Pharmacologic Interventions for Infantile Hemangioma: A Meta-analysis

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abstract

CONTEXT: Infantile hemangiomas (IH) may be associated with significant functional impact.

OBJECTIVE: The objective of this study was to meta-analyze studies of pharmacologic interventions for children with IH.

DATA SOURCES: Data sources were Medline and other databases from 1982 to June 2015.

STUDY SELECTION: Two reviewers assessed studies using predetermined inclusion criteria.

DATA EXTRACTION: One reviewer extracted data with review by a second.

RESULTS: We included 18 studies in a network meta-analysis assessing relative expected rates of IH clearance associated with β-blockers and steroids. Oral propranolol had the largest mean estimate of expected clearance (95%; 95% Bayesian credible interval [BCI]: 88%–99%) relative to oral corticosteroids (43%, 95% BCI: 21%–66%) and control (6%, 95% BCI: 1%–11%). Strength of evidence (SOE) was high for propranolol's effects on reducing lesion size compared with observation/placebo. Corticosteroids demonstrated moderate effectiveness at reducing size/volume (moderate SOE for improvement in IH). SOE was low for effects of topical timolol versus placebo.

LIMITATIONS: Methodologic limitations of available evidence may compromise SOE. Validity of meta-analytic estimates relies on the assumption of exchangeability among studies, conditional on effects of the intervention. Results rely on assumed lack of reporting bias.

CONCLUSIONS: Propranolol is effective at reducing IH size compared with placebo, observation, and other treatments including steroids in most studies. Corticosteroids demonstrate moderate effectiveness at reducing IH size/volume. The meta-analysis estimates provide a relative ranking of anticipated rates of lesion clearance among treatments. Families and clinicians making treatment decisions should also factor in elements such as lesion size, location, number, and type, and patient and family preferences.

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Infantile hemangiomas (IH) are the most common tumors of childhood. IH are benign but possess potential for permanent local tissue damage, ulceration, infection, bleeding, functional impact, and pain. Because of historical inconsistencies in naming conventions, the true prevalence of IH is unclear, but it is estimated that they affect ~4% to 5% of children,[1] with higher prevalence in females and Caucasians.[2,3] In most children, IH will become apparent in the first few weeks of life and reach 80% of total size by ~3 to 5 months.[4,5] With expectant observation, many children may experience a complete or near complete involution without significant sequelae; however, IH frequently occur in cosmetically and functionally sensitive areas. Even with complete involution, some patients have permanent disfigurement and functional compromise.[6] Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.[7,8] Early assessment of the extent of the hemangioma, and early, appropriate treatment of IH may potentially mitigate these complications; however, in a large multicenter treatment analysis, the first specialist visit for infants and children did not occur until a mean age of 5 months.[5] The rapid growth of IH leaves little time for prospective observation to determine which IH will lead to complications and require specialist attention and treatment before complications begin to manifest.

Specific disease characteristics, such as lesion size, location, rate of growth, and persistence as well as child age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or surgically. Lesions that possess immediate risk for morbidity or mortality, such as IH obstructing the airway or visual axis, may require immediate surgical intervention. Lesion characteristics such as size, location, and type (eg, superficial, deep) also influence treatment choice. Both medical and surgical treatment paradigms contain significant variability and lack of consensus.

The β-blocker propranolol was approved by the US Food and Drug Administration for use in IH in March 2014.[9–11] Propranolol was historically used in children for cardiac conditions, and off-label use to treat IH began after the serendipitous discovery of its effects on IH lesions in 2008.[12] Before this discovery, corticosteroids were the drug of choice, but propranolol has become the typical choice for initial medical management in children without contraindications. Steroids may be used in children with contraindications to β-blockers or who do not respond to β-blockers.

This meta-analysis, 1 component of a broader systematic review of pharmacologic and surgical interventions for IH funded by the Agency for Healthcare Research and Quality, summarizes the evidence for the effectiveness of pharmacologic treatments for IH. The full review, which addresses surgical interventions and harms of all treatments, and review protocol (PROSPERO registration: CRD42015015765) are available on the agency's Effective Health Care Web site.[13]

METHODS

Information Sources

We searched the Medline database via PubMed, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Embase from 1982 to June 2015 by using a combination of controlled vocabulary and key terms related to interventions for IH (eg, infantile hemangioma, corticosteroid, propranolol). We also hand-searched the reference lists of included articles and recent reviews of interventions for IH to identify potentially relevant articles. Complete search strategies are available in the full review.

