrath P, Black M, Jani P, Albert DM, Bailey CM. A review of the current management of infantile subglottic haemangioma, including a comparison of CO(2) laser therapy versus tracheostomy. International journal of pediatric otorhinolaryngology. 2002; 64(2):143–57. PMID: 12049827

60. Hunzeker CM, Geronemus RG. Treatment of superficial infantile hemangiomas of the eyelid using the 595-nm pulsed dye laser. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2010; 36(5):590–7.

61. Li DN, Gold MH, Sun ZS, Tang AR, Wang HB, Sheng-Kang L. Treatment of infantile hemangioma with optimal pulse technology. Journal of cosmetic and laser therapy: official publication of the European Society for Laser Dermatology. 2010; 12(3):145–50.

62. Alcantara-Gonzalez J, Boixeda P, Truchuelo-Diez MT, Perez-Garcia B, Alonso-Castro L, Jaen Olasolo P. Infantile hemangiomas treated by sequential application of pulsed dye laser and Nd:YAG laser radiation: a retrospective study. Actas dermo-sifiliograficas. 2013; 104(6):504–11. doi: 10.1016/j.ad.2012.12.010 PMID: 23522740

63. Kaune KM, Lauerer P, Kietz S, Eich C, Thoms KM, Schon MP, et al. Combination therapy of infantile hemangiomas with pulsed dye laser and Nd:YAG laser is effective and safe. Journal Der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG. 2014; 12(6):473–8. doi: 10.1111/ddg.12354 PMID: 24825388

64. Su W, Ke Y, Yue J. Beneficial effects of early treatment of infantile hemangiomas with a long-pulse Alexandrite laser. Lasers in surgery and medicine. 2014; 46(3):173–9. doi: 10.1002/lsm.22221 PMID: 24391080

65. Watanabe S, Takagi S, Sato Y, Hosaka Y. Early surgical intervention for Japanese children with infantile hemangiomas of the craniofacial region. The Journal of craniofacial surgery. 2009; 20 Suppl 1:707–9. PMID: 19218860

66. Kulbersh J, Hochman M. Serial excision of facial hemangiomas. Archives of facial plastic surgery. 2011; 13(3):199–202. doi: 10.1001/archfacial.2011.23 PMID: 21576667

67. Oranje AP, Janmohamed SR, Madern GC, de Laat PC. Treatment of small superficial haemangioma in infants and children with timolol 0.5% ophthalmic solution: a series of 20 cases. Dermatology (Basel, Switzerland). 2011; 223(4):330–4.

68. Chan H, McKay C, Adams S, Wargon O. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. Pediatrics. 2013; 131(6):e1739–47. doi: 10.1542/peds.2012-3828 PMID: 23650294

69. Semkova K, Kazandjieva J. Topical timolol maleate for treatment of infantile haemangiomas: preliminary results of a prospective study. Clinical and experimental dermatology. 2013; 38(2):143–6. doi: 10.1111/j.1365-2230.2012.04425.x PMID: 22731954

70. Sharma VK, Fraulin FO, Dumestre DO, Walker L, Harrop AR. Beta-blockers for the treatment of problematic hemangiomas. The Canadian journal of plastic surgery = Journal canadien de chirurgie plastique. 2013; 21(1):23–8. PMID: 24431932

71. Yu L, Li S, Su B, Liu Z, Fang J, Zhu L, et al. Treatment of superficial infantile hemangiomas with timolol: Evaluation of short-term efficacy and safety in infants. Experimental and therapeutic medicine. 2013; 6(2):388–90. PMID: 24137194

72. Abarzua-Araya A, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. Journal of the American Academy of Dermatology. 2014; 70(6):1045–9. doi: 10.1016/j.jaad.2014.01.905 PMID: 24656727

73. Park KH, Jang YH, Chung HY, Lee WJ, Kim DW, Lee S. Topical timolol maleate 0.5% for infantile hemangioma; it's effectiveness and/or adjunctive pulsed dye laser—single center experience of 102 cases in Korea. The Journal of dermatological treatment. 2014; 1:39–43.

74. Mistry N, Tzifa K. Use of propranolol to treat multicentric airway haemangioma. The Journal of laryngology and otology. 2010; 124(12):1329–32. doi: 10.1056/SLTO2011.1000668X PMID: 20370949

75. Saint-Jean M, Leaute-Labreze C, Mazereeuw-Hautier J, Bodak N, Hamel-Teillac D, Kupfer-Bessa gut J, et al. Propranolol for the treatment of ulcerated infantile hemangiomas. Journal of the American Academy of Dermatology. 2011; 64(5):827–32. doi: 10.1016/j.jaad.2010.12.040 PMID: 21353322

76. Mazereeuw-Hautier J, Hoeger PH, Benlahrech S, Ammour A, Broue P, Vial J, et al. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. The Journal of pediatrics. 2010; 157(2):340–2. doi: 10.1016/j.jpeds.2010.04.003 PMID: 20486455

77. Leaute-Labreze C, Hoeger P, Mazereeuw-Hautier J, Guilbaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. The New England journal of medicine. 2015; 372(8):735–46. doi: 10.1056/NEJMoa1404710 PMID: 25693013
78. Peridis S, Pilgrim G, Athanasopoulos I, Parpounas K. A meta-analysis on the effectiveness of propranolol for the treatment of infantile airway haemangiomas. International journal of pediatric otorhinolaryngology. 2011; 75(4):455–60. doi: 10.1016/j.ijporl.2011.01.028 PMID: 21333364

79. Lou Y, Peng WJ, Cao Y, Cao DS, Xie J, Li HH. The effectiveness of propranolol in treating infantile haemangiomas: a meta-analysis including 35 studies. British journal of clinical pharmacology. 2014; 78(1):44–57. doi: 10.1111/bcp.12235 PMID: 24033819