

## Targeted Update

### Oral propranolol for infantile haemangioma in infants and children.

This is a **Targeted update** of the Cochrane Review

Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Arevalo-Rodriguez I. Interventions for infantile haemangiomas (strawberry birthmarks) of the skin. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD006545. DOI: 10.1002/14651858.CD006545.pub2.

Latest search was performed: **8 June 2015**

Results of the search, list of new references, details of updates to methods, study characteristics, risk of bias assessments, and details of data analyses can be found in [Supplementary material](#).

This **Targeted update** document was prepared by Hanna Bergman<sup>1</sup>, Dennis Kahn<sup>2</sup>, Rachel Marshall<sup>2</sup>, and the Cochrane Skin Group. Data were taken from the previously published full review and from results of the updating process carried out by Rosie Asher<sup>1</sup>, Hanna Bergman<sup>1</sup>, Antonio Grande<sup>1</sup> and Dennis Kahn<sup>2</sup>. The abstract was adapted from the previously published full review.

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### What's a Targeted update?

Targeted Updates are two to three-page documents that use the Cochrane Review as their foundation, but focus on updating only one or two important comparisons, and the seven most relevant outcomes. They include an updated Summary of Findings table and Abstract, and use Cochrane methodology. The full search results, risk of bias assessments, analyses and references do not form part of the Targeted Update, but are available as supplementary information. Targeted Updates are intended to be used by policy makers.

### What's the context for this Targeted Update?

The topic for this Targeted update was identified as important by the Cochrane Skin Group editorial base together with guideline developers.

### What's new

The comparison oral propranolol versus placebo has been added to this Targeted update. We included three studies with 514 participants. There was low/ very low quality evidence that oral propranolol, when used for 24 weeks, may be associated with a large reduction in infantile haemangioma.

This Targeted update is up-to-date as of June 2015.

In a related Targeted update we report on the effects of topical timolol for infantile haemangiomas.

## Outcomes regarding oral propranolol compared to placebo for infantile haemangioma in infants and children:

- Oral propranolol may clear (improve) infantile haemangiomas.
- There is a lack of evidence on what parents/carers think of the results; no studies reported on this outcome.
- The effect on the rate of serious adverse events is very uncertain.

### Background

Infantile haemangiomas (also known as strawberry birthmarks) are a benign overgrowth of blood vessels in the skin, characterized by a bright red surface. They are usually uncomplicated and regress spontaneously over time. However, some haemangiomas can develop complications, especially those in high-risk areas (such as near the eyes and nose); therefore, intervention may be necessary. Oral propranolol has been proposed as a systemic treatment for proliferating haemangiomas, but its efficacy is unclear.

### Objectives

To assess the effects of oral propranolol compared to placebo for infantile haemangiomas in infants and children.

### Search methods

CENTRAL in The Cochrane Library, MEDLINE, Embase, PsycINFO, AMED, LILACS, CINAHL, and Cochrane Skin Group Specialised Register were searched in June 2015. ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform were searched in November 2015, using the terms "haemangiomas", "hemangiomas" and "strawberry", among others.

### Selection criteria

Randomised controlled trials (RCTs) were included.

### Data collection and analysis

Two review authors independently assessed the eligibility and quality of the evidence. Clearance as assessed by clinicians was the primary outcome. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for dichotomous data. Meta-analyses were performed unless heterogeneity was considerable ( $I^2 > 80\%$ ), and a random-effects model was used.

### Main Results

Three studies were included in this targeted update.

Risk of bias was low in all included studies for the randomisation process, which was adequately described, and participants were appropriately accounted for in the reports. However, the larger multicentre study was assessed at high risk of bias, as the company supplying the intervention was also involved in the conduct of the trial, analysis, and interpretation of data. Trials included were published from 2011 to 2015, and few or no serious adverse events have been reported by the included studies. There was low quality evidence of clearance of infantile haemangioma at 24 weeks with propranolol in doses 3 mg/kg per day (1 RCT, 156 infants and children; RR 16.61, 95% CI 4.22 to 65.34), when compared with placebo. This outcome was not reported by the other 2 RCTs. We are uncertain of the effect on the rate of serious adverse events because the quality of the evidence is very low. Further, there is a lack of evidence on improvement as judged by parents and

### Included studies

Two small and one large, parallel, placebo-controlled RCT evaluated the efficacy of oral propranolol in doses from 1 to 3 mg/kg/day. 514 infants and children age 5 weeks to 5 years were randomized and followed up for up to 24 weeks. Infantile haemangiomas were deep and proliferative, requiring systemic therapy.