Eligibility Criteria

We developed inclusion criteria in consultation with an expert panel of clinicians and researchers (Table 1). We included comparative study designs (eg, randomized controlled trials [RCTs], prospective or retrospective cohort studies) to address the effectiveness of treatments and comparative studies and case series with at least 25 participants to evaluate adverse effects. Studies were included in the meta-analysis subset if they satisfied the following additional inclusion criteria:

Outcomes were reported quantitatively, using an objective metric for reporting intervention effects that could be converted into a proportion of IH clearance.

One or more study arms evaluated a single intervention; study arms in which ≥2 treatments were applied were excluded.

Reported outcomes were accompanied by an associated measure of variation or precision.

Noncontrol pharmacologic treatments could be reasonably classified into 1 of the following classes of agents: oral, intralesional, or topical propranolol; intralesional triamcinolone; topical or ophthalmic timolol; and oral steroid.

Data Extraction and Analysis

One team member initially extracted study design, study population characteristics (age, gender, IH site and type), intervention characteristics (dosage, duration, route), and baseline and outcome data on constructs of interest from eligible studies. A second team

TABLE 1 Inclusion Criteria

Category	Criteria
Study population	Newborns, infants, and children up to 18 y of age with IH or suspected IH
Publication languages	English only
Publication year	1982–June 2015
Admissible evidence	Admissible designs: original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results • Benefits of interventions: RCTs and any comparative studies • Harms of interventions: RCTs, any comparative studies, and case series with at least 25 children with IH
Other criteria	Studies must address ≥1 of the following: • Pharmacologic interventions (eg, β-blockers, corticosteroids, immunomodulators, immunosuppressants, angiotensin-converting enzyme inhibitors, antiangiogenic agents, antineoplastics) • Data (including harms) related to interventions for IH for the following outcomes: • Size/volume of hemangioma • Impact on vision • Aesthetic appearance as assessed by clinician or parent • Degree of ulceration • Quality of life • Harms Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (versus individual participant data)

member reviewed extracted data for accuracy and completeness.

Study outcomes were reported in a variety of ways. Most identified an arbitrary threshold of IH clearance (eg, >75%) as a positive outcome or divided the continuous clearance measure into a small number of categories. Others reported visual analog scale scores, either for entire study arms or for individual patients within study arms. To incorporate as many studies as possible, by minimizing the number excluded due to technical constraints on statistical integration, we constructed a Bayesian latent variable model.[14] This model allowed several types of outcome data and a suite of pharmacologic interventions to be analyzed in the same model, thereby maximizing the power for estimating parameters precisely. The estimands of interest were the expected proportion of clearance for each intervention agent, along with associated posterior uncertainty.

For studies that reported the number of outcomes below or above a prespecified threshold, the proportion in each group were incorporated into the analysis using the inverse of the normal cumulative distribution function. For a given clearance threshold, there is a corresponding expected number of observations below and above that threshold, under a particular model for the distribution of clearance rates, which affords an opportunity to use these data to inform the parameters of that model. We used a logit-linear mixed-effects model, with intervention type as a fixed effect and study label as a random effect, combining to predict the distribution of clearance rates. Outcomes from studies reporting mean reduction in size or surface area were included directly in this model, rather than indirectly via the inverse cumulative distribution function method described earlier.

Study Selection and Study Characteristics

We identified 4132 potentially relevant titles or abstracts, with 1273 proceeding to full text review (Fig 1). After dual screening, 18 met all criteria for quantitative synthesis and were included in the meta-analysis (Table 2). Studies included 2 RCTs and 1 cohort study evaluating oral propranolol (doses ranging from 1–4 mg/kg/day) and placebo or observation[15–17]; 1 RCT compared different forms of propranolol (oral 2 mg/kg/day, intralesional 1 mg, topical 1%).[18] Two RCTs and 2 cohort studies compared oral propranolol (2.0–2.7 mg/kg/day) and oral prednisolone or oral prednisone (2–4 mg/kg/day).[19–22] One cohort study compared oral propranolol (2 mg/kg/day) and intralesional bleomycin (0.5 mg/kg)[23]; and 1 RCT and 1 cohort study evaluated oral propranolol (2–3 mg/kg/day) and other β-blockers (1–4 mg/kg/day).[24,25]

