ORIGINAL ARTICLE

Propranolol treatment of infantile hemangioma is not associated with psychological problems at 7 years of age

Andre Vadimovich Moyakine, MD,[a,c] Saskia Spillekom-van Koulil, MSc, PhD,[b,c] and Catharina Joanna Maria van der Vleuten, MD, PhD[a,c]
Nijmegen, The Netherlands

Background: Concern has been raised about the potential long-term effects of propranolol treatment for infantile hemangioma (IH).

Objectives: We sought to assess psychologic (social, emotional, behavioral, and executive) functioning in children treated with propranolol for IH.

Methods: Twenty-seven patients with IH (6.1-7.6 years of age) treated with propranolol for ≥6 months during infancy, and without other developmental risk factors, were recruited. Parents completed the Behavior Rating Inventory of Executive Function, Social Emotional Questionnaire, Child Behavior Checklist, and Strengths and Difficulties Questionnaire. For each questionnaire, the number of patients with abnormal scores, based on established cutoff points, was calculated.

Results: Only 1 child (3.7%) scored outside the normal range. The Hemangioma Severity Scale did not correlate with psychologic problems in these patients. Longer treatment duration was found to correlate with less attention-deficit hyperactivity disorder (ADHD) characteristics ($\rho = -0.476$; $P = .012$) and better executive functioning ($\rho = -0.466$; $P = .014$).

Limitations: Exclusion of children born at gestational age <36 weeks or small for gestational age, no reference group and relatively small study size.

Conclusion: We found no increased risk for psychologic problems at age 7 in IH patients treated with propranolol. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.01.025.)

Key words: adverse effects; central nervous system; development; infantile hemangioma; infants; propranolol; psychologic functioning; treatment.

Propranolol has become first-line treatment for infantile hemangiomas (IHs) with associated morbidity.[1,2]

Little is known about the long-term effects of propranolol treatment. It has been suggested that propranolol could affect the developing central nervous system of infants. Animal studies and studies with adult volunteers taking propranolol found possible impairment in forming emotional arousing memories.[3,4] It is known that long-term suboptimal sleep (a frequently reported side effect) may be detrimental to the brain and behavior in young children.[5-8] In a retrospective pilot study, our group found no negative effect of propranolol treatment during infancy on psychomotor development in 103 toddlers at 2 years of age.[9] We found no increased developmental risk or growth impairment at 4 years of age in 82 patients.[10]

From the Departments of Dermatology[a] and Medical Psychology,[b] Radboud University Medical Centre, and the Radboudumc Expertise-Centre for Hemangioma and Vascular Anomalies (Hecovan),[c] Nijmegen, The Netherlands.
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Reprint requests: Andre Vadimovich Moyakine, MD, PO Box 9101, 6500 HB, Nijmegen, The Netherlands. E-mail: Andre.Moyakine@radboudumc.nl.
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The objective of the present study was to assess the psychologic (social, emotional, behavioral, and executive) functioning of propranolol treated infants at 7 years of age. We also wished to explore the correlation between psychologic functioning and hemangioma severity (assessed by the Hemangioma Severity Scale [HSS][11]), socioeconomic status (SES), age at the start of propranolol treatment, and treatment duration.

CAPSULE SUMMARY

- The long-term effects of propranolol on brain development in young children are unknown.
- Propranolol treatment for infants with infantile hemangioma was not associated with psychological (social, emotional, behavioral, and executive) problems at age 7 years.
- Our results may reassure parents about the long-term effects of propranolol for treatment of infantile hemangioma.

PATIENTS AND METHODS

Patients

Between September 2015 and February 2016, the parents of 66 children born with IH between 2008 and 2010 were asked to participate in this prospective study. The inclusion criteria were 1) propranolol treatment for ≥6 months and 2) age ≥6 years at the time of assessment. Children with known risk factors for developmental delay or growth restriction, including prematurity (<36 weeks' gestation), small for gestational age (birthweight ≤10 percentile for gestational age on Dutch growth charts), or other major congenital malformations were excluded, as were children with relevant comedications during infancy. Fig 1 provides an overview of the sampling procedure. The study was approved by the local institutional medical ethical review board.

Methods

Data on gestational age, sex, birth weight, ethnicity, age at the treatment initiation, and treatment duration were collected from the medical charts. To assess psychologic functioning, parents were asked to complete 4 validated, standardized questionnaires: (1) Child Behavior Checklist (CBCL)[12] to assess behavioral problems; (2) Strengths and Difficulties Questionnaire (SDQ)[13] to assess emotional and behavioral difficulties; (3) Social Emotional Questionnaire (SEQ)[14] to assess symptoms of psychopathology exhibited by a child and consisting of 4 subscales: attention-deficit hyperactivity disorder (ADHD), autism, problematic social behavior, and anxious/negative mood; and (4) Behavior Rating Inventory of Executive Function (BRIEF)[15] to assess executive functioning. The total scores of the BRIEF, CBCL, and SDQ were used and the scores on the 4 SEQ subscales (no total score available according to the manual).

The HSS score, based on photographs taken just before propranolol treatment combined with data from the medical records, was used to measure the severity of the IH.[11] The educational level of the mother was determined to assess SES.

Data analysis

For each questionnaire, the number of patients who scored abnormally (defined as the 95th or 97.7th and higher percentiles, depending on the specific questionnaire) was calculated. The cutoff points were based on the standard Dutch youth population and were sex- and age-matched (except for the SDQ, which has only general cutoff points). Because of the normal distribution of the sample, >1.6 children (>5.8%; >1.5 SD) with an abnormal score on the questionnaires would indicate psychologic dysfunction in our cohort. With this assumption, a reference cohort was not required.

Spearman rank correlation coefficient (or Pearson correlation coefficient in case of normal distribution) was calculated to determine the correlation between the HSS score, SES, age at the start and duration of propranolol treatment, and assessment of psychologic functioning. Correlation coefficients were considered statistically significant at $P < .05$.

RESULTS

Twenty-seven (49.1%) of 55 eligible patients were recruited for the study (Table I). Treatment indications are listed in Table II. Propranolol was started at a mean age of 6.0 months (range, 1.3-29.0 months; SD 5.5). The mean duration of treatment was 12.3 months (range, 6.0-25.9 months).

Only 1 child had an abnormal score on executive functioning (BRIEF), behavioral problems (CBCL), emotional and behavioral difficulties (SDQ), and autism (SEQ). No child scored abnormally on the other 3 subscales of the SEQ.

Significant correlations were found only between propranolol treatment duration and executive functioning (BRIEF) ($\rho = -0.466$; $P = .014$) and ADHD characteristics (subscale SEQ) ($\rho = -0.476$; $P = .012$); therefore, longer treatment duration