Beta-blockers versus corticosteroids in the treatment of infantile hemangioma: an evidence-based systematic review

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Background: **The efficacy and safety of beta-blockers versus corticosteroids in the treatment of infantile hemangiomas (IHs) is controversial. This study aimed to summarize evidence described in the literature and to assess the quality of studies involving beta-blockers and corticosteroids for the treatment of cutaneous IHs.**

Methods: **Comparative studies were collected from 15 online electronic databases, including OVID Medline, PubMed, ISI Web of Science, CENTRAL, CNKI, ChiCTR, JPCTR, CTRIndia, IranCTR, SLCTR, ISRCTRN, NLCTR, GCTR, ANCTR, ClinicalTrial.gov, and associated references. Studies without a control group were excluded, and the remaining studies were assessed by two reviewers independently using the Downs & Black scale for reported quality. The main areas assessed in the included studies were volume changes, overall improvement in appearance, eye function, and adverse events.**

Results: **Ten comparative studies were included with a total of 419 children. A meta-analysis was not performed due to the considerable heterogeneity across studies. Some evidence showed that beta-blockers are superior to steroids in reducing volume and improving the overall appearance of IHs, such as lightening of the color and flattening of the surface. Conclusions regarding improved eye function and adverse events were divided, and no consensus has been reached on the superiority of one treatment over another. No episodes of severe-onset asthma, hypotension, or bradycardia occurred in the beta-blocker treatment due to the rigorous exclusion of patients with contraindications.**

Conclusions: **Available studies indicate that beta-blockers are an alternative option to corticosteroids for IH treatment with respect to volume shrinkage and improvement in appearance. No evidence has shown a significant difference in improved eye function and adverse events between beta-blockers and corticosteroids in the treatment of IH; indeed, there is a lack of well-designed, high-quality randomized control trials.**

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steroids

Systematic review

Introduction

Infantile hemangiomas (IHs) are benign vascular endothelial neoplasms characterized by a bright red surface and occurring in up to 4% of children by 1 year of age.[1] IHs are more likely to occur in low birth-weight, premature infants following maternal infertility treatment.[2] IHs are usually small at the time of birth and enlarge rapidly during the first months of the newborn's life,[3] then shrink slowly over time. Most IHs are self-limited, but may induce complications in high-risk areas if they left untreated. Complications in the periorbital area can lead to amblyopia, displacement of the globe, proptosis, and optic nerve compression.[4-7] Extensive surfaces can cause significant functional and cosmetic deformities; some may lead to permanent scarring, ulceration, or even bleeding,[8] whereas others have been shown to result in residual changes, including telangiectasia and hypopigmentation. Many parents seek treatment rather than follow a "wait-and-see" policy. Therapeutic options include corticosteroids, pulse dye laser,[9] topical imiquimod,[10] beta-blockers, and surgery, with recent emphasis on corticosteroids and beta-blockers. Corticosteroids have been the

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mainstream treatment for IHs for many years.[6,11-17] The effectiveness of corticosteroids is limited to the proliferative phase of IH growth, and various routes of administration (topical, intralesional, oral, and intravenous) may lead to varying degrees of adverse events, such as growth retardation, infections, and pain. The efficacy of propranolol, a non-selective beta-blocker, in the treatment of IHs has been demonstrated since 2008.[18] Numerous reports have suggested that oral propranolol as well as other beta-blockers such as nadolol and timolol hold high promise for IH treatment,[19-26] but appropriate dosages need to be investigated and different opinions regarding adverse effects (hypotension, bradycardia, hypoglycemia, sleep disturbances, and infections) exist. This systematic review collected published studies before September 2012 and aimed to provide an overall assessment on the reported quality of studies involving beta-blockers and corticosteroids for treating cutaneous IHs.

Methods

Search strategies

Two independent investigators searched databases (OVID Medline, PubMed, ISI Web of Science, CENTRAL, CNKI, ChiCTR, JPCTR, CTRIndia, IranCTR, SLCTR, ISRCTRN, NLCTR, GCTR, ANCTR, and ClinicalTrial.gov) on September 27, 2012 using the following key words: "capillary" or "infantile" and "hemangioma or "hemangiomas" or "hemangioma" in combination with "beta-blockers", "propranolol", "timolol", "nadolol", or "steroids", and "corticosteroids". Additional studies from reference lists of eligible articles were considered.