Three cohort studies and 2 RCTs assessed topical timolol (0.5%) compared with placebo or observation or another agent,[26–30] and 1 RCT and 1 cohort study evaluated different steroids, including oral prednisone and intralesional triamcinolone.[31,32] Studies included a total of 1265 children with IH (ages ranging from 2 weeks to 9 years), and most were fair quality.[16–18,20–22,25,28,30]

Studies compared pre- and posttreatment photographs to assess improvement in IH and reported change using varied metrics. Three studies used a visual analog scale.[22,24,28] Ten studies used a subjective rating of response (eg, good, fair, poor; complete, partial, no response), typically with a percentage improvement related

to each grade (eg, good ≥75% size reduction).[15,16,18,20,23,25,26,29–31] Two studies rated improvement as greater or less than either 50%[32] or 75%.[21] The additional studies reported percent reduction,[27] change in total surface area,[19] or mean percentage decrease in size.[17] Fourteen studies explicitly reported using masked assessors to rate changes in IH.[15–17,19–22,24,25,27,29–32] All studies included IH in multiple anatomic locations, and lesion types (when reported) also varied, with the exception of most studies of topical timolol, which generally included only superficial lesions. Supplemental Table 5 outlines key study characteristics.

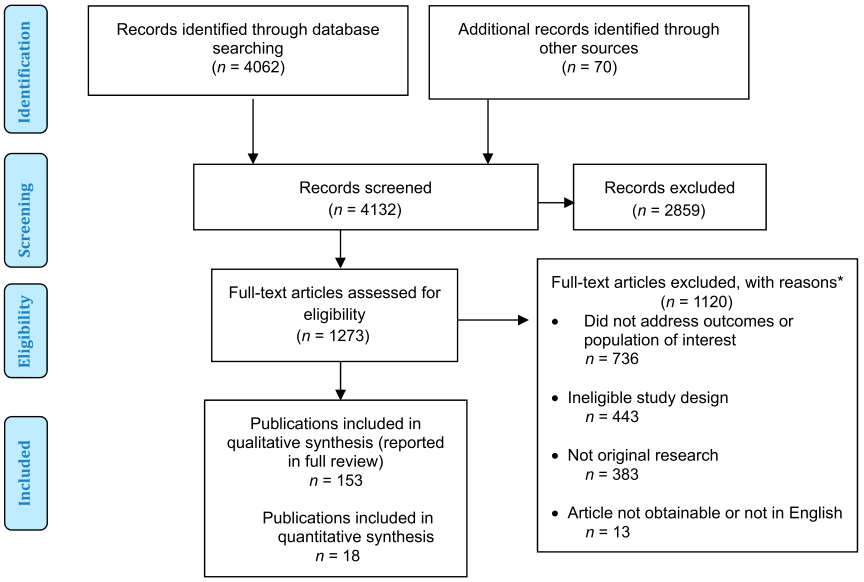

FIGURE 1
Disposition of studies identified for this review. *Numbers do not tally as studies could be excluded for multiple reasons.

Assessment of Study Quality and Strength of Evidence

Two investigators independently evaluated the methodologic quality of studies using separate tools appropriate for specific study designs (eg, the Newcastle-Ottawa Quality Assessment Scale for cohort studies).[33–35] A senior reviewer resolved discrepancies in quality assessment. We considered 4 studies as good quality[15,19,27,31] and 5 as poor quality.[23,24,26,29,32] Two investigators also graded the strength of the body of evidence (confidence in the estimate of effect) by using methods based on the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[36] The full team reviewed the final strength of evidence (SOE) designation with discussion to reach consensus as needed. Table 3 describes these ratings.

RESULTS

We calculated mean expected clearance rates associated with each agent and confidence bounds around the estimates (Fig 2). The expected efficacy of control arms was

TABLE 2 Characteristics of Included Studies

Characteristic	RCTs	Prospective Cohort Studies	Retrospective Cohort Studies	Total Literature
Intervention/comparator				
Corticosteroid/corticosteroid	2	0	0	2
Propranolol/placebo or observation	2	1	0	3
β-blocker/β-blocker	2	1	0	3
Propranolol/corticosteroid	2	0	2	4
Propranolol/other	0	1	0	1
Timolol/placebo or observation	1	1	0	2
Timolol/other agent	1	0	2	3
Population characteristics				
Type of IH[a]				
Superficial	6	2	3	11
Deep	4	2	1	7
Mixed	4	2	1	7
Other	2	0	1	3
Study population				
United States/Canada	2	1	2	5
Europe	2	0	0	2
Asia	2	3	2	7
Other	4	0	0	4
Total *N* participants	783	208	274	1265

