

## Propranolol or atenolol for the management of infantile hemangioma: Implications for long-term health



*To the Editor:* Since 2008, beta-blockers have been the first-line treatment for infantile hemangioma (IH). Because side effects of treatment during infancy may become visible later in life, the aim of this study is to describe the physical health and development of children (aged  $\geq 6$  years) treated for IH during infancy with either propranolol or atenolol.

This 2-center cross-sectional study was part of a larger long-term follow-up project.<sup>1</sup> Between August 2019 and March 2020, all eligible children ( $n = 158$ ) were asked to participate. Eligible children had IH, were aged  $\geq 6$  years, and had been treated during infancy (aged  $\leq 1$  year) for at least 6 months with either propranolol  $\geq 2$  mg/kg/day or atenolol  $\geq 1$  mg/kg/day, as per clinical practice guidelines. Children born preterm ( $< 37$  weeks of gestation), children with low birth weight ( $< 2.5$  SD for gestational age), and children with suspected genetic syndromes (eg, PHACE syndrome) were excluded from the study. All parent(s)/legal guardian(s) provided written consent to participate in this study. Consent for the publication of photographs or other identifiable material is not applicable.

In total, 103 eligible children were included (65% inclusion), of which 35% had been treated with propranolol, and consequently, 65% with atenolol (Table 1). The systolic and diastolic blood pressure values were significantly higher than reference values, adjusted for age, sex, and height (0.88 SD [ $P < .001$ ] and 0.30 SD [ $P = .005$ ], respectively).<sup>2</sup> All other physical measurements did not differ from reference values or between the 2 beta-blocker groups, when corrected for multiple comparisons (Dunn-Sidak corrected alpha = 0.005).<sup>3</sup> Most parents (99%) rated their child's health as "good" or "very good." The following health problems were reported: atopic dermatitis ( $n = 33$  [30%]), asthma ( $n = 9$  [8%]), and respiratory tract infections ( $n = 9$  [8%]). Incidences of all parent-reported health problems did not differ from the general population (Dutch public health registry; Supplementary Material S1, available via Mendeley at <https://doi.org/10.17632/45s3dnp2vr.1>). No differences were found between both beta-blocker groups in any of the parent-

reported health outcomes. No additional health concerns or developmental problems were identified during the systematic clinical examination of the children by the pediatrician (assessed characteristics in Supplementary Material S2, available via Mendeley at <https://doi.org/10.17632/45s3dnp2vr.1>).

Overall, this extensive clinical assessment of children (aged 6-12 years) previously treated with propranolol or atenolol for IH revealed no long-term health or developmental problems. Although we observed statistically higher blood pressure values (systolic blood pressure  $P < .001$ ; diastolic blood pressure  $P = .005$ ), these were not clinically relevant at the assessment age of the children. We hypothesized that higher blood pressure could be due to white coat hypertension, since we used a single measurement of blood pressure and lacked a control group of untreated children with equally severe IH. However, a permanent rise in blood pressure may cause cardiovascular problems later in life. Therefore, a longitudinal study on blood pressure in children treated with beta-blockers for IH, with multiple measurements at each visit, is required to support our findings. International collaboration using a registry could be undertaken to support this design and clarify the association between the decrease in blood pressure during treatment of IH with beta-blocker and a possible permanent rise in blood pressure later in life.<sup>4</sup> This may also elucidate the potential harmful effects and allow unraveling of pathophysiologic mechanisms. Further exploration of alternative agents that induce tumor reduction without cardiovascular sequelae may be of interest.<sup>5</sup>

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**Table I.** Characteristics of children treated with propranolol or atenolol for infantile hemangioma

Demographics	Total group (n = 103)	P value <sup>†</sup>	Propranolol (n = 36)	Atenolol (n = 67)	P value <sup>‡</sup>
Child age, y		NA			.001
Median (IQR)	7.5 (6.9-8.6)		8.1 (7.4-9.1)	7.2 (6.7-8.3)	
Range	6.0-11.9		6.5-11.9	6.0-9.8	
Sex, n (%)		NA			>.99
Female	83 (81)		29 (81)	54 (81)	
Cumulative dose, mg/kg, median (IQR)	581 (390-906)	NA	1123 (719-1282)	419 (311-621)	<.001
Average dose, mg/kg, median (IQR)	1.2 (1.0-1.8)	NA	1.9 (1.8-2.0)	1.0 (1.0-1.0)	<.001
Treatment duration (months), median (IQR)	13.7 (11.0-19.5)	NA	18.6 (12.5-22.7)	13.0 (10.4-15.9)	.001
Age at treatment initiation, mos, median (IQR)	3.5 (2.1-5.1)	NA	3.6 (2.2-5.3)	3.4 (2.1-5.0)	.57
Infantile hemangioma pattern, n (%) <sup>*</sup>		NA			.17
Focal	71 (69)		22 (61)	49 (73)	
Segmental	11 (11)		7 (19)	4 (6)	
Indeterminate	18 (18)		6 (17)	12 (18)	
Multifocal	1 (1)		0 (0)	1 (2)	
<b>Physical measurements<sup>†</sup></b>					
Height					
cm, median (IQR)	128 (123-133)		132 (125-139)	127 (121-132)	
SDS <sup>‡</sup> , mean (SD)	-0.22 (0.96)	.02	-0.13 (0.83)	-0.27 (1.02)	.47
Weight					
kg, median (IQR)	26 (23-30)		28 (23-34)	25 (23-29)	
SDS <sup>‡</sup> , mean (SD)	-0.20 (1.02)	.07	-0.16 (0.96)	-0.22 (1.06)	.80
Head circumference					
cm, median (IQR)	52 (51-53)		52 (51-53)	53 (51-53)	
SDS <sup>‡</sup> , mean (SD)	0.30 (1.09)	.008	0.12 (0.96)	0.39 (1.16)	.23
Systolic blood pressure					
mm Hg, median (IQR)	107 (101-115)		106 (98-111)	108 (102-116)	
SDS <sup>§</sup> , mean (SD)	0.88 (1.28)	<.001	0.53 (0.98)	1.08 (1.39)	.04
Diastolic blood pressure					
mm Hg, median (IQR)	64 (59-68)		61 (56-69)	64 (60-68)	
SDS <sup>§</sup> , mean (SD)	0.30 (1.05)	.005	0.00 (1.10)	0.47 (1.00)	.03
Heart rate					
bpm, median (IQR)	86 (78-96)	NA	82 (76-96)	87 (80-96)	.46
<b>Parent-reported health</b>					
General impression, n (%)		NA			.11
Very good	50 (49)		13 (36)	37 (55)	
Good	52 (50)		23 (64)	29 (43)	
Could be better	1 (1)		0 (0)	1 (2)	
Not good	0 (0)		0 (0)	0 (0)	

bpm, beats per minute; NA, not applicable; SDS, standard deviation score.

\*One propranolol-treated patient and 1 atenolol-treated patient had missing data for infantile hemangioma morphology, n = 101 (propranolol n = 34, atenolol n = 67).

†Alpha corrected for multiple comparisons (Dunn-Sidak alpha = 0.005).

‡Two atenolol-treated patients had missing height, weight, and head circumference scores, n = 101 (propranolol n = 36, atenolol n = 65).

§Three atenolol-treated patients had missing blood pressure scores, n = 100 (propranolol n = 36, atenolol n = 64).

¶P values represent the comparison of physical measurements with reference values (mean, 0.0; SD, 1.0).

‡‡P values represent comparisons between children treated with propranolol and children treated with atenolol.

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#### Conflicts of interest

None disclosed.

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