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MANAGEMENT OF INFANTILE HEMANGIOMAS WITH PROPRANOLOL

LEČENJE DEČJIH HEMANGIOMA PROPRANOLOLOM

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Abstract

Infantile hemangiomas (IHs), are the most common benign, soft tissue tumors of infancy which affect between 4 and 12% of all Caucasian. The pathophysiologic mechanisms leading to endothelial cells proliferation and involution are poorly understood. Clinical appearance allows differentiation between focal, indeterminate and segmental IHs. Most IHs are small, harmless tumors that should be allowed to involute without treatment. Generally, treatment is instituted for complications within the IHs itself, or impairments caused by the hemangioma. Current treatment options are include corticosteroids, interferons, chemotherapy, laser, surgery, or combination of these therapies. Recently propranolol proved itself effective in inducing regression of growing hemangioma. Our report confirms prompt response of hemangioma to propranolol with no major side effects.

INTRODUCTION

Vascular anomalies of infancy and childhood are divided into two major categories: 1) tumors (most being hemangiomas) and 2) vascular malformations [1,2]. The typical infantile hemangiomas (IHs) appears postnataly and evolve through 3 predictable stages: a rapidly proliferating stage (generally lasting 8 to 12 months), followed by prolonged involuting phase (1 to 7 years), entering the involuted phase characterized by fibrofatty residuum [1,3]. Glucose transporter protein 1 (GLUT 1) is specific and useful immunohistochemical marker for IHs during all phases of these lesions [3,4].

Infantile hemangiomas are the most common benign, soft tissue tumors of infancy which affect between 4 and 12% of all Caucasian [1,5,6]. There is a 3:1 predilection for the female sex, and they are weakly associated with prematurity [6,8]. The pathophysiologic mechanisms leading to endothelial cells proliferation and involution are poorly understood [6]. Current theories focus on progenitor cells, development field defects, placental involvement, derangement of angiogenesis and mutations in the cytokine regulatory pathway [6,7]. Involution coincides with increased apoptosis of endothelial and stromal cells [7]. Most IHs involve the head and neck (up to 60%) [1,8].

Clinical appearance allows differentiation between focal, indeterminate and segmental IHs. Size, location and subtype were major factors that predicted complications and need for treatment [9]. Focal type had a tumor-like appearance, and a less common diffuse type had a segmental distribution pattern and plaque like appearance. Segmental IHs exhibit worse prognosis with more complications (ulceration, airway obstruction) [5,9].

Generally, treatment is instituted for complications within the IHs itself (such as ulceration, bleeding, infection), or impairments caused by the hemangioma (amblyopia, impaired breathing, feeding difficulties, heart failure), and the wait-and-see medical management policy for these hemangioma should be replaced by a more active approach [9,10,11]. The management

of hemangioma is an area of great controversy [6]. Current options are conservative treatment (corticosteroids, interferons, hemiotherapy), laser treatment, and surgical treatment (by lenticular excision, with a linear closure, or by circular excision and „purse-string closure") [6-16]. Recently propranolol proved itself effective in inducing regression of growing hemangioma. There are several reports confirming prompt response of hemangioma to propranolol with no major side effects [15-29].

CLINICAL OBSERVATIONS

Our protocol for use of propranolol was ground on protocol determined by Lowely at al and Sans et al [27,28]. A careful patient history and physical exam is performed, to ascertain risk factors or contraindications to using propranolol. We obtain basic laboratory findings, baseline vital signs including pulse and blood pressure, finger stick blood glucose. Patients underwent a cardiologic examination including clinical examination, electrocardiogram (EKG), blood pressure measurements, echocardiogram and abdominal ultrasound.

According to protocol, hospitalized infants received a starting dose of 0,17 mg/kg given at 8-hour intervals. Vital signs and blood glucose are monitored 1 hour after each dose, corresponding with peak absorption time. After first two dose well tolerated, the amount is doubled to 0,33 mg/kg/dose. After two more doses the propranolol is again doubled to 0,67 mg/kg/dose. This is equivalent of 2.0 mg/kg/day and this dose was divided three times daily. Frequent feeds, given every 3-4 hours are strongly encouraged. Dose adjustments (to weight), and patient assessments by telephone interaction or hospital visit were performed monthly. Propranolol was given until 12 months of age (end of proliferative phase). At the end of the therapy, gradual tapering of propranolol over 2 weeks was performed.

