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CLINICAL CASE OF TREATMENT OF HEPATIC HAEMANGIOMA BY PROPRANOLOL IN THE NEWBORN

Clinical observation of conservative treatment of the left hemi-liver haemangioma by propranolol in the full-term newborn with initial symptoms of cardiac failure is presented. Extensive hepatic haemangioma was diagnosed prenatally on the 23–24th week of a gestation. After the birth the clinical diagnosis was confirmed by means of ultrasound investigation (the size — 50×30 mm) and by the data of computer tomography. The starter dose of propranolol made 0.5 mg/kg per day with further increase to 1,5 mg/kg per day; the preparation was prescripted at the age of 2 days of life. Episodes of decrease in cardiac rate to 95 b/min are noted among side effects. The child was dismissed for out-patient observation at the age of 12 days of life in a stable state. The positive dynamics is registered during ultrasound investigation in 6 months after initiation of treatment: lesion was significantly decreased in the size, and there was a considerable decrease in a blood flow. Treatment by propranolol in a dose of 1,5 mg/kg per day was continued. Modern data on possible mechanisms of propranolol effect at haemangiomas in children, regimen, side effects and complications are provided in discussion. It is noted that this drug can be considered as the agent of choice in the treatment of infantile haemangiomas in children of difficult localization since the neonatality period.
Keywords: *hepatic haemangioma, propranolol, newborns.*

Introduction

Liver tumors constitute ca. 5% of all the tumors of fetuses and neonates. The most frequently observed liver tumors are vascular tumors and mesenchymal hamartomas, although malignant hepatoblastomas may develop [1, 2]. The diagnosis may be suspected antenatally with ultrasound or nuclear magnetic resonance imaging; however, precise intrauterine diagnosis may be complicated. Liver tumors may be associated with polyhydramnios and fetal hydrops; postnatal clinical symptoms include abdominal dilation (47.4%), heart failure (35-47.4%), consumption coagulopathy (42.1%), respiratory failure (31.6%); more than 70% of the patients develop hypothyroidism. Mortality at infantile liver hemangioma is 15.6-17.0% [2-5].
Vascular liver tumor is a rare localization for infantile hemangioma; it is usually represented by formations of skin and subcutaneous fat. Infantile hemangiomas are soft tissue tumors observed in 4-10% of infants (the boys/girls ratio is 2.5-4/1). Infantile hemangiomas are characterized by a certain development staging: the quick hemangioma growth stage is observed within the first postnatal weeks; it lasts for 3-6 (sometimes up to 24) months. Then the condition stabilizes for several months. Slow tumor involution is observed in the subsequent 1-5 years, in the course whereof cellular elements are replaced by fibrotic and adipose tissue. Complete regression is observed by the age of 4 years in 60% of the patients, by the age of 7 years – in 76% of the patients. Ca. 10-12% of the children with infantile hemangiomas require treatment at the proliferative stage due to the life-threatening localization of the tumor (respiratory tract or liver), development of local complications (hemorrhages, ulcerations, necroses) or organ malfunctions (vision) [6, 7].