[a] Studies typically included >1 lesion type.

estimated to be 6% (95% Bayesian credible interval [BCI]: 1%–11%), that is, we would expect to see, on average, 6% clearance of IH in children who receive placebo or no treatment during the study period. All noncontrol treatments were estimated to have a larger expected clearance than control. The largest mean estimate of clearance was for oral propranolol (95%, 95% BCI: 88%–99%). Clearance associated with the use of oral steroids was 43% (95% BCI: 21%–66%), thus providing a clearance rate intermediate to control and use of β-blockers. Triamcinolone, an intralesional injectable steroid, had a higher clearance rate than oral steroids, with wide BCI (58%; 95% BCI: 22%–99%). Few data were available for intralesional propranolol, which is reflected in its larger credible interval (estimated clearance: 9%; 95% BCI: 0%–45%). With fairly wide confidence bounds and limited data in some areas, the relative differences among these estimates are of greater importance than absolute effects in interpreting these results.

Figure 3 presents the variability in effects seen across the patient populations in terms of percent clearance. Oral propranolol was estimated to have the largest variability in clearance rate, with some patients experiencing much greater clearance than others ($\sigma = 2.5$, 95% BCI: 2.1–2.9) and timolol ($\sigma = 1.5$, 95% BCI: 1.4–1.6), intralesional triamcinolone ($\sigma = 1.8$, 95% BCI: 1.3–2.3), and oral steroids ($\sigma = 1.3$, 95% BCI: 1.1–1.6) yielding similar, lower estimates. All of the estimates of effect SD were at least nominally higher than the control SD, which may be a reflection of the heterogeneity of the study population in terms of response of IH to treatment.

Because of relatively sparse information from several treatment agents, we were unable to separately estimate variance parameters for all of the interventions and instead fit a simplified model that assumed variances were equal. To check the validity of this assumption, we also fit a model on the subset of interventions with sufficient numbers of studies (>3) to estimate variance parameters and noted that the variance estimates ranged from 1.3 (1.1–1.6) to 2.6 (2.2–2.9) on the logit scale. This was reasonably close to the 1.8 (1.1–2.6) estimated as the pooled variance. To assess for methodologic heterogeneity, we ran additional models with only RCTs and with only good and fair quality studies included. Estimates did not differ markedly when poor-quality studies were removed, although BCI typically

TABLE 3 SOE Grades and Definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, ie, another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Excerpted from Berkman et al 2014.[37]

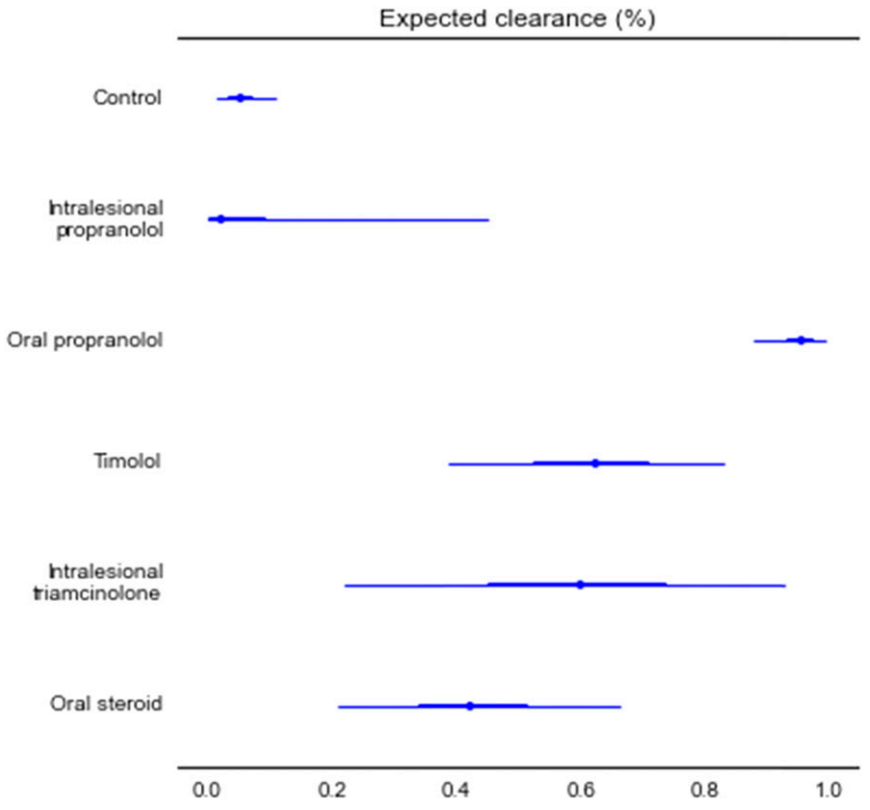

FIGURE 2
Estimates of expected IH clearance. Estimates of expected IH clearance are expressed as percent clearance relative to initial condition for each treatment, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).

