

Aesthetic Outcome of Propranolol vs Atenolol Treatment of Children with Infantile Haemangioma

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Infantile haemangiomas are common benign tumours of infancy, which can be treated effectively with beta-blockers such as propranolol and atenolol. Different types of beta-blockers may result in different long-term aesthetic outcomes. This study evaluated the difference in long-term aesthetic outcomes between infantile haemangiomas treated with either propranolol or atenolol, including the perspective of physicians, parents, and children. Children, aged ≥ 6 years, treated with propranolol or atenolol for infantile haemangioma during infancy, participated in this 2-centre cross-sectional study. The primary endpoint was change in appearance of the infantile haemangioma from pre-treatment to follow-up, using a physician-rated visual analogue scale (VAS). Secondary outcomes were the Patient Observer Scar Assessment Scale (physician- and parent-rated) and a VAS (child-rated), assessing the residual lesion. In total, 103 children (35 treated with propranolol, 68 with atenolol) were analysed. No differences were found between children treated with propranolol and children treated with atenolol on physician-rated VAS ($p=0.10$) or any secondary outcomes. Physicians indicated a large aesthetic improvement from pre-treatment to follow-up. Physicians, parents and children were positive about the current state of the residual lesion. Minor sequelae were common (86%). These results, in combination with the favourable safety profile of atenolol, should be considered when choosing beta-blocker treatment for infantile haemangioma.

Key words: capillary hemangioma; vascular tissue neoplasm; vascular malformation; adrenergic beta-antagonist; esthetics; cicatrix.

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SIGNIFICANCE

Propranolol and atenolol are effective beta-blocker treatments for infantile haemangioma. The aim of this study was to evaluate whether the long-term aesthetic outcome of the infantile haemangioma was different between children (≥ 6 years old) who had been treated during infancy (≤ 1 year old) with either propranolol or atenolol. The results show no differences between these beta-blocker groups. Overall, physicians indicated a large aesthetic improvement from pre-treatment to follow-up. Physicians, parents, and children were positive about the state of the residual lesion. These findings, and the favourable safety profile of atenolol, should be considered when choosing beta-blocker treatment for infantile haemangioma.

Infantile haemangiomas (IH) are the most common benign tumours of childhood, with estimated incidences varying between 2.0% and 4.5% (1–3). IH typically develop within the first few days to weeks after birth. They undergo rapid growth during the first months of life (proliferative phase), before entering a spontaneous and slow involution phase, which can last several years (4). Although the duration of IH involution varies between patients, most involution takes place during the first 4 years of life (5, 6). After involution, up to 69% of untreated IH show sequelae, such as telangiectasia, fibrofatty tissue, and anetodermia (5, 7, 8).

Up to 38% of IH require treatment during infancy to prevent or treat complications, such as ulceration, functional impairment, or disfigurement (9). Since 2008, propranolol has become the first-choice treatment of these complicated IH (10). Propranolol is a non-selective lipophilic beta-blocker that effectively promotes tumour involution. Possible side-effects of propranolol treatment are respiratory symptoms (e.g. bronchospasm), central nervous system effects (e.g. sleep disorders), hypoglycaemia, hyperkalaemia, and cold extremities (11). Atenolol, a predominantly β_1 -selective and hydrophilic

beta-blocker, has also been used in the treatment of IH, either to prevent (β 2-blockade associated) side-effects or to increase compliance as a result of once-daily dosing (12). Several studies have shown equal efficacy and fewer side-effects of atenolol compared with propranolol (12–18).

When choosing a beta-blocker to treat IH, the long-term aesthetic outcome should also be taken into account, as residual lesions and disfigurement may affect appearance and psychosocial functioning of school-age children (19). Previous follow-up of Asian children (mean age 6 years) who had been treated with propranolol for IH during infancy showed that 72.4% had retained significant or severe sequelae, most commonly telangiectasia, fibrofatty tissue, and erythema (20). Although studies about the efficacy of propranolol and atenolol have been published, long-term aesthetic outcome studies comparing propranolol and atenolol treatment for IH are lacking. Furthermore, in previous studies, treatment effect was mostly clinician assessed, while the perspective of parents or children was not reported (21).