Selection of studies

Two reviewers assessed the titles, abstracts, and full texts of publications. Areas of conflicts were subsequently discussed, and a third blinded investigator was consulted when required to resolve any discrepancies. The types of studies included were prospective randomized controlled trials, prospective cohort studies, retrospective cohort studies, and comparative studies. A number of studies were excluded by the process of title and abstract review. The inclusion criteria were as follows: 1) children with IHs <48 months of age because the IHs are sensitive to medications during this period; 2) studies analyzing at least one outcome (volume changes, overall appearance, local functions, and/or adverse events); 3) each patient had at least 1 follow-up visit; and 4) studies including a control group. The following criteria were applied to exclude inappropriate studies: 1) the outcomes of interest could not be calculated; 2) if the same institution reported two or more studies for the same population, the study showing a larger number of patients was included; 3) case series, case reports, expert opinions, and reviews were excluded; 4) a combination with any other rare syndrome, such as Kasabachi-Merritt syndrome or Sturge-Weber syndrome; 5) hemangiomas located in the liver, subglottic, laryngeal, or gastrointestinal tract; and 6) combined treatment with other modalities.

Data extraction and assessment

Two independent reviewers extracted data from studies that met eligibility criteria and evaluated the quality of each study. The quality of each included study was assessed using the Downs & Black scale,[27] with a maximum quality index of 29 points. Studies with scores >20 points were considered to be of good quality, 11-20 points were of moderate quality, and <11 points were of poor quality. Two reviewers independently assessed the quality and resolved differences through discussion.

Statistical analysis

Study parameters obtained by data extraction entered the RevMan version 5.1 for statistical analysis. Ninety-five percent confidence intervals (95% CIs) were calculated. For dichotomous outcomes, the risk ratios were calculated and depicted using forest plots. We evaluated the pooled summary effect using a fixed-effect model to reduce the effects of heterogeneity between trials. Otherwise, the data were combined using a random-effect model. Where a meta-analysis was inappropriate, data were summarized for each trial.

Results

Study delection and methodologic quality

A total of 794 publications were retrieved from the literature search; 89 publications were eliminated by reviewing the titles because of duplications and 681 studies were excluded based on the exclusion criteria. Another 14 studies were excluded for the following reasons: 3 cohort studies focused on the characteristics of hemangiomas, including the subtype, location, size, and complications instead of the interventions; 8 studies did not provide the actual statistics or the data given were not sufficient for calculations; 2 prospective studies indicated that patients were enrolled for propranolol intervention because of previous unsuccessful medication effects; 1 study divided the patients into 2 groups, and used intralesional medications for tumor sizes >25 mm^2 and oral medications for tumor sizes <25 mm^2. Fig. 1 depicts

the selection process in a flowchart. Ten studies were eligible for detailed discussion in this review.[11,12,28-35] Six studies had scores >20 points, which indicated high quality, and the remaining 4 studies were considered to be moderate quality (11-20 points). No low-quality studies were included (Table 1).

Description of the included studies

The studies were conducted in the United States,[35] Australia,[29] Canada,[11,28,32,33] the Netherlands,[30] India,[12] Germany,[31] and Egypt.[34] All of the studies took place after 2007. A total of 419 patients were enrolled and the sample sizes ranged from 19[28] to 99,[12] with an average of 42 patients per study. The duration of clinical follow-up ranged from 8 weeks to 12 months. The age of the patients in most of the studies ranged from 4 to 69 weeks (average: 22.6 weeks). All studies estimated the volume changes using various measures, including changes in size,[29-31,34] percentage or visual analog scale (VAS) of volume shrinkage,[11,28,32,33,35] 5 studies considered the overall appearances of IHs by assessing tumor color or thickness,[12,29,31,33,35] 9 studies compared the adverse events or the relapse of IHs,[11,12,29-35] and 2 studies assessed eye functions.[11,33] The studies were diverse with respect to the measurements; therefore, most of the studies were discussed separately. The detailed characteristics of the 10 studies are listed in Table 1.