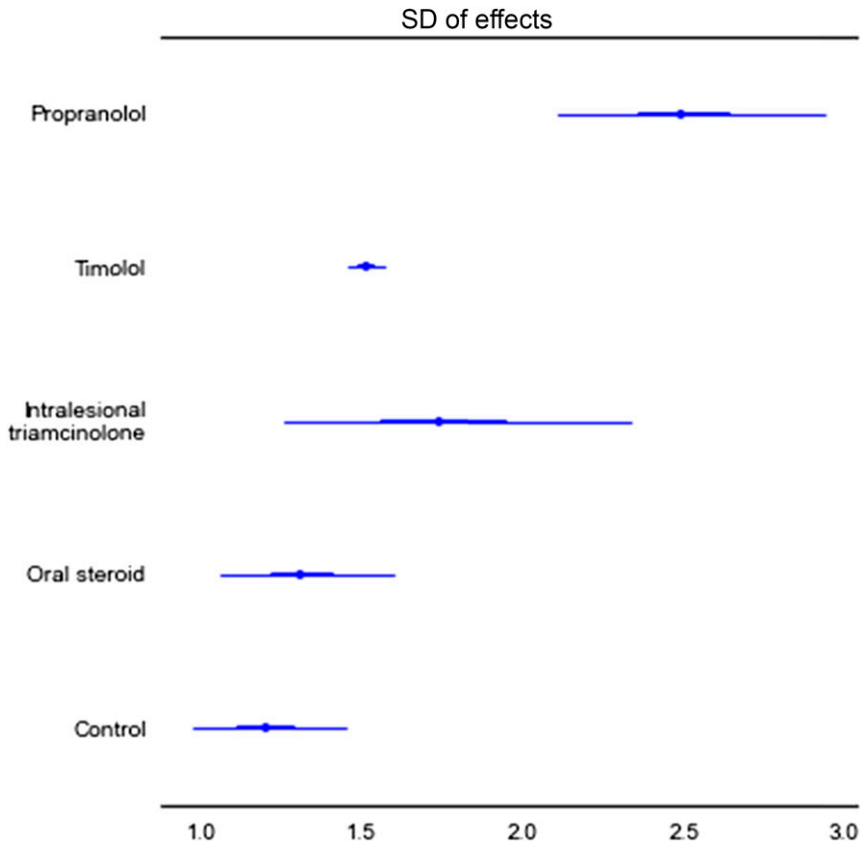

FIGURE 3
Estimates of the variation of each treatment. Estimates of the variation of each treatment are expressed as SD, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).

widened; thus, we report the model with poor-quality studies included. To examine the possible effect of bias due to the inclusion of cohort studies, we fit the same model to RCTs only. The resulting estimates were similar to those of the model fit to all studies but with much wider posterior credible intervals. Because there was no obvious systematic bias due to study design, we report the model estimates based on the entire body of evidence.

On the basis of meta-analysis results and results of individual studies included in the full review, our assessments of SOE ranged from low to high for the interventions and comparators evaluated (Table 4). We considered the SOE to be high for the greater effectiveness of propranolol compared with placebo or observation and moderate for the superiority of propranolol compared with steroids in achieving IH clearance. We also considered SOE as low for topical timolol versus observation.

DISCUSSION

The literature on pharmacologic approaches for the treatment of IH is heterogeneous in terms of populations, interventions, comparators, and outcomes. Comparative studies included individuals with ages of <1 month to 9 years, and lesion types and locations varied across studies. Most studies included children with IH in multiple anatomic locations and of multiple types (eg, deep, superficial) typically without stratifying outcomes on these characteristics. Most studies did not clearly describe diagnostic criteria and few clearly noted whether previous treatment had been administered (*n* = 4 or 18 studies). Comparators also varied across studies and included placebo, observation, historical control groups, and other active interventions. Outcome measures similarly differed. Although studies generally assessed change in lesion size or appearance, scales and methods varied.

