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Research Paper

Treatments for infantile Hemangioma: A systematic review and network meta-analysis

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ABSTRACT

Background: Infantile hemangioma (IH) is common in children, which may bring about cosmetically disfiguring, functional impairment, and exhibiting complications. There had been various therapies and we aimed to assess the efficacy and adverse effects of different therapies through network meta-analysis.
Methods: We searched PubMed, Embase, Cochrane Library and Web of Science (from database inception to April 11, 2020) for studies assessing the efficacy, success rate and adverse effects. Direct pairwise comparison and a network meta-analysis under random effects were performed. We also assessed the ranking probability.
Findings: A total of 30 randomized clinical trials with more than 20 different therapeutic regimens were identified. Treatment combined propranolol orally with laser could improve the curative effect than monotherapy. Laser with topical β blockers showed more efficiency than others whether in children under 6 months or not. The long-pulsed dye laser might be the best laser therapy. A higher dose and a longer treatment duration of propranolol orally achieved a higher success rate and increased side effects. Plus pulse dye laser with propranolol had the lowest incidence of adverse reactions, such as ulcer, color sink and color reduction.
Interpretation: A combination of β blockers and laser might be the first-line treatment of IHs and a longer pulsed dye laser is preferred.
Funding: No funding was received.

1. Introduction

Infantile hemangioma (IH) is known as one of the most common tumors of childhood, with an incidence of 5–10% in infants [1,2]. Risk factors of IHs include prematurity, low birth weight infants, white race and females [3]. IHs often involve the head and neck, and can result in local tissue damage, ulceration, infection, bleeding, functional impact, and disfigurement [2–4]. Early treatment of IHs may potentially mitigate complications. However, there are so many therapeutic protocols (systemic or topical β-blockers, corticosteroids, imiquimod, laser therapy and so on) for clinical doctors [2,4,5], it is virtually impossible to cover all the combinations in direct head-to-head RCTs in order to determine the optimal option. The application of network meta-analysis (NMA), which is able to synthesize the results of direct and indirect comparisons simultaneously to obtain a more accurate and precise statistical result, makes it possible to overcome the limitation [6]. Therefore, we aimed to perform an evidence-based systematic review and NMA so as to evaluate the efficacy and adverse effects of these therapeutic choices.

2. Methods

This review was conducted in accordance with The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [7]. (Supplement 15)

2.1. Search strategy

We performed a systematic review and network meta-analysis. An electronic search of PubMed, Embase, Cochrane Library and Web of Science (WOS) was conducted for research published between database inception to April 11, 2020 using Medical Subject Headings (MeSH) for 'Hemangioma', 'Therapeutics', 'Lasers' and other drugs

Abbreviation: IH, infantile hemangioma; PRO, propranolol; PDL, pulsed dye laser; LPDL, PDL at a long pulse duration; Nd, Nd:YAG laser; Laser, PDL and Nd:YAG laser; β, topical β-blockers treatment; ATL, atenolol; PED, prednisone; IMQ, imiquimod; TA, triamcinolone; CAP, captopril; OR, odds ratios; CI, confidence intervals; RCT, randomized clinical trials; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve; H, a higher dose; L, a longer treatment duration; S, a shorter treatment duration

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Panel: Research in context

Evidence before this study

Infantile hemangiomas (IHs) are very common in children and can cause many adverse effects. With the development, there are many different treatment regimens applied to the treatment of this disease.

Added value of this study

We performed a systematic review and network meta-analysis evaluating the efficiency, success rate, and incidence of adverse events of different treatment regimens for IHs. Finally, there were 30 articles and more than 20 therapeutic regimens included in our study.

Implications of all the available evidence

We found that combined β blockers with laser might was superior to other treatments, regardless of age and type of IHs.

which might be used in the treatment of IHs, with no language restrictions. (Details in Supplement 14)

2.2. Inclusion and exclusion criteria

Inclusion criteria were:

(1) studies were RCTs involving children patients with treatments for IHs
(2) studies with two arms of treatments at least;
(3) studies' endpoint(s) concluded the efficacy, success rate or incidence of adverse effects. (Definition described in Supplement 3)

Exclusion criteria were:

(1) studies not adhere to the inclusion criteria;
(2) studies with only an abstract or could not extract available data;
(3) studies with patients previously been treated
(4) studies ongoing and without result.