Volume change

It was difficult to pool findings from all studies because of the heterogeneity in volume measures. We identified nine studies for which the authors described volume changes in patients with IHs; two studies compared beta-blockers with a placebo or an observation-controlled group.[29,35] Both studies showed a significant change in volume using beta-blockers at the end of the follow-up (P=0.01, 95% CI=-80.3 to -11.4; P=0.016, 95% CI=1.45 to 59.65). Three studies focused on a comparison between beta-blockers and corticosteroids,[31,33,34] all of which revealed beta-blockers as the more effective treatment in the shrinkage of IH volumes. Rossler et al[31] reported a statistically significant decrease in IH size for propranolol (from 4.0 cm^2 to 2.0 cm^2) compared with steroids (from 4.0 cm^2 to 3.5 cm^2; P=0.006). Bertrand et al[33] also observed an improvement in treatment with propranolol compared with prednisone using a VAS (78.7% *vs.* 44.8%, P<0.001). Awadein et al[34] reported that 66.7% of patients showed good-to-excellent efficacy in volume change in the beta-blocker group compared with 60% in the corticosteroid group (P=0.75, 95% CI=0.58 to 2.12). One small, high-quality cohort study compared oral nadolol with propranolol for percentage improvement in size during a 24-week follow-up period using a VAS.[28] Oral nadolol showed a better volume shrinkage percentage than propranolol in this 19-patient study at the end of the follow-up (VAS=97%, SD=3.05 for nadolol; VAS=86%, SD=14.82 for propranolol, P<0.001). One high-quality retrospective, multicenter cohort study[32] examined the effect of dosage and treatment duration of topical timolol maleate gel-forming solution on patients with IHs. Two dosages (0.5% *vs.* 0.1%) and two treatment durations (<3 months *vs.* >3 months) were analyzed in this study, and a greater improvement in IH shrinkage was observed at a higher dosage and a higher treatment duration (VAS=24±29 for 0.1% timolol *vs.* VAS=48±28 for 0.5% timolol, P=0.01; VAS=38±28 for <3 months *vs.* VAS=52±30 for >3 months treatment, P=0.04). One double-blinded randomized low dropout trial evaluated the improvement in volume change using a VAS in 20 patients.[11] A greater shrinkage of IH was observed in the oral corticosteroid group compared

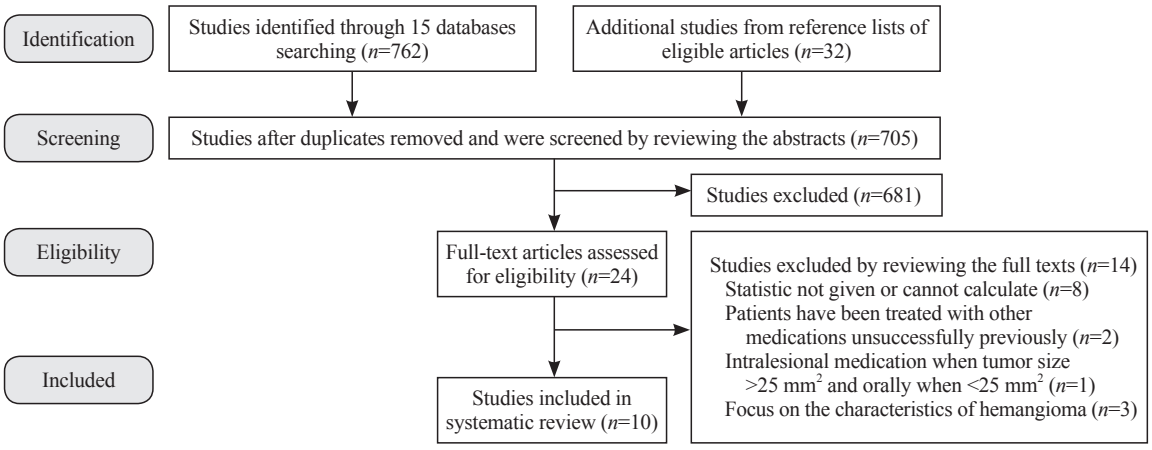

Fig. 1. Flow chart of selection process for the publication included.