Until fairly recently, corticosteroids were the treatment of choice for IH. Corticosteroids demonstrate some effectiveness but are associated with clinically significant side effects. More recently, β-blockers, and propranolol specifically, have been studied and recommended for use. Studies of propranolol compared its effectiveness with placebo/observation, with corticosteroids and other modalities, and with other β-blockers. Relative to observation or placebo arms, oral propranolol was consistently superior in individual studies and in our meta-analysis. Relative to other active modalities, we find that propranolol is generally superior with the exception of no significant differences in reducing lesion size in 1 study comparing it with steroids[19] and 1 comparing it with bleomycin.[23] Finally, given that propranolol has been demonstrated to be associated with positive outcomes, the question of whether effectiveness is associated with propranolol specifically or β-blockers in general has been studied. Although there were only 2 small studies of these agents in our meta-analysis, early results for atenolol and nadolol are as positive as those noted for propranolol, and we believe that they suggest that these and potentially other β-blockers may also be effective, potentially with fewer side effects. These findings, however, are preliminary and require further investigation.

Studies of topical timolol, typically used to treat superficial IH, also reported greater effectiveness for timolol compared with placebo/observation in reducing IH lesion

TABLE 4 SOE

Intervention Category	Intervention Type/No. of Studies (Total *N* Participants)	Key Outcome(s)	SOE Grade	Findings
Steroids	Oral steroids versus observation or placebo	Improvement in IH	Moderate	In network meta-analysis oral steroids had a mean expected clearance rate of 43% (95% BCI: 21%–66%) compared with 6% (95% BCI: 1%–11%) for placebo/observation arms.
	Network meta-analysis			
	Intralesional steroids versus observation or placebo	Improvement in IH	Low	In network meta-analysis intralesional steroids had a mean expected clearance rate of 58% (95% BCI: 22%–93%) compared with 6% (95% BCI: 1%–11%) for placebo/observation arms.
	Network meta-analysis			Low SOE for greater effectiveness of intralesional steroids versus placebo/observation given relatively small numbers of participants contributing to this comparison and low precision.
β-blockers	Oral propranolol versus placebo or observation	Improvement in IH	High	In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% (95% BCI: 88%–99%) relative to 6% (95% BCI: 1%–11%) for placebo/observation arms; greater reductions in IH size in propranolol arms versus control in all individual studies.
	Network meta-analysis			High SOE for greater effectiveness of propranolol versus placebo or observation based on individual comparisons and the meta-analysis.
	RCT: 3 (510) Cohort studies: 1 (45)			
	Propranolol versus steroids	Improvement in IH	Moderate	In head-to-head comparisons, propranolol was more effective than steroids in 3 studies; 2 other studies reported no significant difference between oral or intralesional propranolol and oral or intralesional steroids. In network meta-analysis, pulling data from multiple studies, propranolol was superior to oral steroids (95% clearance versus 43% clearance).
	Network meta-analysis			Combined effects from individual studies and meta-analysis confer moderate SOE for superiority of propranolol over steroids at achieving clearance.
	RCT: 1 (19) Cohort studies: 4 (216)			
	Topical timolol versus placebo or observation	Improvement in IH	Low	Timolol was more effective than placebo or observation in 3 comparative studies. In network meta-analysis, the mean expected clearance rate for topical timolol was 64% relative to 2% for placebo or observation arms.
	Network meta-analysis			Low SOE for effectiveness of timolol versus placebo or observation based on the need for additional studies.
	RCT: 1 (41) Cohort studies: 2 (147)			

size.[26,27] One study comparing ophthalmic timolol and imiquimod reported no differences in effects.[28] Two studies using laser as a comparator reported mixed results: no differences in average overall improvement in 1 study comparing timolol and timolol plus laser modalities[30] and greater response to timolol in superficial IH, with greater response of mixed IH to timolol plus laser in another.[29]

In our network meta-analysis specifically, all noncontrol treatments were estimated to have a larger expected clearance than control arms. The largest mean estimate of expected clearance was for oral

propranolol (95%, 95% BCI: 88%–99%), followed by timolol (62%, 95% BCI: 39%–83%) and intralesional triamcinolone (58%, 95% BCI: 22%–93%), albeit with wider confidence bounds. Oral steroids had a clearance rate of 43% (95% BCI: 21%–66%). The preponderance of available evidence used in the meta-analysis was derived from studies of propranolol and corticosteroids.