The aim of the current study was to compare the long-term aesthetic outcome of IH treated with propranolol or atenolol during infancy, including the perspective of physicians, parents, and patients. Considering the comparable impact on IH involution of both beta-blockers, we expected no long-term aesthetic differences between propranolol and atenolol treatment (12–18).

MATERIALS AND METHODS

Design and setting

This study was part of a 2-centre cross-sectional study conducted at the vascular anomaly centres of the Erasmus Medical Center (MC), University Medical Center Rotterdam (Erasmus MC, Rotterdam, The Netherlands) and the University Medical Center Utrecht (UMCU, Utrecht, The Netherlands). Both centres introduced propranolol treatment in 2008. UMCU switched to atenolol treatment in 2009 and Erasmus MC switched to atenolol treatment in 2013. This condition enabled studying an internationally unique cohort of school-aged children, who had received either propranolol or atenolol, independent of their disease characteristics. This study was exempt from the Dutch Medical Research Involving Human Subjects Act according to the Institutional Review Boards of Erasmus MC (MEC-2019-0268) and UMCU (19-115/C). All parent(s)/guardian(s) provided written informed consent.

Participants

All children born between 2008 and 2014 (age ≥ 6 years on enrollment in the study) and treated for IH at Erasmus MC or UMCU were screened for participation. Children were actively recruited between April and December 2019, with the last child assessed in March 2020. Eligible children had IH treated previously with either oral propranolol at ≥ 2 mg/kg/day or oral atenolol at ≥ 1 mg/kg/day; had a treatment duration of ≥ 6 months; and were ≤ 1 year old at initiation of beta-blocker treatment. Children who had received treatment for IH subsequent to oral propranolol or atenolol treatment (e.g. laser, surgery, cryotherapy, or oral or intralesional corticosteroids), were excluded from the study.

In addition, complete subcutaneous IH, not eligible for clinical scoring, were excluded from the analyses.

All participating children received a dermatological examination (follow-up visit) by a paediatric dermatologist (MdG, SP), who was blinded to the type of beta-blocker treatment. During the dermatological examination, the paediatric dermatologist, a parent, and the child independently rated the current state of the residual lesion. A professional photographer took 3 standardized photographs of each residual lesion; 1 frontal and 2 sagittal (both sides) photographs, all including a ruler. From medical records photographs of the IH prior to beta-blocker treatment, information about the clinical characteristics of the patient, clinical characteristics of the IH, details of the beta-blocker treatment, and occurrence of side-effects during beta-blocker treatment were retrieved.

Measurements

The primary endpoint was the overall aesthetic improvement in the IH. The paediatric dermatologists (MdG, SP) and a paediatric plastic surgeon (CB), all 3 blinded for the type of beta-blocker treatment, individually scored the improvement in the IH in a specific child, between pre-treatment photographs and photographs of the lesions at follow-up. A total score for each child was determined during a consensus meeting. Since no standard measure to assess the long-term aesthetic outcome of IH exists, a visual analogue scale (VAS physician) was used, which ranges from 0 (meaning 0% improvement compared with pre-treatment photographs) to +100 (meaning 100% improvement compared with pre-treatment photographs/no residual lesion; **Fig. 1**) (22, 23). When scoring the VAS, the physicians took into account the extent to which telangiectasia, fibrofatty tissue, atrophic scar, excess skin, erythema, hyperpigmentation, impression, and hypopigmentation were present.