2.3. Data extraction and outcomes

All basic information of studies was extracted independently by two investigators (F.Q. and L.Y.). Disagreements were settled by discussion and a senior reviewer (Dr. Yuan). The data included the first author, origin, year of publication, sample size, age, therapeutic regimens, the number of patients treated effectively and successfully, the number of adverse events. The primary outcomes were the success rate and occurrence of adverse effects of different treatments as mentioned above with dichotomous data. Secondary outcome was the efficiency of therapies.

2.4. Quality assessment and risk of bias

The risk of bias for each RCT was assessed using the Cochrane Collaboration Risk of Bias Tool [8] which examined potential selection bias, performance bias, detection bias, attrition bias, and reporting bias and other bias. Included RCTs were categorized as follows based on the risk of bias: low, high, or unclear. Funnel plots were utilized to investigate signs of publication bias. (Supplement 5 and the 'Funnel plot' section of Supplement 6–12) We used the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) for grading the certainty of direct and network evidence (Supplement 13).

2.5. Statistical analysis

We performed a random effects network meta-analysis using STATA15 software (StataCorp, College Station, TX, USA). Evidence from both direct and indirect comparisons was combined in the analysis. The primary endpoints, the success rate and occurrence of adverse effects, were described in the inclusion criteria. A network plot was generated to represent the overall information of the RCTs included in our study. Nodes size represents the number of patients for each treatment and lines thickness represents the number of available direct comparisons (in the 'Network plot' section of Supplement 6–12) [9]. We evaluated summary odds ratios (ORs) for dichotomous outcomes with 95% confidence intervals (CI) (in the 'Indirect comparisons' section of Supplement 6–12). A surface under the cumulative ranking curve (SUCRA), considered the more precise estimation of cumulative ranking probabilities, was used to provide a hierarchy of the efficacy, success rate and adverse reactions of the treatments (in the 'Treatment relative ranking of model' section of Supplement 6–12), the higher the SUCRA value is, the higher efficacy and incidence of adverse effects of the treatment has [10]. (More details in Supplement 2)

2.6. Role of the funding source

This systematic review and network meta-analysis was not funded.

3. Results

Our systematic search identified 7769 citations of which we included 30 articles finally in NMA. The flow of the systematic review is presented in Fig. 1. There were 1189 duplicates. We identified a total of 89 relevant references followed by a review of titles and abstracts. We read the full-text articles and excluded 56 articles not meeting the inclusion criteria or meeting the exclusion criteria (18 were non-RCTs; 11 without any endpoint we need; 7 without full-text; 7 letters; 5 single-arm study; 3 had duplicate content; 3 studies with patients treated before; 1 review; and 1 article's study design was not eligible). Moreover, treatments of Wu's (surgical resection and pingyangmycin) [11], Jung's (soft X-ray radiation) [12] and Zhu's