Table 1. Detailed characteristics of each study and quality assessment

Studies	Ethnic origin	Cases	Interventions and dosage	Age (wk) of initial treatment	Follow-up (wk)	Quality score	Key outcomes
Bertrand[33] 2011	Canadian	24	**Oral propranolol/oral prednisone** Propranolol: mean dose, 2.7 mg/kg/d (range: 2.5-3.5) Prednisone: mean dose, 2.8 mg/kg/d (range: 2.0-4.0)	15	0, 4, 6, 24	20	1) Percentage of volume improvement using VAS; 2) Clinical improvement, overall appearance of serial photographs
Hermans[30] 2011	Netherlands	40	**Oral propranolol/other treatments** Propranolol: in hospital, start from dose of 0.7 to 1.0 mg/kg/d TID, and increasing over a 3-day period to 2.0-2.5 mg/kg/d. Blood pressure was measured Treatment was continued at home until the age of 1 year	14	0, 6, 12, 18, 24	23	1) Size of IH; 2) Age at onset of ulceration and extent of ulceration; 3) Adverse effects
Hogeling[29] 2011	Australian	39	**Oral propranolol/oral placebo** Propranolol: initiated at 1 mg/kg/d TID for 1 wk, 2 mg/kg/d TID for 2-24 wk	69	0, 4, 8, 12, 16, 20, 24	24	1) Volume estimation; 2) Color: redness or blueness; 3) Elevation; 4) Adverse effect
Pandey[12] 2010	Indian	99	**Top steroids/intralesional steroids** Top: applied as a thin film TID IL: triamcinolone injected monthly 1-2 mg/kg/d	Not given	24-32	16	1) Response to interventions in which excellent responses mean meet 3 parameters followed: a) cessation of growth, b) lightening of color, c) flattening of surface; 2) Complications
Pope[11] 2007	Canadian	20	**Oral steroid/IV steroids** Oral: prednisolone 2 mg/kg/d BID for 3 mon, followed by tapering 1 mg/mon over 6-9 mon IV: pulses of 30 mg/kg/d methylprednisolone infused over 1 h/d×3d monthly for 3 mon	11.5	0, 4, 8, 12	25	1) Change in the size of IH measured by blinded assessors and parents using -100 to +100 VAS; 2) Change in the visual function at 1 year in infants with periorbital hemangioma; 3) Adverse effects; 4) Changes over time in angiogenesis markers
Rössler[31] 2012	Germany	60	**Oral propranolol/oral steroids** Prednisone: 2 mg/kg/d BID for 2 wk then tapered to 2 mg/kg/d BID for another 2-4 wk Propranolol: initiated at 1 mg/kg/d BID for day 1 and 2 mg/kg/d BID for the rest days	16	visit/wk till 12th wk	16	1) Size of IH (cm^2); 2) IH score: color (red=2 points, reddish=1 point, pale=0), skin level (prominent=2 points, raised=1 point, plane=0), turgor (tight=2 points, soft=1 point, normal=0); 3) Adverse events
Chakkittakandiyil 2012	Canadian	73	**0.5%/0.1% topical timolol maleate gel** Timolol maleate 0.1% or 0.5% gel-forming solution/d	17	4-24	21	1) Change in appearance of IH using VAS; 2) Shrinkage of IH; 3) Frequency of adverse events
Chambers[35] 2012	American	23	**Topical 0.25% Timolol Maleate Gel/observation** 2 drops of 0.25% timolol-maleate gel BID on the lesion and rub over the entire lesion with a finger for 5s	17	8	21	1) Change in lesion size; 2) Tumor color; 3) Tumor thickness; 4) Systematic or ocular adverse events
Awadein[34] 2011	Egypt	22	**Intralesional propranolol/intralesional steroids** Propranolol: 1 mg/mL Steroids: triamcinolone 40 mg/mL 0.2 mL injected/cm of lesion diameter with a max volume of 1 mL for a lesion of 5 cm diameter	24	0-16	22	1) Size of IH (cm^2); 2) Change in refractive error; 3) Degree of ptosis; 4) Rebound growth; 5) Side effects
Pope[28] 2013	Canadian	19	**Oral propranolol/oral nadolol** Propranolol: up to max 2-3 mg/kg/d, TID >6 mon Nadolol: 0.5 mg/kg/d, BID with weekly increments of 0.5 mg/kg up to max 4 mg/kg/d	18	24	20	1) Percent improvement in size at 24 wk; 2) Assessments of frequency and severity of adverse events

VAS: Visual Analogue Scale; IH: infantile hemangioma; BID: twice daily; IV: intravenous; TIP: three times a day; IL: intralesional.

with the IV corticosteroid group 3 months and 1 year after treatment [VAS=70, Inter-Quartile-Range (IQR): 54-80 *vs.* VAS=12, IQR:-18-39 for 3 months, *P*=0.002; VAS=50, IQR: 35-67 *vs.* VAS=-1.5, IQR:-35-22 for 1 year, *P*=0.005].