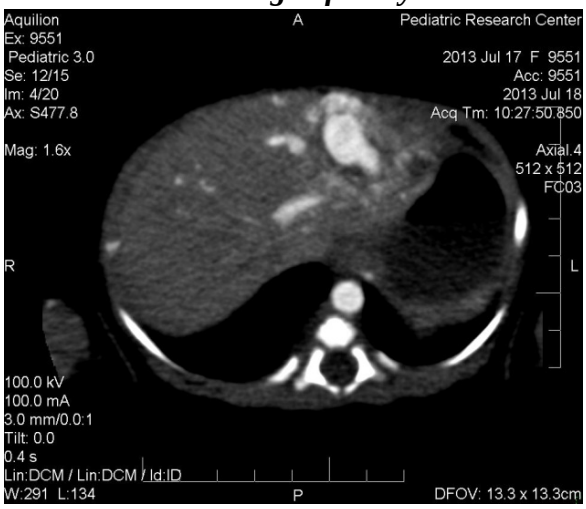
Clinical case

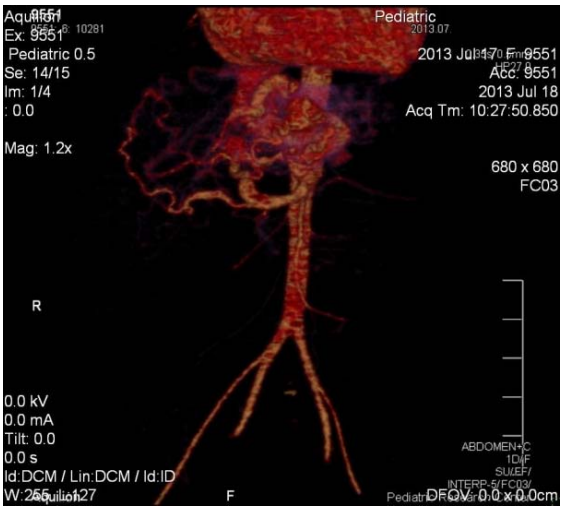
We would like to present a case of conservative propranol treatment of a large liver hemangioma in a neonate.

The girl of the first pregnancy, the first operative delivery at the term of 38-39 weeks, body weight – 3,626 g, length – 52 cm, Apgar score – 8/8. The fetus was diagnosed with hemangioma of the left hepatic lobe in the 23rd-24th gestational week with ultrasound examination. Immediately after birth, the child's condition was estimated as moderate, due to respiratory failure (tachypnea caused by delayed resorption of fetal lung fluid) and neurological symptoms (central nervous system excitation syndrome).

At the age of 6 hours, the child was admitted to the neonatal surgery and resuscitation unit of the Scientific Center of Children's Health (Moscow). Ultrasound examination identified a 50x30 mm heterogenous nodular formation with indistinct boundaries and multiple enlarged (1.5-7 mm) convoluted vessels; high blood flow rate (108 cm/s) in the upper hepatic enlarged convoluted vein. Echocardiography identified enlargement of the right heart (right atrium – 18 mm, right ventricle – 13 mm) and the aorta (12 mm on the sinus level); normal systolic function (systolic discharge – 9.23 ml, Teicholz ejection fraction – 0.6). Electrocardiogram: right deviation of the cardiac electric axis, delayed intraatrial conduction, moderate repolarization disorders, physiological prevalence of the right ventricular myocardium. Computed tomography revealed a supernumerary space-occupying hepatic lesion represented by a vascular component: convoluted and drastically enlarged vascular loops up to 8 mm in diameter (abdominal aorta is 8.5 mm in diameter on this level) were visualized in the left hepatic lobe region and in segment IVa and b of the right hepatic lobe; accumulation and removal of the contrast agent thereby do not differ from accumulation and removal of the contrast agent by aorta and other normally located arteries; irregular-shaped hypodense areas with irregular indistinct boundaries (13 x 12 x 10 and 8.5 x 4 x 4.5 mm) – apparently, cystic cavities – were visualized in segment III (pic. 1).

Pic. 1. ***NMRI at the age of 1 day***





Taking into consideration large size of the lesion and initial symptoms of heart failure, the council of physicians concluded to start propranol treatment. First, we obtained written informed consent of the parents to prescription of the drug and approval of the establishment's Ethics Committee. At the age of 2 days, the child was prescribed propranol orally in the initial dose of 0.5 mg/kg per day (in 2 intakes) with subsequent dose increase by 0.5 mg/kg per day every 2 days up to 1.5 mg/kg per day. We also monitored heart rate and arterial pressure, respiratory rate and glycemic level. We observed episodes of heart rate reduction down to 95 bpm in the setting of the therapy employing β-blockers; arterial pressure remained stable. Control electrocardiography performed after 3 days of treatment registered the heart rate of 109 bpm. According to ultrasound examination, hepatic lesion remained stable after 1 week of propranol therapy; echocardiography registered persisting high pressure in the pulmonary artery (36 mm Hg). The child was discharged for outpatient observations at the age of 12 days in a stable condition.

Control computed tomography performed 3 months after the examination of 18.07.2013 revealed ambiguous dynamics in the form of narrowing of hepatic arteries and enlargement of the space-occupying lesion (pic. 2). The propranol dose was corrected – increased up to 3 mg / 12 hours under hourly heart rate control, arterial pressure control every 3 hours and glycemic level control once per 2 days.

