Management of Infantile Hemangioma

Focus of This Summary

This is a summary of a systematic review evaluating the evidence regarding the efficacy, comparative effectiveness, and harms of therapies for infantile hemangioma. The systematic review included 148 unique studies published from 1982 to June 2015. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/infantile-hemangioma.* This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Infantile hemangioma (IH) is the most common tumor of childhood and is estimated to affect about 4 to 5 percent of children, with higher prevalence in premature infants and in whites. IH tends to go through growth and involution phases, although the complete natural history of IH has not been described. In most affected children, IH becomes apparent in the first few weeks of life and reaches 80 percent of total size by around age 3 to 5 months.

With a course of expectant observation, many patients experience a complete involution without significant sequelae. However, in a fraction of patients, early referral for treatment is important. These include:

- patients who have IH in functionally sensitive areas (e.g., eyes, liver, or airways);
- patients with IH that causes pain, ulceration, and bleeding; and
- patients with IH that causes significant disfigurement (e.g., large lesions on the face).

Currently available treatments include pharmacological interventions (such as beta-blockers and steroids) and surgical interventions (such as laser therapy or excision in appropriate cases). The beta-blocker propranolol was approved by the U.S. Food and Drug Administration (FDA) in March 2014 as a treatment for IH and is typically the first-line treatment choice in children without contraindications. Steroids used to treat IH mainly include oral steroids and intralesional steroids (e.g., triamcinolone). The most common type of lasers used to treat IH are pulse dye lasers (PDL). These lasers are mainly used for IH lesions that do not involute completely and show residual redness at the age of 4 years. PDL therapy only fades IH lesions and does not stop their proliferation.

Uncertainty remains around which interventions might be most beneficial as first-line therapies, when alternative or adjunctive therapies are appropriate after first-line treatment is unsuccessful, and how the disease site informs treatment decisions. This review aims to address some of these issues.

Conclusions

Propranolol is effective at reducing IH lesion size (i.e., lesion clearance) when compared with placebo or observation (high strength of evidence [SOE]) and when compared with steroids (moderate SOE). In a network meta-analysis, the largest mean estimate of expected clearance was for oral propranolol at 95 percent (95% Bayesian credible interval [BCI]: 88% to 99%), followed by timolol at 62 percent (95% BCI: 39% to 83%). These clearance rates provide estimates for the expected level of improvement in IH appearance with the various treatment options. The SOE for these findings is presented in Table 1. The mean clearance rate was 58 percent (95% BCI: 22% to 93%) for intralesional steroids and 43 percent (95% BCI: 21% to 66%) for oral steroids. The efficacy of steroids may be higher than reflected in this analysis. The expected clearance rate for placebo or observation was 6 percent (95% BCI: 1% to 11%). Clinicians making decisions about the treatment modality must also consider parent or caregiver preferences, as well as factors such as lesion size, location, type, and number (e.g., smaller, superficial lesions are typically treated with topical timolol, whereas some larger lesions may require steroid treatment).

Propranolol was associated with short-term (<6 months) adverse effects such as hypotension, hypoglycemia, bradycardia, sleep disturbances, cold extremities, gastrointestinal symptoms, and bronchial irritation (moderate SOE). However, few studies have assessed potential long-term harms associated with beta-blocker use in infants and children. There was moderate SOE that steroids were associated with harms — some of which may be short lived — such as Cushingoid facies, irritability or mood changes, growth retardation, infection, and hypertension.

There was low SOE that PDL treatments were more effective in clearing IH lesions when compared with placebo or observation. Resolution outcomes were similar between laser types (low SOE). Overall, the role of laser therapy in treating IH lesions is not clearly described in the literature.

Data are inadequate to address the role of imaging in guiding IH treatment. Findings were limited by study size, lack of standard processes, and lack of direct comparison at the same time point using the various imaging modalities.