Overall appearances

We retrieved 5 studies that reported on the overall appearance of IHs. Two of the studies demonstrated the efficacy of beta-blockers in erythematous changes and in the change of elevation of IH compared with an observation or placebo group.[29,35] One of the two studies was a high-quality randomized control trial (RCT) involving 39 patients in which the efficacy of oral propranolol was compared against a placebo group with a 24-week follow-up. The differences in erythema scores and elevation of IHs were significant at week 12 in the propranolol group (*P*=0.04 and *P*=0.001) and the elevation was significantly improved by 24 weeks after treatment (*P*=0.01). Another high-quality controlled study comparing topical 0.25% timolol maleate gel with an observation group; the study found that 92.3% (12/13) of the patients demonstrated a decrease in erythema and elevation of lesions in the timolol group, whereas 100% of patients (10/10) in the observation group had erythema of the lesions.[35] Two studies compared propranolol and corticosteroids and concluded that a statistically greater decrease was observed in IH erythema and skin elevation using propranolol compared with prednisone [*P*<0.001 (Rossler) *P*<0.001 for 6 months (Bertrand)].[31,33] The last of the five studies, a randomized controlled study,[12] assessed the cessation of growth, lightening of color, and flattening of the surface of IHs in patients using topical or intralesional corticosteroids. And there was no significant difference between the two groups (*P*=0.11, 95% CI=0.80 to 1.02).

Eye functions

Among 419 patients, 82 children from 7 studies had eye involvement, but only 2 prospective studies assessed eye functions, including astigmatism, amblyopia, ptosis and spherical errors when IHs were located periorbitally. One double-blind randomized low dropout trial included patients who had eye involvement with various degrees of function disorders.[11] After systematic administration of corticosteroids, 75% of the patients showed an improvement in astigmatism, increased intraocular pressure, and amblyopia. Awadein et al[34] reported a reduction in astigmatism errors immediately after intralesional injection of corticosteroids and propranolol, as well as at the 4-month follow-up (*P*=0.03 and *P*=0.02), but no significant difference was observed between the 2 groups (*P*=0.34). The reduction in degree of ptosis was statistically significant in the propranolol (*P*=0.02) and steroid groups (*P*=0.02). There was no statistically significant difference in the degree of ptosis between the groups (*P*=0.46).

Adverse events

Nine studies discussed the adverse events of interventions; three of the studies compared beta-blockers with a placebo or a "wait and see" policy. In a study conducted by Hermans et al,[30] 55% of propranolol patients reported mild adverse events. In another study conducted by Chambers et al,[35] no patient demonstrated any systemic or ocular side effects from topical timolol gel application. Both studies reported adverse events in the control group. Only one study[29] compared the adverse events induced by beta-blockers and corticosteroids and stated that the beta-blocker group developed some adverse events, but it is unclear whether or not these events were secondary to the medications. Two prospective studies assessed the adverse events due to different routes of administration. One study compared oral prednisolone with intravenous methylprednisolone and found no difference between the two groups with respect to irritability, excessive crying, apathy, vomiting, abdominal pain, or behavioral changes (*P*>0.05).[11] However, patients in the oral group had more severe growth retardation at 1 year of age in height and weight (*P*<0.001 and *P*=0.003). The other study compared topical corticosteroids with the intralesional injection of triamcinolone and showed