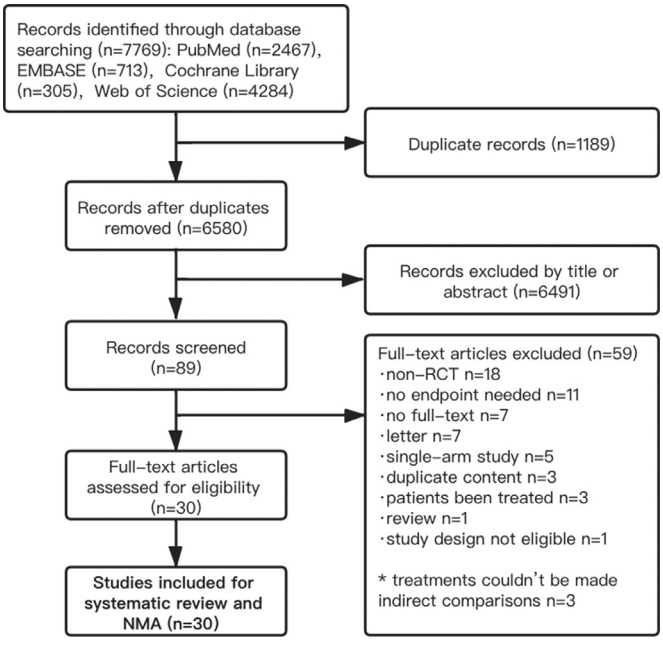

Fig. 1. Flow diagram of search process.

(^{90}Sr-^{90}Y therapy) [13] could not be made indirect comparison with other studies, because they were the only ones who had studied the therapies, we excluded them. Eventually, 30 RCTs met the eligibility criteria for our study with an acceptable risk of bias among them. The characteristics of the 30 included trials are summarized in 'S Table'. The studies were conducted worldwide including Asia, Africa, Europe, Oceania and America, and were published between 2002 and 2019. One trial included 5 arms involving 446 patients, [14] 6 studies with 3 arms involving 326 patients [15–20], while the others included two arms involving 1351 patients. One of the studies used self-comparison [21]. Our study was registered with PROSPERO, number CRD42020179986.

Totally, there were more than 20 therapeutic regimens (Details in Supplement 4) and 7 NMAs from different perspectives conducted, the efficacy of different treatments (Supplement 6), different lasers (Supplement 8), different topical β blockers (Supplement 11), treatments used in children younger than 6 months (Supplement 10) and treatments for superficial IHs (Supplement 12), success rate (Supplement 7) and occurrence of adverse effects (Supplement 9) of different treatments. Heterogeneity and inconsistency of these NMAs were assessed (Supplement 6.1–12.1) based on a design-by-treatment interaction model, [22] no significant inconsistency between direct and indirect evidence was identified within the evidence network (P>0.05) and consistency models were supported. There was no significant publication bias in the NMAs (In the 'Funnel plot' section of Supplement 6–12).

For the success rate, the network map was shown in Fig. 2A. There were 11 various treatments included, not all of which had a placebo-controlled trial, but they were more effective than placebo or observation (SUCRA of Placebo: 0.037, ranking 11th of 11 kinds of treatments). Combination therapy of propranolol orally with Nd:YAG did excellent (SUCRA of PRO-*L*+Nd: 0.98, ranking 1st of 11). Different doses and different durations of propranolol were also compared (PRO-S vs PRO-L: OR: 0.07, 95%CI: 0.02–0.32; H-PRO-S vs H-PRO-L: OR: 0.09, 95%CI: 0.02–0.37).

In terms of efficacy, combined propranolol orally with laser could improve the curative effect than monotherapy (PRO-L vs PRO-*L*+Laser: OR: 0.16, 95%CI: 0.03–0.81; Laser vs PRO-L+Laser: OR: 0.21, 95%CI: 0.06–0.69). Laser with topical β blockers showed more efficiency than others (β+Laser vs PRO-L: OR: 50.69, 95%CI: 1.01–2566.32; β+Laser vs Laser: OR: 39.00, 95%CI: 0.99–1539.15). SUCRA analysis indicated that β+Laser was likely to be the most effective treatment (SUCRA=0.92, PrBest 0.731, ranking 1st). This result also held for children under 6 months (SUCRA of β+Laser=0.806, ranking 1st). However, the comparison between different topical β blockers was not statistically significant (β-PRO vs β-TIM, OR=3.15, CI: 0.09–110.53). In addition, effects varied across different lasers, among which the long-pulsed dye laser (LPDL) might be the best (SUCRA of LPDL: 0.730, ranking 1st of 4 kinds of lasers). For superficial IHs therapy, the combination of propranolol orally and laser ranked in 1st of 6 regimens.