Pic. 2. ***NMRI at the age of 3 months***

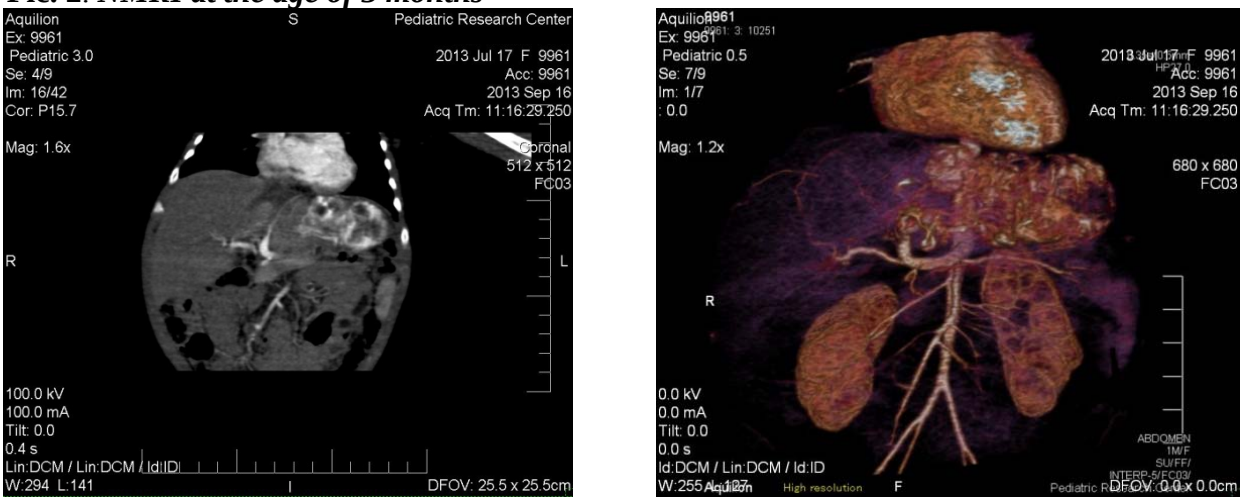


Table. ***Dynamics of several laboratory parameters of the child***

Parameter	1 day of life	1.5 months of life	6 months of life	Unit of measurement
Hemoglobin	171	94	109	g/l
Platelets	248	380	328	10^9/l
ALT	8	32	19	U/l
AST	26	25	29	U/l
GGT	152	53	14	U/l
α-fetoprotein	> 2,479.34	-	186.34	MU/l
Glucose	3.33	4.7	4.91	Mmol/l

Ultrasound examination of abdominal organs after 6 months of therapy revealed 2 heterogeneously-structured space-occupying tissular lesions in the left hepatic lobe: 12 (with blood flow) and 14 mm (no blood flow observed) in diameter. Both lesions were located subcapsular. Echocardiography revealed that morphometric and functional parameters of the heart were within the normal range. Follow-up monitoring observed considerable reduction in α-fetoprotein concentration, whereas the activity of hepatic enzymes and the platelet count remained within the normal range. We did not observe glycemic episodes throughout the treatment. The child's condition at the age of 6 months was considered satisfactory: physical and neuropsychic development were age-adequate. Propranol treatment in the dose of 1.5 mg/kg per day was resumed.

Discussion

Variants of treatment at liver hemangiomas include expectant management, pharmacological therapy (steroidal hormones, interferon α-2a, vincristine, propranol), surgical resection, embolization/ligation of the hepatic artery and liver transplantation [2, 3].

Successful surgical treatment of infantile liver hemangiomas had been primarily reported until 1990 [8-11]: since then, surgical treatment has only been employed if the conservative treatment proved ineffective [3]. R.D. Ranne reported on partial hepatectomy in two neonates, which required intraoperational connection of the cardiopulmonary bypass pump [8]. It has been

demonstrated that ligation and embolization of hepatic vessels have only limited effect in some cases: patients may require more than one embolization (the average number of procedures - 2 [1-6]), whereas the survival rate is 66.7% [3, 9-11].