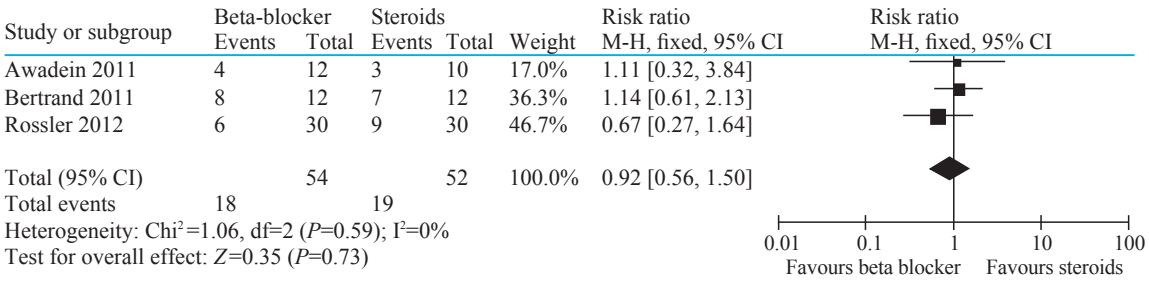

Fig. 2. Forest plot of adverse events between oral propranolol and steroids. CI: confidence interval.

that all patients in the intralesional group perceived more pain than patients in the topical group. Moreover, the rate of complications was 72.3% (34/47) in the intralesional group in contrast to the 26.9% (14/52) in the topical group ($P<0.001$).[12] Three studies demonstrated the adverse events of beta-blockers versus corticosteroids and these data were pooled in a meta-analysis.[31,33,34] No difference existed between the two groups ($P=0.73$, $I^2=0\%$, 95% CI=0.56 to 1.50; Fig. 2). One study performed a horizontal comparison between different types of beta-blockers and the resultant adverse events. Oral nadolol showed less adverse effects including cold extremities and gastrointestinal symptoms than propranolol [$P=0.021$, risk ratio (RR)=0.07, 95% CI=0.00 to 1.09].[28] Most of the studies which have used beta-blockers as treatment carefully monitored heart rate, electrocardiogram, blood pressure, and blood glucose before the initiation of treatment.[28,29,31,34,35] Infants were followed by their pediatricians to monitor blood pressure, heart rate, and blood glucose after the first treatment, throughout the treatment course, and at each visit. The results showed no changes in heart rate, blood pressure, or glucose level during and after treatment. The adverse events from different interventions are listed in Table 2.

Discussion

This systematic review revealed a lack of adequately powered, high-quality studies evaluating the efficacy and safety of beta-blockers or corticosteroids in the treatment of IHs. Given the limited number of eligible studies, we included 10 comparison studies in this review on different interventions and dosages for the treatment of IHs, and compared the efficacy of and adverse events from these treatments.

This systematic review showed that patients who received beta-blockers for IHs had greater shrinkage of volume, improvement in elevation, and improvement in erythema than placebo or corticosteroids. The onset of non-specific adverse events, including transient cool extremities, bronchiolitis, viral-induced reactive airways, upper respiratory tract infections, IH ulceration, itching, and hypopigmentation were similar between the beta-blocker and corticosteroid groups. While some studies have reported serious adverse events, including bradycardia, low blood pressure,[36-39] bradycardia, and onset of asthma,[40] others have reported that the side-effect profile appears to be favorable, but further follow-up is required to identify unexpected long-term side-effects.[41] In our systematic review, beta-blockers were generally well-tolerated hemodynamically; none of the included studies reported arrhythmias, hyperglycemia, hypertension, or hypotension due to strict patient recruitment criteria for beta-blocker treatment. Children at risk for heart or asthmatic attacks were excluded, and patients were closely monitored for vital signs and blood markers before and after treatment. This set of inclusion and exclusion criteria may skew the resulting data and lead to the conclusion that propranolol appears to be a good choice for treating IHs. Intralesional injection of propranolol may also be considered effective to reduce astigmatism, spherical error, ptosis, and aesthetic purposes.[42] A further study associated with relevant