Case 1

A 40-days-old girl was referred to our department for a segmental hemangioma of the head and neck. The lesion began growing at 2 weeks of age, and on initial evaluation involved her anterior part of the neck, beard, lover lip, left orbital and frontal region, left temporal region and left retroaurical region (Fig 1. A,B). Laboratory findings were within the normal range. Cardiological exam revealed normal finding. Ophthalmological evaluation revealed partial visual field obstruction. Orbital ultrasound revealed hemangioma involving left upper eyelid and orbit up to 20 mm. Bronchoscopy revealed presence of hemangioma

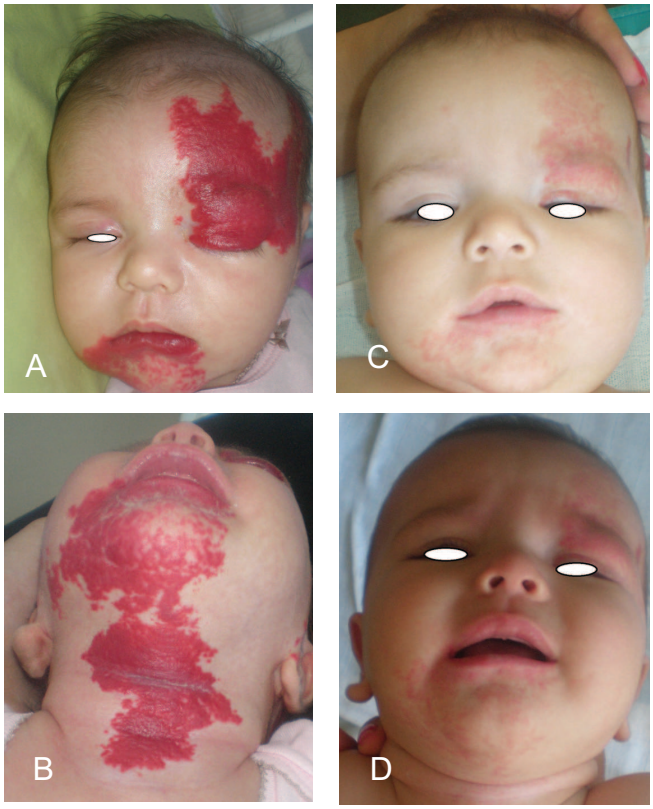

Figure 1. Segmental IH of the head and neck (A,B), the result after 4 months treatment with propranolol (C,D).

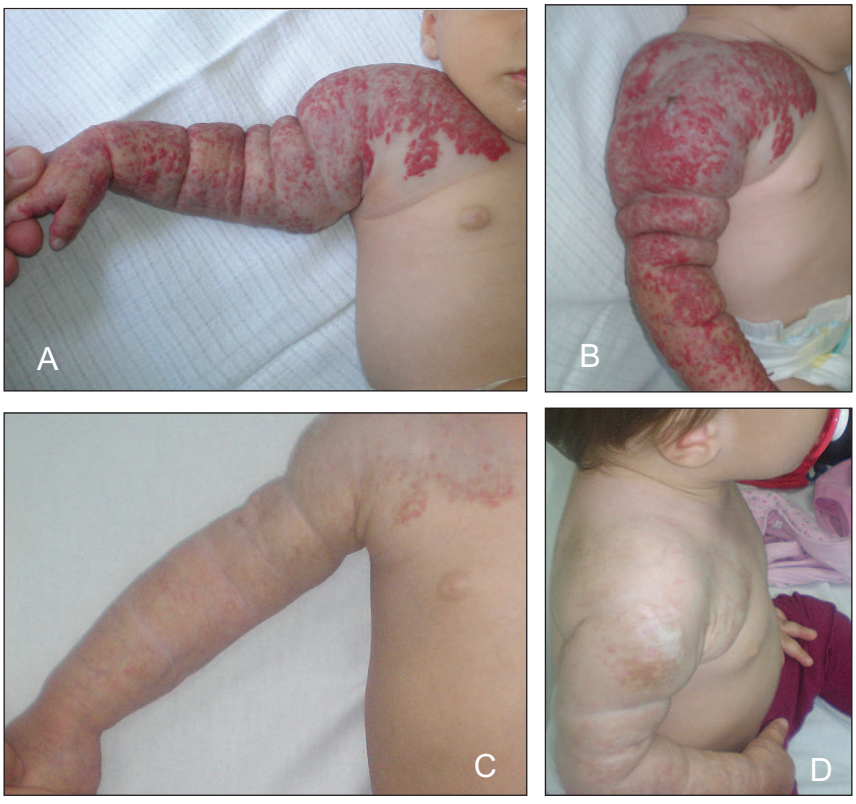

Figure 2. Segmental IH of the right upper extremity, right pectoral, deltoid and scapular region (A,B), the result after 8 months treatment with propranolol (C,D).

in supraglottic and transglottic area. Magnetic resonance imaging of the brain revealed no pathological findings. The propranolol was initiated by protocol. The result after 4 months treatment is presented at Fig. 1 (C,D).

