TREATMENT OF VASCULAR ANOMALIES IN CHILDREN WITH ORAL PROPRANOLOL: PROS AND CONS

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Abstract

Introduction: Most vascular anomalies are clinically easy to recognize. The age is the most prominent element to take into consideration for the diagnostic. Lesions differ by the moment of appearance: congenital hemangiomas and hemangioendotheliomas (occurred at birth); lymphatic- and venous malformations (emerged in the first week of life-unprogressive), infantile hemangiomas (emerged in the first week of life-fast evolutive) and arterio-venous malformations (appeared throughout childhood). One may diagnose up to 90% of cases based on aspect (color, depth, local temperature, presence of murmur). Doppler ultrasound and MRI may help in difficult cases. *Materials and methods:* We performed a prospective study of 54 cases with vascular anomalies from May 2010 to April 2013. Thirty-six girls and 18 boys treated with Propranolol – unselective beta-blocker. There were 50 vascular tumors and 4 vascular malformations. All patients underwent ECG and echocardiography before treatment. Four patients excluded based on consent withdrawal. *Results:* Treatment**:** age m=9,24 months, duration m=9,15 months and response: very good-66,66%, good-12,96%, partial-7,40%, no response-9,25% and aggravation-3,70%. As a *conclusion*, our results support the use of Propranolol in vascular anomalies.

Key words: vascular anomalies, Propranolol, treatment, children

Introduction

Muliken and Glowacki helped in classifying vascular anomalies based on morphology[1]. Adding clinical and radiological characteristics[2,3], in 1996 the International Society for the Study of Vascular Anomalies (ISSVA) proposed the classification of vascular anomalies. They were divided into tumors and malformations. Diagnosis of vascular anomalies is based on medical history and physical examination. Imagistic techniques (Doppler ultrasound <<US>>, MRI, CT, angiography) are used to evaluate the extent of the lesion, differential diagnosis and follow-up response to treatment[4].

In the early 1960s, James W. Black[5] synthesized Propranolol and ever since, it has been used extensively in pediatric cardiology on children and neonates. Forty-eight years later, in 2008, Leaute-Labreze due to an accidental association of infantile hemangiomas to Propranolol, published successful results with this association[6]. Therefore, indications for Propranolol use have exceeded the spectrum of cardiology[7]. The drug posology includes migraines[8], infantile hemangiomas[6], portal hypertension[9], post-traumatic stress disorder[10] and cancer[11,12].

Material and methods

Fifty-four children with vascular anomalies received oral Propranolol in between May 2010 and April 2013. In all cases, an informed consent from the parents/guardians was needed. The lesions were photographed before treatment onset and at each subsequent visit. Inclusion criteria were vascular anomalies with difficult surgical approach; high functional and esthetic risk lesions and complicated vascular tumors. Exclusion criteria included children previously treated with local or systemic corticosteroids and cardio-respiratory comorbidities.

Unselective beta-blocker treatment was administered in 36 girls and 18 boys. Forty-three patients had infantile hemangiomas, 6 congenital hemangiomas, 1 kaposiform hemangioendothelioma, 3 capillary malformations and 1 venous malformation. Prior to drug administration, all patients underwent cardiologic and dermatological evaluation. ECG and echocardiography were compulsory.

Therapeutic protocol: Propranolol was initiated with 1 mg/kg/day divided into 3 equal parts - day1 and 2 mg/kg/day divided into 3 equal parts starting from day 2 throughout the rest of the treatment. We initiated the treatment in the Department of Pediatric Cardiology. The blood pressure, glycemia and heart rate were carefully monitored in order to avoid complications. If the drug was well tolerated the treatment was continued on an outpatient base.

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The patient was brought in for a first follow-up visit after a week of treatment and, each subsequent month. Monthly, we evaluated the clinical and photographic evolution of the lesions and monitored the heart rate, blood pressure, ECG and glycemia. Echocardiogram was performed, again, after 2 months of treatment. Withdrawal from study was possible whenever the patient was cured; vascular malformations were with no clinical response or in the case of refuse to continue.

The outcome of each lesion was defined by its status at the last recorded visit. Outcomes are classified as: (1) very good – final observation indicates that the lesion has more than 95% healing, (2) good – lesion with more than 75% healing, (3) partial – lesion with less than 50% healing, (4) no response, (5) aggravation-proliferation under treatment.