Pharmacological therapy has been commonly acknowledged as a primary type of therapy during the proliferative phase of infantile hemangiomas. Treatment with steroidal hormones has until recently been the first-choice therapy for critical hemangiomas of any localization in children. I. Yeh reported on successful treatment of liver hemangiomas with steroidal hormones in combination with vincristine or propranol on four children [4]. J. Morris reported on successful prenatal glucocorticoid therapy of infantile hemangioma in a fetus at the term of 28 weeks [12]. However, treatment with steroidal hormones is not always effective: T. Kuroda et al. reported on 23.1% of the patients (n = 19) with infantile liver hemangiomas, who were completely unaffected by the therapy [3].

The first communication of propranol effect on infantile hemangioma reduction acceleration was reported by French doctors from a pediatric hospital in Bordeaux in 2008 [13]. Further clinical use of propranol for treating hemangiomas of varying localization demonstrated an almost immediate effect, low risk of side effects and the best effect in terms of tumor regression in comparison with other drugs [14, 15]. Only one study cites data on successful propranol therapy at liver hemangiomas in 8 neonates [16]. However, the mechanism accounting for this effect is unknown. The issues of optimal dosage and treatment duration also remain open. The data provided by the expert council in Chicago in 2011 introduce some clarity in this regard [5]. The hypotheses regarding possible propranol modes of action at infantile hemangiomas include vasoconstriction, reduced renin production, angiogenesis inhibition and apoptosis stimulation [5, 6, 17].

The recommended initial dose is 0.5-1 mg/kg per day; the optimal therapeutic dose is 2 (1.5-3) mg/kg per day (in 2-3 intakes). The therapy continues for 4-8 months or until the end of the proliferative phase or until tumor disappearance. Possible regrowth of the hemangioma after propranol withdrawal within 0-6 months has been reported for 6.7-19% of the cases [5, 18]. In our case, we started treatment with the dose of 0.5 mg/kg per day (in 2 intakes) under continuous monitoring of hemodynamic parameters and gradual dose increase up to 1.5 mg/kg per day. We decided against further drug dose increase due to the tendency to heart rate reduction.

Propranol contraindications for infantile hemangiomas include prematurity, the age under 2 weeks, congenital heart diseases (when β-blockers are contraindicated), obstructive bronchites, central nervous system disorders and renal diseases [19]. According to the published literature, the youngest child to start undergoing propranol therapy was 3 weeks of age [18]. The treatment we started in child with liver hemangioma at the age of 2 days was based on the presence of symptoms of incipient heart failure in the setting of a large-sized lesion and generally stable condition of the girl.

Literature sources report that side effects of propranol treatment of hemangiomas in children include hypotension (2.8-14.5%), pulmonary symptoms (1.4-8.0%), hypoglycemia (0.9-11.4%), bradycardia (0.9-8.7%), sleep disorders (3.7-13.5%), sleepiness (2.2-11.8%), extremity coldness (1.7-8.9%), diarrhea (0.8-17.0%) and gastroesophageal reflux (0.7-6.0%). There were also reports on 2 cases of hyperkalemia [15]. Propranol affects hemodynamics more than anything else and thus requires dose monitoring in the tittering process: the propranol effect on heart rate and arterial pressure in the event of oral intake is maximal 1-3 hours after the drug intake (bradycardia is registered in neonates if the heart rate is below 70 bpm, hypotonia – if the systolic arterial pressure is below 57-64 mm Hg). To prevent hypoglycemia, it is recommended to administer propranol in the afternoon and eat immediately after the intake thereof. Parents must be informed on the possible development of hypoglycemia and provide the neonate with food at least every 4 hours [5, 7, 19]. In this clinical case we observed a tendency to bradycardia; we registered no other adverse effects of propranol.

Conclusion

Most studies confirm excellent effect and good tolerability of propranol treatment in infants, including neonates; this drug has been suggested as a drug of choice for infantile hemangiomas [5, 7, 19, 20]. However, propranol remains off-label for treating infantile hemangiomas all over the world. The propranol application protocol for infantile hemangiomas in neonates and infants is being developed; researchers continue analyzing safety and remote effects of the therapy and accumulate experience of using the drug at hemangiomas of rare localization.

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