Case 2

A 4 months and 20 days-old girl was referred to our department for a segmental hemangioma of right upper extremity, right pectoral, deltoid and scapular region (Fig. 2. A,B). The lesion began growing at 2 weeks of age. Standard diagnostic procedures by protocol were performed. Laboratory findings were within normal range. Cardiological evaluation revealed left ventricle hypertrophy. According to cardiologist there was no contraindication for propranolol treatment. The treatment with propranolol was initiated. The result after 8 months is presented at Figure 2. (C,D). There were no significant side effects. Cardiological evaluation revealed major regression of the left ventricle hypertrophy. After 8 months the therapy was ceased. There was minor sign of rebound growth, without need to restart the therapy.

DISCUSSION

There is currently no well-studied or Food and Drug Administration (FDA) - approved systemic therapy for IHs [27]. Each treatment option for IHs (corticosteroids, interferons, hemiotherapy, laser treatment, surgical treatment) has limited benefit with its own adverse-effect profile and risks [24]. Propranolol is a non-selective beta-blocker which has previously been used in young infants for a variety of indications, primarily for hypertension, supraventricular tachycardia, long Q-T syndrome, congestive heart failure, conditions where infants are often being treated in an inpatient hospital setting [16,20,29]. The use of propranolol in the treatment of IHs was serendipitously discovered in 2008 by Léauté-Labrze et al, with an attempt to treat the adverse cardiac effects in 2 children that developed as a result of high-dose systemic corticosteroids [15,21,25,27]. Since their initial report, propranolol has dramatically altered the management of IHs [16-21]. The explosion of Internet reports on this topic demonstrates how rapidly propranolol is being adopted worldwide for this indication [21].

Potential explanation for the therapeutic effect of propranolol on IHs include vasoconstriction, decreased expression of VEGF and bFGF genes and the triggering of apoptosis of endothelial cells[15]. Clinically apparent adverse effects occur in at least 18% of patient and include bradycardia, hypotension, hypoglycemia, bronchospasm, restless sleep, rash, gastrointestinal discomfort, fatigue [16,17,21]. All of this adverse effects are seen at dosses >2 mg/kg/day [19]. Most adverse effects were managed by decreasing the dose of propranolol [21,23,27]. For our 2 patients with segmental IHs, treatment with propranolol was very effective, without any relevant adverse effects.

To determine the safety profile and true value of propranolol as a first line therapy for IH, clinical investigators must 1) carefully monitor patients and initiation of therapy until they are tolerating the medication, 2) determine the success of therapy by objective means and in relationship to early outcome, and 3) prospectively collect and report adverse effects [21].

CONCLUSION

Propranolol administrated orally at 2 to 3 mg/kg per day had a rapid therapeutic effect in most of the cases with a significant regression without any relevant adverse effects. Our experience supports other reports indicating that propranolol is remarkably effective drug for treating IHs. Clearly, a controlled prospective trial is requisite to determine practice standards for medical therapy of hemangiomas based on long-term outcomes of safety and efficacy with -blockers compared with other medications.

Apstrakt

Dečji hemangiomi (DH) predstavljaju najčešće, benigne, mekotkivne tumore dečjeg uzrasta koji se javljaju kod 4 do 12 % bele populacije. Patofiziološki mehanizmi koji vode do proliferacije endotelnih ćelija i njihove involucije se slabo poznati. Klinička prezentacija omogućava diferencijaciju između fokalnih, nedefinisanih i segmentnih DH. Najveći broj DH su mali, bezopasni tumori kojima treba dozvoliti da se spontano povuku bez terapije. Lečenje se uglavnom primenjuje kod komplikacija koje se javljaju na samim hemangiomima, ili kod poremećaja koji su uzrokovani od strane hemangioma. Sadašnje opcije u lečenju hemangioma su: primena kortikosteroida, interferona, hemioterapija, tretman laserom, hirurško lečenje, ili kombinacija ovih terapija. U novije vreme propranolol se pokazao kao veoma efikasan lek, izazivajući smanjenje hemangioma koji je u fazi rasta. Naš rad potvrđuje brzi odgovor hemangioma na propranolol, bez značajnih neželjenih efekata.

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