Targeted Update

Topical timolol (beta blocker) 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[1], Dennis Kahn[1], Rachel Marshall[2], 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[1], Hanna Bergman[1], Antonio Grande[1] and Dennis Kahn[1]. 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 topical timolol versus placebo has been added to this Targeted update. One low quality study with 41 participants was identified. There is a lack of evidence on clearance as assessed by a clinician, on parental reported measures of improvement, and on adverse events related to topical timolol, such as burning, stinging and irritant reactions. Topical timolol (beta blocker) may be associated with a large reduction in redness and volume of infantile haemangioma when used for 24 weeks.

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

In a related Targeted update we report on oral propranolol for infantile haemangioma.

Outcomes regarding topical timolol (beta-blocker) compared to placebo for infantile haemangioma in infants:

- There is a lack of evidence on clearance, parental/carer assessment of treatment response, and adverse events related to topical timolol; no study reported on any of these outcomes.
- Evidence suggests topical timolol may resolve redness and reduce volume of infantile haemangiomas.

Background

Infantile haemangiomas (IH, also known as strawberry birthmarks) are benign overgrowths 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. Timolol (beta-blocker) has been proposed as a topical treatment for superficial haemangiomas, but its efficacy is unclear.

Objectives

To assess the effects of topical timolol (beta-blocker) compared to placebo for superficial 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

One study published in 2013 was included in this Targeted update. Six ongoing RCTs comparing topical timolol to placebo in infants with haemangioma were identified.

The risk of bias was low as the randomisation process, allocation concealment, and blinding were adequately described in the report. However, the study included only 41 participants.

There is a lack of evidence on clearance as assessed by a clinician, on parental/carer measures of improvement, and on adverse events, such as burning, stinging, and irritant reactions related to the use of topical timolol maleate 0.5% gel twice a day; the included study did not report these outcomes. Further, there was low quality evidence that topical timolol maleate may resolve redness (reported as "no redness") (1 RCT, 41 infants; RR 8.11, 95% CI 1.09 to 60.09) and reduce the volume (reported as ≥5% IH volume reduction) (1 RCT, 41 infants; RR 5.21, 95% CI 1.28 to 21.21) of infantile haemangiomas when compared with placebo in 5-24 week old infants followed up for 24 weeks.

Included study

One small (N=41), parallel, placebo-controlled RCT evaluated the efficacy of topical (beta blocker) timolol maleate 0.5% gel in infants 5-24 weeks of age. Infantile haemangiomas were small, focal, and superficial and did not require systemic therapy. The study reported the efficacy of timolol maleate 0.5% gel, assessed as no redness by a clinician. However, this study did not report our main outcomes such as clearance as assessed by a clinician, parental measures of improvement, and adverse events related to topical timolol, such as burning, stinging and irritant reactions.
Six ongoing studies were identified.

Reference: 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.

Implications and conclusions

There is a lack of evidence on clearance as assessed by a clinician, on parental/carer measures of improvement, and on adverse events such as burning, stinging, and irritant reactions related to topical timolol. Further, there was some evidence that topical timolol (beta-blocker) may reduce redness and volume of superficial infantile haemangiomas. However, the quality of the evidence was low due to serious imprecision in the results, and further research is very likely to have an important impact on these estimates.

Summary of Findings: Topical timolol (beta blocker) for infantile haemangioma

***Patients and setting*: Infants from 5-24 weeks of age with a superficial infantile haemangioma not requiring systemic therapy. Studies were set in Australia.**
***Comparison:* Topical timolol (beta blocker) versus placebo**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo	Topical timolol		
Clearance, as assessed by a clinician	None of the included studies reported on this outcome.				
A subjective measure of improvement, as assessed by the parent or child	None of the included studies reported on this outcome.				
Other measures of resolution: No redness as assessed by a clinician	Topical timolol (beta blocker) may help clearing the redness of superficial haemangioma in infants 5-24 weeks of age followed up for 24 weeks.	45 per 1000	369 per 1000	RR 8.11 (1.09 to 60.84) Based on data from 41 participants in 1 study	⊕⊕OO LOW[1]
		Difference 324 more per 1000 participants (95% CI: 4 to 1000 more per 1000 participants)			
Other measures of resolution: IH volume reduction of ≥5%, as assessed by a clinician	Topical timolol (beta blocker) may help reducing the size of superficial haemangioma in infants 5-24 weeks of age followed up for 24 weeks.	91 per 1000	474 per 1000	RR 5.21 (1.28 to 21.21) Based on data from 41 participants in 1 study	⊕⊕OO LOW[1]
		Difference 383 more per 1000 participants (95% CI: 25 to 1000 more per 1000 participants)			
Adverse events: burning, stinging, and irritant reactions[2]	None of the included studies reported on this outcome.				

CI= confidence interval; RR=Risk ratio [1] Downgraded two levels due to serious imprecision: Optimal information size criterion was not met and a wide confidence interval (CI) around the estimate of the effect. [2] Chan et. al reported that there were no cases of bradycardia or hypotensive episodes. Also, authors reported measurements of both heart rate and blood pressure at baseline and with every visit.