Results

Localization: facial 35,19%; thorax 16,67%; upper limb 9,26%; lower limb 12,96%; multifocal 25,93%. The treatment did not affect blood pressure and heart rate. Adverse effects were noted in 6 cases as dyspneea and cough; and one case accused sleep disorders. Thirty-six of 54 have completed the treatment (Figure 1). Four cases were withdrawn based on parental/guardian decision and 2 cases with capillary malformation were withdrawn after 3 months of treatment.

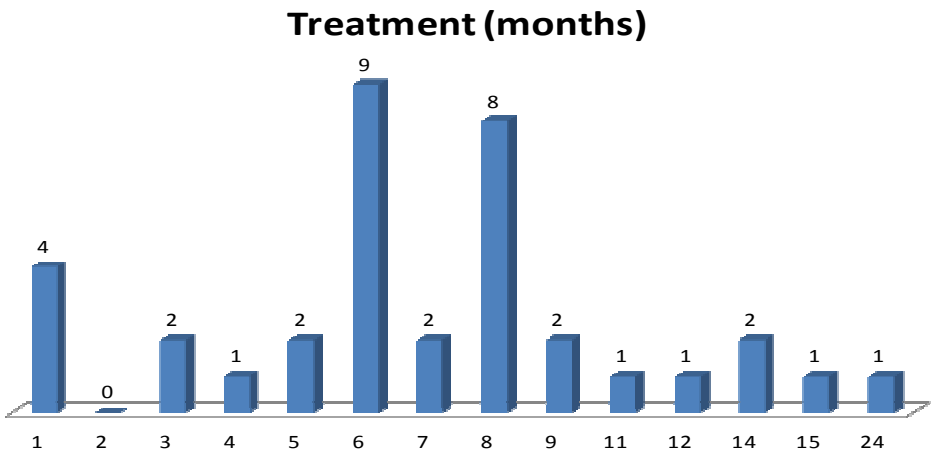

Figure 1. Completed treatment (36/54 patients).

Overall mean age for Propranolol treatment onset was 9,24 months (2 weeks-8 years) with 5,52 months for infantile hemangioma and 34,21 months for all other vascular anomalies. Main reasons for Propranolol treatment were: 44,44% esthetics, 27,78% functional, 27,78% local or general complications.

In two cases with infantile hemangioma, aggravation was encountered due to vascular proliferation. There were no side effects concerning hypoglycemia, bradycardia and electrolyte disorders.

One case, with PHACE syndrome, had a favorable outcome with healing of the lower lip ulcerated hemangioma after 1 month of treatment (Figure 2).

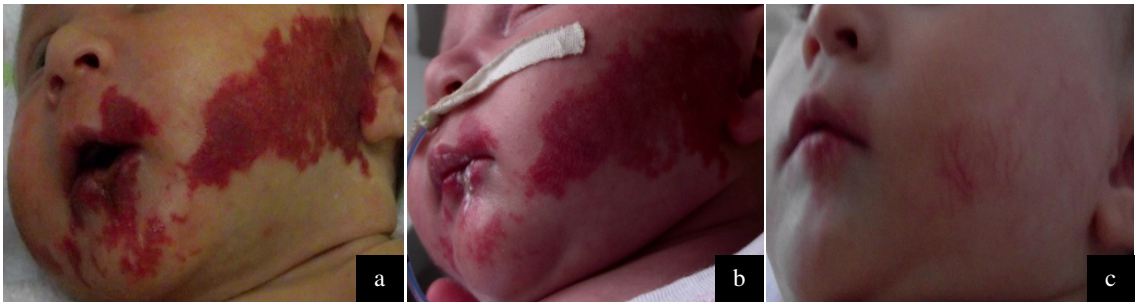

Figure 2. PHACE syndrome: a – before treatment, b – after 5 days, c – after 6 months.

Out of the 6 cases with dyspneea only two were excluded from the treatment schedule, as there was no improvement and 1 had Klippel-Trenaunay syndrome. The other 4 presented temporary dyspneea during intercurrent respiratory infections and the beta-blocker was temporarily stopped. The treatment with Propranolol was reintroduced with favorable outcomes.

All three cases with capillary malformations were unresponsive to treatment. Out of the 43 patients with infantile hemangioma 74,41% had a very good response to treatment after a mean duration of 8,16 months. There were four cases of infantile hemangioma (2 cases – no response to oral treatment, 2 cases – aggravation under treatment) and a case of venous malformation (Figure 3) that underwent surgical procedures.

Overall outcomes are: very good - 66,66%, good - 12,96%, partial - 7,40%, no response - 9,25%, aggravation - 3,70%.