Our findings are limited by several factors. We included only studies published in English and did not seek unpublished data. We were also dependent on the characterization of IH as presented in each study. Given changes in nomenclature and variations in the way IH are described and treated, it may be that some studies included non-IH lesions or that some used older treatment regimens that may no longer be commonly used. We also note that other approaches to meta-analysis could be used but that our estimates of a high anticipated response to propranolol largely align with those in other reviews of propranolol.[38–41]

The evidence base for IH treatment is limited by a small number of comparative studies including a limited number of participants. A growing number of studies address β-blockers, but current studies are limited by a general lack of long-term follow-up and analyses to explore differences in response among subgroups. Few comparative studies addressed steroids, and indications for steroid treatment compared with β-blockers are unclear. Studies are also limited by the use of multiple and variable outcome measures to assess resolution of lesions. Because no objective laboratory value or other measures exist to determine size changes, investigators have developed multiple techniques, and studies did not always report scales or other approaches clearly. The variety of scales (eg, percentage change, mean change, visual analog scale) makes combining outcomes challenging. Similarly, studies typically included multiple lesion types in multiple locations, which also makes understanding potential differences in response difficult. In addition, few studies reported baseline physical characteristics of the lesion, so understanding the magnitude of change reported is challenging. Most studies included children with problematic IH (10 of 16 clearly reporting this information), so change was likely substantial, and parents and children may value any lessening of lesion size or change in color or texture.

The most important deficiency in the reported outcomes across studies is the tendency for the reporting of discretized outcomes, when the underlying outcome is a continuous variable. Specifically, although outcomes are likely recorded as a continuous measure (ie, the proportion of an existing lesion that is cleared or reduced in size after treatment), authors often chose an arbitrary cutoff proportion (or a small number of "bins") and reported only the numbers in each of the resulting categories. This results in an immediate and unrecoverable loss in power for any quantitative meta-analyses. Researchers should be encouraged to report outcome variables as they were recorded, without transforming them in such a way that information is lost.

Other areas for future research include a better understanding of appropriate dosing and timing of propranolol treatment and optimal duration of β-blocker use. In addition, characteristics such as lesion size, location, and persistence, as well as modifiers such as patient age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or surgically. Lesion characteristics also influence the choice of specific pharmacologic agents. Most studies included multiple lesion types and in multiple locations, and few included specific modifier analyses or reported outcomes by lesion characteristics. Research to improve understanding of which lesions are likely to respond best to specific agents is critical, especially given that understanding of the effectiveness of β-blockers in the involution phase is limited. Optimal treatment in the proliferative phase may be key to maximal resolution of IH.

CONCLUSIONS

Corticosteroids demonstrate moderate effectiveness in reducing IH size/volume. Propranolol is effective at reducing the size of IH, with high SOE for effects on reducing lesion size and compared with placebo, observation, and other treatment methods, including steroids, in most studies. The meta-analysis estimates reported here provide a relative ranking of anticipated rates of lesion clearance among treatment options. Families and clinicians making treatment decisions should also factor in elements such as lesion size, location, type, and number, which may affect choice of treatment modality, as well as patient/family preferences.

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ABBREVIATIONS

BCI: Bayesian credible interval
IH: infantile hemangioma
RCT: randomized controlled trial
SOE: strength of evidence