For the occurrence of side effects, the network plot was shown in Fig. 2B. There were twenty-five out of thirty trials included and eighteen various therapy regimens compared, of which PRO-L had the largest sample size. The treatment of plus PDL with propranolol orally had the lowest incidence of adverse reactions (SUCRA of PDL+PRO-L=0.086, ranking 18th of 19th, the 19th was Placebo) followed by topical use of β blockers alone (SUCRA of β=0.156). PDL had fewer adverse reactions than Nd:YAG (PDL vs Nd, OR=0.04, CI: 0.00–0.74). The most adverse reactions occurred in intravenous therapy of triamcinolone (SUCRA of TA=0.867, ranking 1st).

Table 1 shows the primary results of our NMA. There were eleven treatment regimens compared both success rate and incidence of adverse reactions. SUCRA rankings for success rate and incidence of adverse reactions were evaluated in Fig. 3.

4. Discussion

This systematic review and NMA included 30 RCTs which assigned 2123 children patients diagnosed IH to more than 20 kinds of

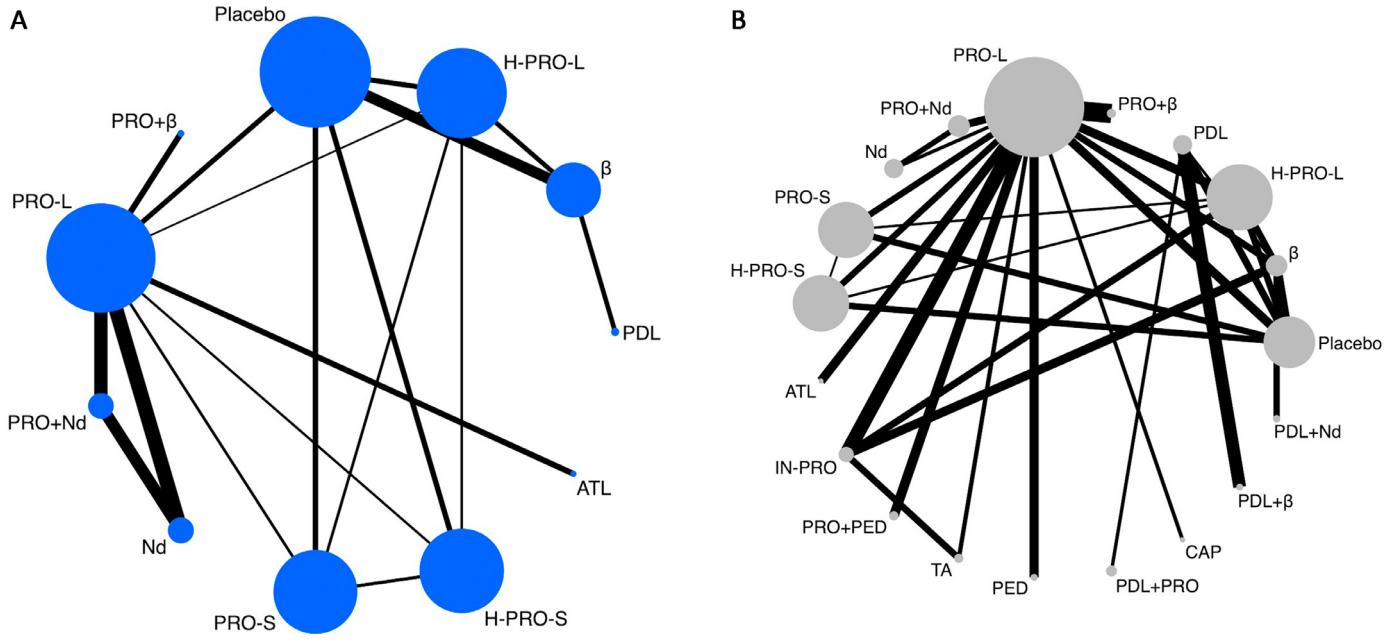

Fig. 2. (A). Network meta-analysis of eligible comparisons for success rate. (B). Network meta-analysis of eligible comparisons for incidence of adverse effects. Placebo: placebo or observation; β: topical β-blockers treatment; PRO-L: propranolol orally at 1–2 mg per kilogram per day for a longer treatment duration (6 months or so); PRO-S: propranolol orally at 1–2 mg per kilogram per day for a shorter treatment duration (3 months or so); H-PRO-L: propranolol orally at a higher dose (3 mg per kilogram per day) for a longer treatment duration (6 months or so); H-PRO-S: propranolol orally at a higher dose (3 mg per kilogram per day) for a shorter treatment duration (3 months or so); PDL: pulsed dye laser; Nd: Nd:YAG laser; ATL: atenolol at 1 mg per kilogram per day for 6 months; PRO-L+Nd: PRO-L with Nd:YAG laser; PRO-*L*+β: PRO-L with topical β-blockers.

Table 1
Comparisons for success rate and incidence of adverse effects of the 11 treatments.

success rate | comparison | incidence of adverse effects

ATL	7.98‡ (0.07,881.90)	0.71‡ (0.01,59.91)	2.38‡ (0.03,180.74)	1.61‡ (0.02,117.40)	1.29† (0.02,76.06)	1.15‡ (0.02,87.96)	0.10‡ (0.00,11.69)	1.74‡ (0.02,125.16)	0.04‡ (0.00,3.73)	**0.00† (0.00,0.56)**