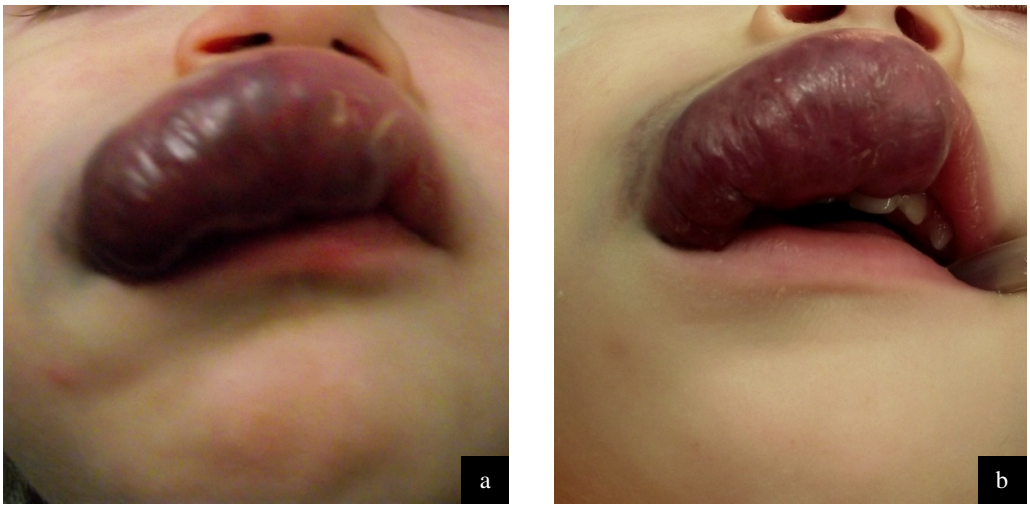

Figure 3. Venous malformation: a – before treatment, b – after 6 months.

Discussions

The etiology and pathogenesis of vascular anomalies together with the action of Propranolol remains unknown. New theories focus on progenitor cells, derangement of angiogenesis, mutation in the cytokine regulatory pathway, and developmental field defects[13,14].

The methods of treatment for vascular malformations, includes: systemic corticotherapy, bleomycin, vincristine, cyclophosphamide, interferon α, laser therapy, cryotherapy surgical excision, radiotherapy and Propranolol[15]. Until recently, first line therapy for complicated infantile hemangioma was systemic corticosteroids[16-19]. Due to numerous complications (aseptic necrosis of the femoral head, diabetes, osteoporosis, adrenal insufficiency, cataracts, glaucoma, infection, gastric irritation, elevated blood pressure, Cushing-like aspect, and hypothalamic-pituitary-adrenal axis suppression)[20-24] we exclude such therapy from our study.

We decided to use Propranolol as first step in treatment of vascular anomalies. There are some reports concerning side effects for Propranolol usage[25-28], but we had no major complications in our study.

Potential explanations for the therapeutic effect of Propranolol on infantile hemangioma include vasoconstriction, which is immediately visible as a change in color, associated with a palpable softening of the hemangioma[29,30].

Laute-Labreze et al in 2008 mention that the mean age of treatment onset was of 2-6 months[6], whereas Sans et al 2009[31] reported 4,2 months and 31 months; Theletsane et al 2009[32]-6 weeks; Mazereeuw-Hautier J et al. 2010[33]: 4 months; Bigorre et al 2009[34] 6 weeks-13 months; Leboulanger N et al 2010[35]; 5,2 months Vlastarakos et al 2012[36]: 5,1 months comparable to our results.

Christine Leauté -Labrèze et al 2008[6] reported a treatment duration with beta-blocker of 3-10 months, period comparable to our results. Thus, diagnosis was made in an efficient manner.

Aggravation under Propranolol treatment was encountered in 2 cases, one of which the dosage was diminished by caregivers (< 1 mg/kg/day) and the other in which we found no explanation. Compared to these, Bagazgoitia et al[37] found a relapse of 19% after ceasing treatment with Propranolol.

Even though there are pros and cons against Propranolol, our results encourage in prescribing and using Propranolol in children.

Conclusions

For the past 40 years, the use of Propranolol has been shown to be safe in children with cardiac disease. Even though Propranolol is the first intention for infantile hemangioma and congenital hemangioma, it is not recommended for capillary and venous malformations.

RCT should be developed to compare propranolol to corticosteroid therapy.

Ongoing research will bring us closer to the understanding of hemangiomas' formation, which will provide opportunities for personalized therapies.

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