As secondary endpoints, a paediatric dermatologist (MdG, SP), a parent, and the child evaluated the residual lesion at follow-up by using the Patient and Observer Scar Assessment Scale (POSAS) and a VAS child. The POSAS consists of 2 components, of which the Observer Scar Assessment Scale (OSAS) was evaluated by the paediatric dermatologist and the Patient Scar Assessment Scale (PSAS) was evaluated by a parent (24). The OSAS includes an evaluation of the vascularity, pigmentation, thickness, surface relief, pliability, and surface area of the residual lesion, and an evaluation of the overall appearance of the residual lesion. The PSAS includes an evaluation of pain, itching, colour, stiffness, thickness, and irregularities in relation to the residual lesion, and an evaluation of the overall appearance of the residual lesion. All items are scored on a 10-point rating scale, in which 1 corresponds to "normal skin" appearance and 10 corresponds to the worst imaginable residual lesion. The child was asked to rate the current appearance of the IH on a VAS ruler, on which different smiley faces corresponded to the outcomes 0 (excellent) to 10 (poor; a link to an image of the VAS ruler is provided in the reference) (25). Previous research has shown that the validity of the VAS is adequate in children at this age (26). Subsequently, children were asked to explain why they gave a particular score. The paediatric dermatologist additionally recorded whether telangiectasia, fibrofatty tissue, atrophic scar, excess skin tissue, erythema, hyperpigmentation, impression, and hypopigmentation were present (1) or absent (0). Finally, the child's skin type was categorized according to the Fitzpatrick classification (27).

Data analysis

In case of multiple IH, the most problematic tumour (i.e. the tumour that was the indication to initiate beta-blocker treatment) was included in the analyses. To analyse differences between children treated with propranolol and atenolol on the primary



Fig. 1. Infantile haemangioma (IH) on the nose: (a) at 3 months of age before initiation of beta-blocker treatment (atenolol); and (b) at follow-up, showing 96% improvement on the physician-rated visual analogue scale (VAS physician) at 7 years of age. Written permission is given by both parents to publish these photos.

outcome (VAS physician) and all secondary outcomes (POSAS, VAS child), Mann-Whitney U tests were used. A multivariate linear regression was performed to control for confounders (sex, follow-up time, age at treatment initiation, treatment duration, and cumulative dose), using the VAS physician or any secondary outcome as the dependent variable and beta-blocker type as predictor. If residuals were not normally distributed, an inverse square root data transformation was performed. Qualitative data, i.e. children's comments on their VAS scores, were evaluated with an exploratory thematic analysis (28).

Data collected during the follow-up visits were entered into an online OpenClinica 3.12.2 database. All data were analysed using SPSS 25.0. As missing data were rare (<5% of data), complete case analysis was used. A 2-sided $p < 0.05$ was considered significant in the analysis of the primary outcome. Accounting for 6 multiple comparisons, a 2-sided $p < 0.009$ was considered significant in analysis of the secondary outcomes (Dunn-Šidák correction).

RESULTS

Participant characteristics

Fig. 2 shows the recruitment flowchart. In total, 103 children were included in the study analyses (66% of 157 eligible children). Of these children, 35 (34%) had been treated with propranolol and 68 (66%) had been treated with atenolol (**Table I**).

Nine children (2 propranolol-treated, 7 atenolol-treated; 3% of all 299 screened patients) were excluded, because they received surgical excision of their residual lesion subsequent to beta-blocker treatment. During the study, the parents of 2 children (1 propranolol-treated, 1 atenolol-treated) expressed interest in surgical excision of the residual lesion, but their child had not yet received surgery.