6.79‡ (0.56,82.89)	**H-PRO-S**	0.87† (0.25,3.03)	2.91‡ (0.30,28.67)	1.98‡ (0.22,17.74)	1.57† (0.27,9.17)	1.41† (0.15,13.61)	0.12† (0.01,1.50)	2.14† (0.55,8.28)	**0.05† (0.00,0.45)**	**0.01* (0.00,0.06)**
10.42‡ (0.83,131.24)	1.53† (0.33,7.12)	**PRO-S**	3.36‡ (0.34,32.78)	2.28‡ (0.26,20.28)	1.82† (0.32,10.46)	1.63† (0.17,15.56)	0.14† (0.01,1.72)	2.47† (0.65,9.40)	**0.05† (0.01,0.51)**	**0.01* (0.00,0.07)**
1.03‡ (0.07,14.11)	0.15‡ (0.02,1.29)	**0.10† (0.01,0.87)**	**Nd**	0.68† (0.25,1.86)	0.54† (0.13,2.31)	0.48† (0.06,3.82)	**0.04* (0.00,0.74)**	0.73† (0.11,5.07)	**0.02† (0.00,0.20)**	**0.00† (0.00,0.04)**
0.09‡ (0.01,1.15)	**0.01† (0.00,0.10)**	**0.01† (0.00,0.07)**	**0.09* (0.02,0.38)**	**PRO-L+Nd**	0.80† (0.21,2.97)	0.71† (0.10,5.12)	0.06† (0.00,1.02)	1.08† (0.17,6.70)	**0.02† (0.00,0.28)**	**0.00† (0.00,0.05)**
0.78† (0.10,6.13)	**0.11* (0.03,0.47)**	**0.07* (0.02,0.32)**	0.76† (0.15,3.81)	**8.78† (1.91,40.42)**	**PRO-L**	0.89† (0.21,3.89)	**0.08* (0.01,0.93)**	1.36† (0.38,4.83)	**0.03* (0.00,0.24)**	**0.00* (0.00,0.04)**
0.42‡ (0.02,7.86)	**0.06† (0.00,0.77)**	**0.04† (0.00,0.52)**	0.41‡ (0.03,5.70)	4.70‡ (0.35,62.59)	0.54‡ (0.07,4.33)	**PRO-L+β**	0.08† (0.00,1.51)	1.52† (0.22,10.28)	**0.03† (0.00,0.42)**	**0.00† (0.00,0.07)**
1.96‡ (0.08,50.55)	0.29‡ (0.02,3.70)	0.19‡ (0.01,2.48)	1.91‡ (0.10,37.95)	**22.09† (1.18,412.01)**	2.52‡ (0.20,31.04)	4.70‡ (0.18,123.37)	**PDL**	**17.94† (1.78,180.75)**	0.39† (0.09,1.70)	**0.05* (0.00,0.46)**
0.64‡ (0.06,7.35)	**0.09* (0.02,0.37)**	**0.06* (0.01,0.26)**	0.62‡ (0.08,4.96)	7.21‡ (0.96,53.93)	0.82† (0.22,3.03)	1.53‡ (0.13,18.03)	0.33‡ (0.03,3.27)	**H-PRO-L**	**0.02* (0.00,0.16)**	**0.00* (0.00,0.03)**
3.85‡ (0.26,57.65)	0.57‡ (0.09,3.45)	0.37‡ (0.06,2.35)	3.76‡ (0.35,40.80)	43.49† (4.34,435.56)	4.96‡ (0.86,28.49)	9.25‡ (0.61,141.18)	1.97† (0.32,11.96)	**6.03* (1.44,25.24)**	**β**	0.12† (0.01,1.09)
20.97† (1.46,300.74)	3.09† (0.54,17.60)	2.01† (0.34,12.00)	**20.44† (2.00,208.82)**	**236.68* (23.68,2365.86)**	**26.97* (5.01,145.12)**	**50.34† (3.44,736.70)**	**10.72† (1.21,95.15)**	**32.82* (7.59,141.92)**	**5.44* (1.59,18.64)**	**Placebo**