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Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Overview of the Clinical Evidence

Table 1: Summary of Findings and Strength of Evidence for the Effectiveness of Treatment Interventions for Infantile Hemangioma

Intervention	Outcome	Studies	Finding	Effect Size	SOE
BETA-BLOCKERS					
Propranolol vs. observation or placebo	Improvement in IH	Network meta-analysis 4 additional studies (555 subjects)	Propranolol more effective	Clearance rate: Propranolol 95%† (95% BCI, 88% to 99%) Observation/placebo 6% (95% BCI, 1% to 11%)	●●●
	Rebound growth/need for further treatment	2 studies (501 subjects)	Low level of rebound growth or need for further treatment in propranolol arm (fewer than 15% of children)	NA	●●○
Propranolol vs. steroids	Improvement in IH	Network meta-analysis 5 additional studies (237 subjects)	Propranolol more effective	Clearance rate: Propranolol 95% (95% BCI, 88% to 99%) Steroids 43% (95% BCI, 21% to 66%)	●●○
Propranolol vs. other beta-blockers (atenolol or nadolol)	Improvement in IH	3 studies (100 subjects)	Equivalent response	NA	●○○
Topical timolol vs. placebo or observation	Improvement in IH	Network meta-analysis 3 additional studies (188 subjects)	Timolol more effective	Clearance rate: Timolol 62% (95% BCI, 39% to 83%) Observation/placebo 6% (95% BCI, 1% to 11%)	●○○
STEROIDS					
Oral steroids vs. observation or placebo	Improvement in IH	Network meta-analysis	Oral steroids more effective	Clearance rate: Steroids 43% (95% BCI, 21% to 66%) Observation/placebo 6% (95% BCI, 1% to 11%)	●●○
Intralesional steroids (triamcinolone) vs. observation or placebo	Improvement in IH	Network meta-analysis	Intralesional steroids more effective	Clearance rate: Steroids 58% (95% BCI, 22% to 93%) Observation/placebo 6% (95% BCI, 1% to 11%)	●○○
LASER TREATMENTS					
Pulse dye laser vs. observation	Improvement in IH	2 studies (143 subjects)	Pulse dye laser more effective	NA	●○○
	Quality of life	2 studies (143 subjects)	No significant difference	NA	●○○
Long-pulse dye laser vs. other laser types and protocols	Improvement in IH	3 studies (264 subjects)	No significant difference	NA	●○○

95% BCI = 95-percent Bayesian credible interval; IH = infantile hemangioma; NA = not applicable; SOE = strength of evidence

† As an example to aid in interpreting the effect sizes, this result implies that one would expect to see, on average, 95-percent clearance of IH in a child receiving propranolol. The estimated clearance of IH in a child could be as low as 88 percent or as high as 99 percent.

Strength of Evidence Scale*

- High: ●●● High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: ○○○ Evidence either is unavailable or does not permit a conclusion.

*The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. Other domains that were considered, as appropriate, included dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). For additional details on the methodology used to assess strength of evidence, please refer to: Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

Overview of the Clinical Evidence *(Continued)*

Table 2: Summary of Findings and Strength of Evidence for Adverse Effects of Treatment Interventions for Infantile Hemangioma

Intervention	Outcome	N Studies	N Subjects	Finding	SOE
BETA-BLOCKERS					
Propranolol (oral)	Adverse effects	24	2066	Propranolol was associated with clinically important adverse effects such as hypotension, bradycardia, bronchospasm, hypoglycemia, and seizures. Minor adverse effects such as cold extremities, diarrhea, rash, and sleep changes were also reported.	●●○
Timolol (topical)	Adverse effects	4	353	No adverse effects were observed.	●○○
STEROIDS					
All steroids	Adverse effects	16	3291	Steroids were associated with clinically important adverse effects, including Cushingoid facies, growth retardation, mood changes/ irritability, abdominal pain, hypertension, and infection. Intralesional triamcinolone* was associated with hypopigmentation and ulceration in addition to the adverse effects listed above.	●●○
LASER TREATMENTS					
Pulse dye laser	Pigmentation changes	9	1263	Hypopigmentation or hyperpigmentation was consistently reported with the pulse dye laser, with hypopigmentation being reported more frequently.	●●○
	Bleeding	1	121	No significant difference in bleeding was found between pulse dye laser treatment and observation.	●○○
Neodymium-doped yttrium aluminum garnet	Scarring	6	1340	The incidence of scarring was low (≤5%).	●○○

N = number; SOE = strength of evidence

* Intralesional triamcinolone injection contains benzyl alcohol and is, therefore, contraindicated in neonates. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and with an increased incidence of kernicterus, particularly in small preterm infants.