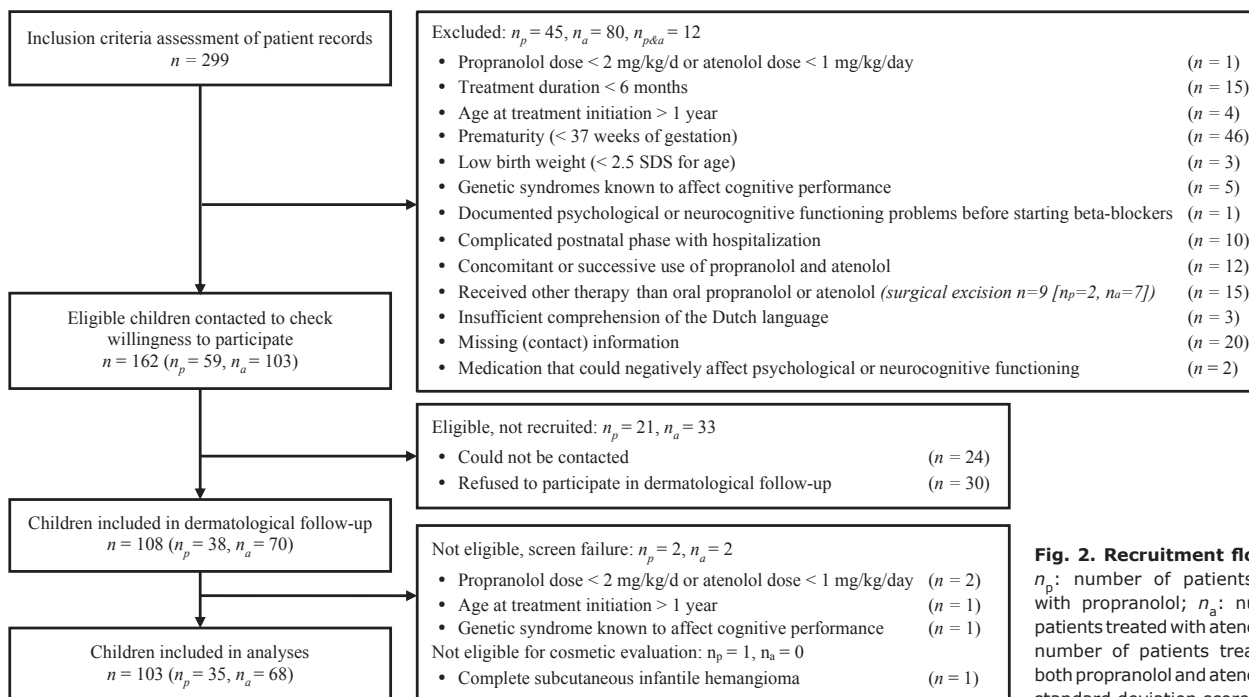


Fig. 2. Recruitment flowchart. n_p : number of patients treated with propranolol; n_a : number of patients treated with atenolol; $n_{p&a}$: number of patients treated with both propranolol and atenolol. SDS: standard deviation score.

Table I. Participant characteristics

	All (n = 103)	Propranolol (n = 35)	Atenolol (n = 68)
<i>Demographics</i>			
Child age, years, median (IQR)	7.5 (6.9–8.6)	8.1 (7.3–9.2)	7.2 (6.7–8.3)
Female sex, n (%)	84 (81)	28 (80)	56 (81)
Skin type (Fitzpatrick), n (%)			
I – Pale white skin	45 (44)	18 (51)	27 (40)
II – Fair skin	38 (37)	11 (31)	27 (40)
III – Darker white skin	17 (17)	5 (14)	12 (18)
≥IV – (Light – dark) brown skin	3 (3)	1 (3)	2 (3)
<i>Beta-blocker treatment</i>			
Cumulative dose, mg/kg, median (IQR)	568.3 (385.6–855.2)	1,101.7 (707.7–1,280.2)	418.7 (310.0–619.7)
Treatment duration, months, median (IQR)	13.7 (10.9–19.3)	18.0 (12.2–22.0)	13.0 (10.4–15.8)
Average dose, mg/kg, median (IQR)	1.2 (1.0–1.8)	1.9 (1.8–2.0)	1.0 (1.0–1.2)
Peak dose, mg/kg, median (IQR)	1.6 (1.0–2.1)	2.1 (2.0–2.4)	1.0 (1.0–1.6)
Age at treatment initiation, months, median (IQR)	3.5 (2.3–5.1)	3.6 (2.7–5.4)	3.4 (2.2–5.0)
Follow-up time, years, median (IQR)	5.9 (5.4–6.6)	6.2 (5.6–6.7)	5.8 (5.4–6.5)
<i>Haemangioma characteristics</i>			
Size ^a , n (%)			
< 1 cm	19 (19)	4 (12)	15 (22)
1–3 cm	42 (41)	12 (35)	30 (45)
3–5 cm	19 (19)	7 (21)	12 (18)
> 5 cm	21 (21)	11 (32)	10 (15)
Ulceration, n (%)			
Absent	75 (72)	22 (63)	53 (77)
Present	29 (28)	13 (37)	16 (23)
Depth ^a , n (%)			
Superficial	40 (40)	13 (38)	27 (40)
Deep	12 (12)	5 (15)	7 (10)
Mixed	49 (48)	16 (47)	33 (49)
Morphology ^a , n (%)			
Focal	71 (70)	21 (62)	50 (75)
Segmental	11 (11)	7 (21)	4 (6)
Indeterminate	18 (18)	6 (18)	12 (18)
Multifocal	1 (1)	0 (0)	1 (2)
Location, n (%)			
Head and neck	82 (79)	22 (63)	60 (87)
Genital area	12 (12)	7 (20)	5 (7)
Other	10 (9)	6 (17)	4 (6)