Placebo: placebo or observation; β: topical β-blockers treatment, like propranolol ointment, 2% carteolol hydrochloride, 0.5% timolol maleate eye drops or gel; H-PRO-L: propranolol orally at a higher dose (3 mg per kilogram per day) for a longer treatment duration (6 months or so); PDL: pulsed dye laser; PRO-L+β: combined propranolol orally with topical β-blockers; PRO-L: propranolol orally at 1−2 mg per kilogram per day for a longer treatment duration (6 months or so); PRO-L+Nd: combined propranolol orally with Nd:YAG laser; Nd: Nd:YAG laser; PRO-S: propranolol orally at 1−2 mg per kilogram per day for a shorter treatment duration (3 months or so); H-PRO-S: propranolol orally at a higher dose (3 mg per kilogram per day) for a shorter treatment duration (3 months or so); ATL: atenolol at 1 mg per kilogram per day for 6 months; *: Moderate quality of evidence; †: Low quality of evidence; ‡: Very low quality of evidence.

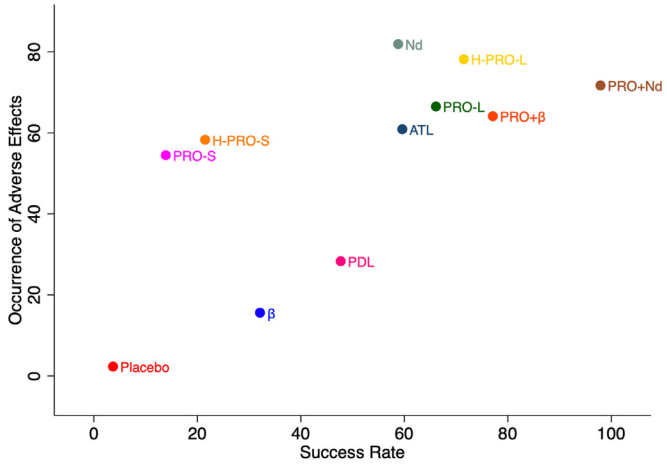

Fig. 3. Two-dimensional graphs about success rate and incidence of adverse effects in all studies by SUCRA. Placebo: placebo or observation; β: topical β-blockers treatment; PRO-L: propranolol orally at 1−2 mg per kilogram per day for a longer treatment duration (6 months or so); PRO-S: propranolol orally at 1−2 mg per kilogram per day for a shorter treatment duration (3 months or so); H-PRO-L: propranolol orally at a higher dose (3 mg per kilogram per day) for a longer treatment duration (6 months or so); H-PRO-S: propranolol orally at a higher dose (3 mg per kilogram per day) for a shorter treatment duration (3 months or so); PDL: pulsed dye laser; Nd: Nd:YAG laser; ATL: atenolol at 1 mg per kilogram per day for 6 months; PRO-L+Nd: PRO-L with Nd: YAG laser; PRO-L+β: PRO-L with topical β-blockers.