Table 2. Summary of adverse events in different interventions

References	Intervention group	Adverse events									
		Sleep disturbance	Cold extremities	Gastrointestinal symptoms	Growth retardation	Pain	Infection	Bleeding	Cushing syndrome	Behavioral change	Hypertension/ hypotention
Bertrand[33] 2011	Oral propranolol	+	-	+	-	-	-	-	-	-	+
	Oral prednisone	+	-	-	+	-	+	-	-	-	+
Hermans[30] 2011	Oral propranolol	+	+	+	-	-	-	-	-	+	-
	Other treatments	-	-	-	-	+	-	-	-	-	-
Hogeling[29] 2011	Oral propranolol	+	+	+	-	-	+	-	-	-	-
	Oral placebo	+	-	-	-	-	+	-	-	-	-
Pandey[12] 2010	Topical steroids	-	-	-	-	-	-	-	-	-	-
	Intralesional steroids	-	-	-	+	+	+	+	+	-	-
Pope[11] 2007	Oral steroids	+	-	-	+	-	-	-	-	+	-
	Intravenous steroids	-	-	-	-	-	-	-	-	+	-
Rössler[31] 2012	Oral propranolol	+	-	-	-	-	-	-	-	-	-
	Oral steroids	+	-	-	+	-	-	-	+	+	+
Chambers[35] 2012	Topical 0.25% timolol	-	-	-	-	-	-	-	-	-	-
	Observation	-	-	-	-	-	-	-	-	-	-
Awadein[34] 2011	Intralesional propranolol	-	-	-	-	-	-	-	-	-	-
	Intralesional steroids	-	-	-	-	-	-	-	-	-	-
Pope[28] 2013	Oral propranolol	+	+	+	-	-	-	-	-	-	-
	Oral nadolol	-	-	-	-	-	-	-	-	-	-

adverse effects is necessary.

Other non-selective beta-blockers, such as nadolol and topical timolol maleate gel,[43] share the same mechanism of action as propranolol and are thought to have fewer systemic adverse effects. However, this idea was not rigorously tested in existing studies as most studies were either case series or consecutive non-randomized single-blind studies. We included two cohort studies to assess whether differences exist between the beta-blockers.[3] The study involving 19 patients in which oral nadolol and propranolol were compared showed that oral nadolol had a better shrinkage volume percentage than propranolol, with no significant differences in the associated adverse effects. Although this study had a small sample, the findings from the study were still valuable because this trial was assessor-blinded, had a low dropout, and the groups were randomly selected with matched age and location. A multicenter cohort study involving 73 patients revealed that the major advantages of topical timolol application were ease of administration and minimal risk of drug-related adverse events, especially when applied to the face and periorbital area with a longer duration of treatment and a higher concentration.[32] RCTs with larger sample sizes are necessary to assess the efficacy of various beta-blockers and whether or not there are significant differences in adverse effects between different routes of administration.

Despite reports of successful corticosteroid treatment of IHs,[13,31-33] evidence for the efficacy and safety of oral, topical, intralesional, or intravenous corticosteroids are scant. We included two prospective trials[11,12] which showed that oral corticosteroids performed better than intravenous corticosteroids in volume shrinkage. There was no significant difference in adverse effects between the oral and high-dose pulse intravenous corticosteroids; although growth retardation existed in the oral corticosteroid groups, the growth curve exhibited a temporary fall-off and caught up by 24 months of age in most of the cases. Nieuwenhuis et al[15] confirmed that intermittent, short course, systemic, high-dose glucocorticosteroid therapy is a more effective and safer treatment for IH, with a substantially lower cumulative dose of glucocorticosteroids compared to prolonged therapy.

No significant difference in response rates was shown between intralesional and topical steroids, whereas all of the patients receiving intralesional treatment had pain in spite of using 24-gauge needles. Thus, topical corticosteroids may be considered an optimal choice because of the painlessness. However, evidence has shown that a single intralesional dose of corticosteroids in patients resulted in a greater reduction in the mean astigmatism, intraocular pressure, and amblyopia induced by periorbital IH,[10,44] an observation supported by other studies.[6,45]

There was a lack of adequately powered, well-designed RCTs evaluating two interventions in the treatment of IH available for inclusion in this systematic review. The study designs were partially retrospective, and because of the heterogeneity of the nature of the studies, the statistics could not be pooled into forest plots. Furthermore, one study[12] had a restriction on lesion size and number, which might narrow the application of the conclusions. Other limitations include inadequate follow-up, incomplete data collection, and lack of well-documented side-effects of the included studies. Finally, publication bias is inevitable because articles without positive results are less likely to be accepted for publication.

Conclusions

We found some evidence that beta-blockers are superior to corticosteroids in volume shrinkage and overall improvement in appearance of cutaneous IHs. No evidence showed a significant difference in the improvement of eye function and adverse events between beta-blockers and corticosteroids. This study revealed that there is a lack of well-designed high quality RCTs regarding a comparison between beta-blockers and corticosteroids.

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Ethical approval: Not needed.

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