^aMissing data: 2 children (1 treated with propranolol and 1 treated with atenolol) were not photographed prior to beta-blocker treatment, n = 101 (propranolol n = 34, atenolol n = 67).

IQR: interquartile range.

Most children were female (n = 83, 81%), had Fitzpatrick skin type I or II (pale white or fair skin; n = 83, 81%), and had IH located in the head or neck area (n = 81, 79%). These participant characteristics did not differ between children treated with propranolol and children treated with atenolol. The seemingly proportionate differences between both beta-blocker groups related to ulceration and morphology were also not significant ($p = 0.12$ and $p = 0.09$, respectively). The median [interquartile range (IQR)] time since end of beta-blocker treatment (follow-up time) was 5.9 (5.7–6.6) years and did not differ between both beta-blocker groups. Given the standard treatment dose of 2 mg/kg/day for propranolol and 1 mg/kg/day for atenolol, differences in treatment dose were as expected. The median [IQR] treatment duration was longer in the propranolol group (18.0 [12.2–22.0]) compared with children treated with atenolol (13.0 [10.4–15.8]). Two children had experienced severe side-effects (defined as side-effects requiring dose adjustment or treatment discontinuation). These included 1 child treated with propranolol, who experienced hypoglycaemia, which led to a physician-initiated discontinuation of treatment. The other child was treated with atenolol and experienced severe sleep disturbance, which led to

a physician-initiated adjustment of treatment dose below the standard 1 mg/kg/day.

Comparison between propranolol and atenolol

The median [IQR] VAS physician did not differ between children treated with propranolol (95 [90–99]) and children treated with atenolol (96 [90–99]; $p = 0.89$) in univariate analyses (**Table II**). Similarly, analysis corrected for confounders showed no significant association of beta-blocker type with VAS physician scores ($p = 0.10$). Secondary outcomes (physician-rated OSAS, parent-rated PSAS, and VAS child) also did not differ between children treated with propranolol and those treated with atenolol.

Overall aesthetic outcome after beta-blocker treatment

Overall, median [IQR] VAS physician scores indicated strong improvement in the IH (95 [90–99]). At follow-up, the residual lesion was assessed by the physician, parent, and child. Most IH seemed to resemble normal skin, as indicated by the physician-rated OSAS (2 [1–3]) and the parent-rated PSAS (2 [1–4]). The scores of physicians and parents were highly correlated ($p \leq 0.001$, Spearman's $\rho = 0.71$).

Table II. Long-term aesthetic outcome of infantile haemangioma (IH) treated with propranolol or atenolol during infancy