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REFERENCES

1. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol*. 2008;25(2):168–173
2. Hoornweg MJ, Smeulders MJ, van der Horst CM. Prevalence and characteristics of haemangiomas in young children [in Dutch]. *Ned Tijdschr Geneeskd*. 2005;149(44):2455–2458
3. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics*. 1976;58(2):218–222
4. Enjolras O, Mulliken JB. The current management of vascular birthmarks. *Pediatr Dermatol*. 1993;10(4):311–313
5. 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
6. Ceisler EJ, Santos L, Blei F. Periocular hemangiomas: what every physician should know. *Pediatr Dermatol*. 2004;21(1):1–9
7. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol*. 2001;44(6):962–972
8. Chamlin SL, Haggstrom AN, Drolet BA, et al Multicenter prospective study of ulcerated hemangiomas. J Pediatr. 2007;151(6):684–689, 689.e681
9. 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
10. 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
11. Georgountzou A, Karavitakis E, Klimentopoulou A, Xaidara A, Kakourou T. Propranolol treatment for severe infantile hemangiomas: a single-centre 3-year experience. *Acta Paediatr*. 2012;101(10):e469–e474
12. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358(24):2649–2651
13. Agency for Healthcare Research and Quality. Effective Health Care Program. Strategies to Treat and Manage Infantile Hemangioma: Research Protocol. Available at: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2016. Accessed December 9, 2015
14. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian Data Analysis*. 3rd ed. Boca Raton, FL: CRC Press; 2013
15. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med*. 2015;372(8):735–746
16. 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. *J Pediatr Hematol Oncol*. 2013;35(7):493–499
17. Léauté-Labrèze C, Dumas de la Roque E, Nacka F, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. *Br J Dermatol*. 2013;169(1):181–183
18. Zaher H, Rasheed H, Esmat S, et al. Propranolol and infantile hemangiomas: different routes of administration, a randomized clinical trial. *Eur J Dermatol*. 2013;23(5):646–652
19. Bauman NM, McCarter RJ, Guzzetta PC, et al. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2014;140(4):323–330
20. Bertrand J, McCuaig C, Dubois J, Hatami A, Ondrejchak S, Powell J. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. *Pediatr Dermatol*. 2011;28(6):649–654
21. Price CJ, Lattouf C, Baum B, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. *Arch Dermatol*. 2011;147(12):1371–1376
22. Malik MA, Menon P, Rao KL, Samujh R. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: a randomized controlled study. *J Pediatr Surg*. 2013;48(12):2453–2459
23. Thayal PK, Bhandari PS, Sarin YK. Comparison of efficacy of intralesional bleomycin and oral propanolol in

management of hemangiomas. *Plast Reconstr Surg*. 2012;129(4):733e–735e

24. Pope E, Chakkittakandiyil A, Lara-Corrales I, Maki E, Weinstein M. Expanding the therapeutic repertoire of infantile haemangiomas: cohort-blinded study of oral nadolol compared with propranolol. *Br J Dermatol*. 2013;168(1):222–224
25. Ábarzúa-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. *J Am Acad Dermatol*. 2014;70(6):1045–1049
26. Yu L, Li S, Su B, et al. Treatment of superficial infantile hemangiomas with timolol: evaluation of short-term efficacy and safety in infants. *Exp Ther Med*. 2013;6(2):388–390
27. 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). Available at: www.pediatrics.org/cgi/content/full/131/6/e1739
28. Qiu Y, Ma G, Yang J, et al. Imiquimod 5% cream versus timolol 0.5% ophthalmic solution for treating superficial proliferating infantile haemangiomas: a retrospective study. *Clin Exp Dermatol*. 2013;38(8):845–850
29. Park KH, Jang YH, Chung HY, Lee WJ, Kim DW, Lee S. Topical timolol maleate 0.5% for infantile hemangioma; its effectiveness and/or adjunctive pulsed dye laser—single center experience of 102 cases in Korea. *J Dermatolog Treat*. 2015;26(4):389–391
30. Tawfik AA, Alsharnoubi J. Topical timolol solution versus laser in treatment of infantile hemangioma: a comparative study. *Pediatr Dermatol*. 2015;32(3):369–376
31. Pope E, Krafchik BR, Macarthur C, et al. Oral versus high-dose pulse corticosteroids for problematic infantile hemangiomas: a randomized, controlled trial. *Pediatrics*. 2007;119(6). Available at: www.pediatrics.org/cgi/content/full/119/6/e1239
32. Jalil S, Akhtar J, Ahmed S. Corticosteroids therapy in the management of infantile cutaneous hemangiomas. *J Coll Physicians Surg Pak*. 2006;16(10):662–665
33. Viswanathan M, Ansari MT, Berkman ND, et al. *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions*. Rockville, MD: Methods Guide for Effectiveness and Comparative Effectiveness Reviews; 2008
34. Wells G, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 9, 2015
35. McMaster University Centre for Evidence-based Practice. *McMaster Quality Assessment Scale of Harms (McHarm) for Primary Studies*. Hamilton, ON: McMaster University; 2008
36. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: http://www.effectivehealthcare.ahrq.gov. Accessed December 9, 2015
37. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;68(11):1312–1324
38. Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2013;131(3):601–613
39. 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. *Br J Clin Pharmacol*. 2014;78(1):44–57
40. Gunturi N, Ramgopal S, Balagopal S, Scott JX. Propranolol therapy for infantile hemangioma. *Indian Pediatr*. 2013;50(3):307–313
41. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol*. 2013;30(2):182–191

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