therapeutic regimens randomly. There was no head-to-head comparison of most therapies, so indirect comparison played a major role in our study. We analyzed from the aspects of efficiency, success rate, adverse reactions, different lasers, age of patients, and superficial IHs. We found that all the treatments included in this analysis were more efficacious than placebo or 'wait-and-see' in children with IHs.

Our study found that combined β blockers with laser might be the most appropriate treatment for IHs, whether superficial or not. This conclusion also applied to children under 6 months which was known as the proliferative phase [23]. There were 4 kinds of β blockers (propranolol, timolol, atenolol and carteolol) included in our analysis and both systemic and topical usage of propranolol were compared. The applications of propranolol orally and 0.5% timolol maleate eye drops for IHs therapy were first reported by Leaute-Labreze et al. in 2009 and Guo et al. in 2010 respectively, which turned out well [24,25]. From then on, more and more studies on β blockers in IH treatment reported [14,26−28]. The mechanism of β-blockers on IHs may include constriction of capillaries, inhibition of angiogenesis, and trigger of capillary endothelial cell apoptosis [29,30]. A higher dose and a longer treatment duration of propranolol orally achieved a higher success rate and increased side effects. And topical β blockade therapy, either propranolol or timolol, had similar therapeutic efficacy to 1−2 mg/kg per day propranolol treatment orally with fewer adverse effects. Intralesional propranolol hydrochloride had fewer side effects than oral administration, but its efficiency is not satisfactory. The common side effects of propranolol include sleep disorders, peripheral coldness and peripheral coldness, [31] which attributed to propranolol's β blockade activity and lipophilicity. Atenolol, a hydrophilic, selective beta-blocker, might be as effective as propranolol and was well tolerated.

The laser acts on the chromophore with oxygen-containing hemoglobin being predominant in IHs. The chromophore absorbs light to heat the lesion and causes coagulation, thereby exerting therapeutic effects [5]. Different lasers have different scopes of application, we compared four laser modalities used in IHs, PDL, LPDL, Nd: YAG and PDL+ Nd: YAG. The pulse dye laser is usually the first choice of vascular laser therapy and mostly reported and applied in IHs laser therapy [32]. A longer pulse has a higher efficiency due to its advantage in transdermal depth. Nd:YAG laser is an infrared laser with a wavelength of 1064 nm that can penetrate deeply into the skin, showing good therapeutic effects on thick tumors [33]. Combined Nd: YAG with PDL was not superior than PDL alone. In addition, compared with PDL, Nd:YAG had worse efficiency and more adverse reactions occurred. What's more, the adverse effects, such as ulcer, color sink

and color reduction, were occurred the least with combined using of propranolol orally and PDL. The reason should be that the usage of PDL could reduce the dosage and duration of propranolol, thus effectively shortening the treatment cycle while reducing the adverse reaction [34].

Our study has some limitations and strengths. The quality of some indirect comparisons was low according to GRADE. No study was reported on the success rate of PRO-L+PDL (it had the lowest incidence of adverse reactions) or β+PDL/Nd (β+Laser ranked first in the efficacy), so that PRO-L+Nd (it ranked first in the success rate) could not be compared with them. We did not group the children by sex. However, this is the first comprehensive synthesis of various treatments for IHs that allows estimates of head-to-head comparisons for different therapies from different angles. Pediatricians and researchers could more visibly judge the treatment differences among them.

In conclusion, a combination of β blockers and laser might be the first-line treatment of IHs and a longer pulsed dye laser is preferred. More well-designed RCTs are needed to confirm our findings.

Data sharing statement

No additional unpublished data are available.

Declaration of Competing Interest

All the authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100506.

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