	All (n=103) Median (IQR)	Propranolol (n=35) Median (IQR)	Atenolol (n=68) Median (IQR)	Univariate analysis p-value ^a	Multivariate analysis	
					B (95% CI)	p-value ^a
Physician Visual Analogue Scale ^b	95 (90–99)	95 (90–99)	96 (90–99)	0.89	0.7 (–0.1–1.6)	0.10
Observer Scar Assessment Scale ^c						
Overall appearance	2 (1–3)	3 (1–4)	2 (1–3)	0.062	0.2 (–0.7–1.1)	0.72
Vascularity	2 (1–4)	2 (1–5)	2 (2–3)			
Pigmentation	1 (1–1)	1 (1–1)	1 (1–1)			
Thickness	2 (1–2)	2 (1–2)	1 (1–2)			
Relief	1 (1–2)	1 (1–3)	1 (1–2)			
Pliability	1 (1–2)	1 (1–2)	1 (1–2)			
Surface area	1 (1–2)	1 (1–2)	1 (1–1)			
Patient Scar Assessment Scale ^c						
Overall appearance	2 (1–4)	2 (1–4)	2 (1–3)	0.60	0.0 (–0.3–0.4)	0.80
Pain	1 (1–1)	1 (1–1)	1 (1–1)			
Itching	1 (1–1)	1 (1–1)	1 (1–1)			
Colour	3 (2–4)	3 (1–4)	2 (2–4)			
Stiffness	1 (1–3)	2 (1–4)	1 (1–3)			
Thickness	2 (1–4)	3 (1–4)	2 (1–3)			
Irregularities	2 (1–4)	3 (1–6)	1 (1–3)			
Child Visual Analogue Scale ^d	2 (0–3)	2 (0–4)	2 (0–2)	0.032	–0.4 (–1.9–1.1)	0.60

^ap-values indicate differences between children treated with propranolol or atenolol. Outcomes are analysed with Mann-Whitney U tests and multivariate linear regression, adjusted for the child's sex, follow-up time, the child's age at treatment initiation, and cumulative dose. ^bMissing data: 2 children (1 treated with propranolol and 1 treated with atenolol) were not photographed prior to beta-blocker treatment, n=101 (propranolol n=34, atenolol n=67). ^cMissing data: 1 child in the atenolol group did not participate in the dermatological assessment, n=102 (propranolol n=35, atenolol n=68). ^dMissing data: 1 child in the atenolol group did not participate in the dermatological assessment and 1 child in the propranolol group did not provide a VAS score, n=101 (propranolol n=34, atenolol n=67). IQR: interquartile range; 95% CI: 95% confidence interval.

Children generally gave low VAS scores (i.e. positive ratings) to the current residual lesion (median (IQR) 2 (0–4)). Children's scores were weakly correlated with those of physicians ($p=0.014$, Spearman's $\rho=0.24$) and parents ($p=0.004$, Spearman's $\rho=0.29$). The following themes emerged from the children's comments: judgement based on lesion visibility (e.g. "I can hardly see it anymore.", "Because [the lesion] is pretty. It's part of who I am.", "It bothers me that other people can see [the lesion] when I'm wearing a bathing suit."); comparison with peers (e.g. "I find [the lesion] very special, I'm actually quite happy about it. Not many children have it", "[The lesion] doesn't hurt, but I sometimes find it unpleasant because I am the only one."); comments from peers (e.g. "It's pretty fun to have, but everyone asks me 'what's on your face?'", "I don't mind, but it's annoying when other children ask questions about it.", "It doesn't really matter to me, if people ask about it I just tell them about it."); and physical complaints (e.g. "Because it doesn't hurt and you can't really see it. I'm not unhappy about it. It actually doesn't matter to me.", "Sometimes it still hurts a little bit.").

Most IH had one or more types of sequelae ($n=87$, 86%; **Table III**), most frequently telangiectasia ($n=67$, 66%), fibrofatty tissue ($n=44$, 44%), and erythema ($n=37$, 36%).

DISCUSSION

This study showed, as hypothesized, no differences in long-term aesthetic outcome of IH treated with either propranolol or atenolol, corrected for characteristics such as treatment duration, age of treatment initiation, and follow-up time. Overall, physicians, parents, and child-

ren were positive about the current state of the residual lesion. Telangiectasia, fibrofatty tissue, and erythema were common, but minor, sequelae.