No ongoing studies were identified.

#### References:

Hogeling M, Adams S, Wargon O. *Pediatrics* 2011; **128**(2): e259-66.  
Leaute-Labreze C, Dumas de la Roque E, Nacka F, et al. *Br. J. Dermatology* 2013; **169**(1): 181-3.  
Leaute-Labreze C, Hoeger P, Mazereeuw-Hautier J, et al. *NEJM* 2015; **372**(8): 735-46.

carers; none of the included studies reported on this outcome.

### Implications and conclusions

There was some evidence that oral propranolol may improve and clear infantile haemangiomas and that the effect on the rate of serious adverse events is very uncertain. For all outcomes the quality of the evidence was low or very low due to serious imprecision in the results and a conflict of interest in one of the included studies. Further research is very likely to have an important impact on these estimates.

## Summary of Findings: Oral propranolol for infantile haemangioma

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**Patients and setting:** Infants and children from 5 weeks to 5 years of age with a proliferating infantile haemangioma requiring systemic therapy. Studies were set in Australia, France, Germany, Peru, Poland, Spain, and the USA.

**Comparison:** Oral propranolol versus placebo

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Placebo	Oral propranolol		
Clearance, as assessed by a clinician (3mg/kg/day)	3 mg/kg/day of oral propranolol may help to clear haemangioma in infants and children followed up for 24 weeks.	36 per 1000	604 per 1000	RR 16.61 (4.22 to 65.34) Based on data from 156 participants in 1 study	⊕⊕⊕⊕ LOW <sup>1,2</sup>
Subjective measure of improvement as assessed by parent or child	None of the included studies reported on this outcome.				
Serious adverse events	We are very uncertain about the effect of oral propranolol on the rate of serious adverse events in infants and children followed up for 24 weeks.	37 per 1000	38 per 1000	RR 1.05 (0.33 to 3.39) Based on data from 509 participants in 3 studies	⊕⊕⊕⊕ VERY LOW <sup>1,3</sup>
Serious cardiovascular adverse events: Bradycardia (slow heart beat)	We are very uncertain about the effect of oral propranolol on the rate of slow heart beat in infants and children followed up for 24 weeks.	0 per 1000	0 per 1000 <sup>4</sup>	RR 0.70 (0.03 to 14.32) Based on data from 509 participants in 3 studies	⊕⊕⊕⊕ VERY LOW <sup>1,3</sup>
Serious cardiovascular adverse events: Hypotension (low blood pressure)	We are very uncertain about the effect of oral propranolol on the rate of low blood pressure in infants and children followed up for 24 weeks.	12 per 1000	10 per 1000	RR 0.82 (0.10 to 6.71) Based on data from 509 participants in 3 studies	⊕⊕⊕⊕ VERY LOW <sup>1,3</sup>
Adverse events: Bronchospasm (tightening of the airways)	We are very uncertain about the effect of oral propranolol on the rate of tightening of the airways in infants and children followed up for 24 weeks.	18 per 1000	7 per 1000	RR 0.41 (0.04 to 3.89) Based on data from 456 participants in 1 study	⊕⊕⊕⊕ VERY LOW <sup>1,3</sup>
Adverse events: Hypoglycemia (low blood sugar)	We are very uncertain about the effect of oral propranolol on low blood sugar in infants and children followed up for 24 weeks.	0 per 1000	0 per 1000 <sup>5</sup>	RR 0.70 (0.03 to 14.32) Based on data from 456 participants in 1 study	⊕⊕⊕⊕ VERY LOW <sup>1,3</sup>

CI= confidence interval; RR=Risk ratio <sup>1</sup>Downgraded one level for high risk of industry bias. <sup>2</sup>Downgraded one level for imprecision: wide confidence interval (CI) around the estimate of the effect. <sup>3</sup>Downgraded two levels for imprecision: Optimal information size criterion was not met, and the 95% CI show both appreciable benefit and appreciable harm for the intervention. <sup>4</sup> Two cases of bradycardia were reported for oral propranolol group. <sup>5</sup> Two cases of hypoglycaemia were reported for oral propranolol group.