Other Findings of the Review

- Data are inadequate to address the role of imaging in guiding IH treatment. Studies of imaging modalities addressed different approaches and different anatomic locations (intraspinal IH, hepatic IH). Findings were limited by study size, lack of standard processes, and lack of direct comparison at the same time point using the various imaging modalities.
- The narrative review of the literature suggested that indications for referral include large lesion size; segmental type; risk for complications, including bleeding, ulceration, and pain; involvement of critical structures and interference with normal function; risk factors for occult or dangerous lesions (numerous cutaneous lesions, beard distribution); and the potential for psychosocial problems that might be related to permanent disfigurement.
- Case series have reported associations between multiple cutaneous IH lesions and increased risk for hepatic IH. Segmental cutaneous IH lesions in the beard distribution suggest possible concern for airway IH.
- Larger lesions and involvement of more than one facial segment were found to be risk factors for PHACE syndrome (posterior fossa malformations, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft, and supraumbilical raphe).
- Midline lumbosacral or segmental IH lesions in the lumbosacral or pelvic area may be at risk for associated abnormalities and may require treatment of the lesions to avoid functional or cosmetic sequelae.

Gaps in Knowledge and Limitations of the Evidence Base

- Indications for treatment and treatment referral were often not clearly described in the studies evaluated. This makes the interpretation of the findings of some of the studies challenging.
- Some studies of steroids may have used lower concentrations than are currently used in practice, and the review included few studies of steroids. For these reasons, efficacy may be higher than that reflected in this analysis.
- Evidence related to the effectiveness and harms of beta-blockers other than propranolol and timolol for treating IH was limited.
- Additional research is needed to determine the appropriate dosing, timing, and duration of propranolol that is most effective for treating IH.
- A proportion of children with IH were reported to have limited or no response to beta-blockers. However, the studies were too small to determine factors that might have affected response to these agents.
- Few studies have assessed the potential long-term harms associated with using beta-blockers to treat IH. Longer term effects on cardiovascular and metabolic parameters known to be affected by beta-blocker use and effects on cognition, memory, and the central nervous system are not well understood in the population of very young children receiving beta-blockers for IH.

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Gaps in Knowledge and Limitations of the Evidence Base *(Continued from page 3)*

- Evidence related to surgical treatments for IH other than PDL treatment is insufficient to permit meaningful conclusions about their effectiveness and harms.
- No studies were identified that reported data on second-line therapies for IH when beta-blockers or corticosteroid therapies were unsuccessful.
- Studies used multiple and variable outcome measures to assess resolution of lesions, which makes it difficult to combine or compare outcomes across studies. Research to improve standardization of outcome measures is, therefore, crucial.

Applicability Issues

- Applicability of studies assessing laser treatments for IH is limited by historical changes in care and technology.
  - Most laser studies evaluated lasers as first-line treatment, which is currently a less common practice in the United States since the advent of beta-blocker treatment.
  - Furthermore, newer lasers with adjunctive features, such as dynamic cooling, have outmoded older lasers, thus limiting the applicability of studies conducted with older models.
- Studies differed widely in terms of IH stage and lesion location. It is unclear if findings are applicable to children of specific ages, with a particular stage of IH, or with specific lesion types.
- Studies of steroids were typically older and compared various doses and routes of administration. It is unclear if the findings from these studies are applicable to the current standard of care for children with IH in the United States.
- Most studies assessed in this review included children with IH in multiple anatomic locations. The type of IH was not consistently reported.

What To Discuss With Parents and Caregivers

- What IH is and the natural history of the disease
- The currently available treatment options for IH (pharmacological vs. surgical)
- For pharmacological interventions, information about how the drugs work to treat IH, their formulation, and the frequency of their administration
- The available evidence for the efficacy and relative effectiveness of the various interventions for IH
- The available evidence for the adverse effects associated with the different interventions for IH
- Potential long-term adverse effects related to the different interventions

Companion Resource for Parents and Caregivers

Treating Infantile Hemangiomas in Children: A Review of the Research for Parents and Caregivers is a free companion to this clinician research summary. It can help parents and caregivers of children with IH talk with their health care professionals about IH and the various treatment options that are available for this condition.

Ordering Information

For electronic copies of this clinician research summary, the companion patient resource, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/infantile-hemangioma.* To order free print copies of the patient resource, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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