In the daily practice of treating IH with beta-blockers, reducing the chance of side-effects without sacrificing effectiveness in both the short- and long-term is important (12–18). Previous studies comparing short-term effectiveness of propranolol and atenolol treatment showed both beta-blockers induce similar reduction in haemangioma activity, ulceration healing time, and rebound rates, with fewer side-effects reported for atenolol (16, 17). This is in line with our finding that the long-term aesthetic outcome did not differ between IH treated with propranolol or atenolol. This finding, together with the reduced number of side-effects of atenolol treatment (due to its β_1 -selective and hydrophilic properties), should be taken into consideration when choosing beta-blocker treatment for IH (12, 16).

Physicians, parents, and children generally gave positive ratings of the residual lesion, and their scores

Table III. Residual lesion of infantile haemangioma (IH) treated with propranolol or atenolol during infancy

	All (n = 102)	Propranolol (n = 35)	Atenolol (n = 66) ^a
Type of sequelae, n (%)			
Telangiectasias	67 (65)	19 (55)	48 (71)
Fibrofatty tissue	44 (43)	16 (46)	28 (41)
Atrophic scar tissue	31 (30)	14 (40)	17 (25)
Excess skin tissue	28 (27)	8 (23)	20 (29)
Erythema	37 (36)	14 (40)	23 (34)
Hyperpigmentation	10 (10)	3 (9)	7 (10)
Impression	4 (4)	1 (3)	3 (4)
Hypopigmentation	16 (16)	8 (23)	8 (12)
One or more types of sequelae	87 (86)	30 (86)	57 (86)

^aMissing data: 1 child in the atenolol group was not assessed on types of sequelae, n=102 (propranolol n=35, atenolol n=66).

were significantly correlated. So far, only a few children had received surgical excision of the residual lesion. In contrast, previous long-term follow-up of Asian children (mean age 6 years) treated with propranolol for IH concluded that 72.4% of the studied IH left significant or severe residual lesions that required subsequent laser therapy or surgery (20). The magnetic resonance imaging (MRI) analysis used in this study may have yielded other results than a standard clinical evaluation, as used in the current study. Furthermore, the importance of physical appearance and the fear of psychosocial consequences of visible residual lesion may vary culturally (29). Considering IH are most common in Caucasian children, and Asian skin may be more susceptible to sequelae such as hyperpigmentation, the results of this follow-up study may not be applicable to all children with IH (30, 31).

Nonetheless, in the current study, 86% of IH treated with beta-blockers had 1 or more types of sequelae, while in previous follow-up of untreated IH or uncomplicated IH treated with intralesional lauromacrogol injections, 43–69% of untreated IH had 1 or more types of sequelae (5, 8, 32). The current study may have involved more severe IH than some previous studies, since we included complicated IH requiring beta-blocker treatment at a tertiary treatment centre. It is likely that IH severity is associated with the number of sequelae and overall aesthetic outcome in the long-term (7). Further research into clinical characteristics of the IH associated with poor aesthetic outcome after treatment with beta-blockers could help physicians to predict high-risk lesions and guide further management of the residual lesion.

A strength of the current study is the multi-informant (physicians, parents, and patients) assessment of the residual lesion. Furthermore, this study involved live evaluation in addition to photograph assessments, both completed by physicians who were blinded towards treatment type. Consequently, this research closely reflects clinical practice. This research was limited by the lack of validated outcome measures to assess the severity of the long-term residual lesion (7, 33). Because the current study excluded children who received surgical excision (3% of total screened population) of their residual lesion subsequent to beta-blocker treatment, some of the more severe haemangioma may have been excluded. This might have influenced the current results.

In conclusion, this study shows that the long-term aesthetic outcome does not differ between IH treated with propranolol or atenolol. Physicians, parents, and children were generally positive about the long-term aesthetic outcome. These results, in combination with the favourable safety profile of atenolol, should be considered when choosing beta-blocker treatment for IH. Future research should be directed towards clinical characteristics of the IH, which could be indicative of long-term aesthetic outcome, rather than beta-blocker treatment type.

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Netherlands Trial Register, NL7703 <https://www.trialregister.nl/trial/7703>.

The authors have no conflicts of interest to declare.

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