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Letter to the Editor

Treatment of Symptomatic Focal Hepatic Hemangioma with Propranolol in Neonates: Is It Efficient?

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ABSTRACT

Hepatic hemangiomas (HH) – classified into congenital hepatic hemangiomas (CHH) or infantile hepatic hemangiomas (IHH) – are benign vascular tumors that are mainly asymptomatic, but may cause clinical problems that require treatment. While focal, multifocal, and diffuse IHH are responsive to propranolol treatment, CHH is mainly focal and thought to be resistant to treatment with propranolol. The clinical and imaging distinctions between CHH and IHH in cases of focal lesions can be challenging, while histopathological distinction is mostly lacking in the clinical setting. We report 4 neonatal symptomatic cases of focal HH treated with propranolol, with partial or complete resolution of the tumor, and the positive hemodynamic effect of propranolol in one case. We believe that although clear differentiation cannot be achieved between CHH and IHH without histopathological examination in cases of focal HH in neonates, propranolol treatment should be attempted in symptomatic cases since its benefits outweigh the possible small risk of side effects of propranolol.

Keywords: Liver; Hemangioma; Infantile hemangioma; Congenital hemangioma; Propranolol; Newborn

INTRODUCTION

Hepatic hemangiomas (HH) are the most common benign liver tumors in neonates. According to the International Society for the Study of Vascular Anomalies (ISSVA), liver vascular tumors in infants are classified as congenital hepatic hemangiomas (CHH) or infantile hepatic hemangiomas (IHH) [1,2]. Although clear guidelines for the evaluation and monitoring of HH based on the ISSVA classification have been published [1], there is much more uncertainty regarding the best treatment algorithm. For asymptomatic HH, observation only is advised, whereas other therapeutic options (medication, interventional, and surgical procedures) are possible for symptomatic lesions [3,4].

Conflict of Interest
The authors have no financial conflicts of interest.

The currently proposed treatment algorithm is based on the pattern of presentation of HH (focal, multifocal, and diffuse) [3], which has been well described by researchers of the Liver Hemangioma Registry (LHR) of Boston Children's Hospital [5,6]. The initial medical treatment for multifocal and diffuse HH, most commonly IHH, is propranolol; embolization is an alternative treatment for these HHs in cases of problematic shunting. For focal HH that is mostly assumed to be CHH, drug treatment is not recommended; in cases of shunting with high flow and high output cardiac failure, embolization [3], or alternatively steroid treatment or surgical excision is proposed [4,6,7]. Considering the successful management of focal HH with propranolol reported in the literature [8-13], we believe that the current treatment recommendations for focal HH should be redefined.

Over a 10-year period (2010–2020), 15 neonates were diagnosed with HH at Ljubljana University Children's Hospital. Eleven of them were asymptomatic; in 10 patients, HH was a coincidental finding on abdominal ultrasonography (US), and in one patient, US was indicated due to multiple small infantile hemangiomas (IH) of the skin. Four neonates, all with focal HH, were symptomatic and treatment with propranolol was initiated. None of the patients had relevant histopathological type verification, and an exact classification into CHH or IHH was not possible. Age at presentation, presenting symptoms, diagnostic procedures, tumor location and size, treatment, and outcomes are presented in **Table 1**. Informed signed consent was obtained from all parents. This study was approved by the National Medical Ethics Committee (No. 0120-546/2020/4).

Case 1

The first patient was a full-term male neonate, who developed signs of respiratory distress and infection after birth. Initially, his clinical status normalized after antibiotic treatment, but he later developed feeding problems, reflux, tachypnea, high blood pressure, and appeared to be in pain. On the 17th day of life, a palpable mass was detected in the epigastrium on physical examination. Abdominal US, which had been performed previously at 3 days of age and reported to be unremarkable, later revealed a hypervascular lesion bulging from the left hepatic lobe. Abdominal magnetic resonance imaging (MRI) confirmed the diagnosis of a hepatic hemangioma (3×4×5 cm) compressing the stomach. Laboratory results and echocardiograms were normal. Histopathological results from the needle biopsies were not diagnostic. Propranolol was administered (maximum dose, 2 mg/kg/day). After 5 days of therapy, clinical improvement was observed, and analgesic treatment was discontinued. The infant's subsequent growth was normal, and total regression of the HH was observed at 9 months of age.

Case 2

The second patient was a male neonate. Pale appearance, petechia, and cephalic and back hematomas were observed in the first hours of life. Due to anemia (hemoglobin [Hb] 9.5 g/dL) and severe thrombocytopenia (platelet count, 7×10^9/L), the laboratory tests were extended, revealing abnormal coagulation results, in accordance with disseminated intravascular coagulation. The cephalohematoma enlarged significantly, and symptomatic treatment with blood components was indicated. Abdominal US showed a large HH (6.5×4.5×3.5 cm), which was confirmed via MRI. The increase in HH size was measured over the first five days of life. After clinical stabilization, propranolol (maximum dose 2.5 mg/kg/day) was started at 4 days of age. After the introduction of propranolol, severe thrombocytopenia resolved, while moderate asymptomatic thrombocytopenia persisted for 2 more months. Initially, the HH showed no regression in size; nevertheless, treatment with

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pghn

Table 1. Clinical characteristics of neonates with hepatic hemangiomas hospitalized at the Department of Neonatology, University Children's Hospital, Ljubljana, between 2010 and 2020

No.	Initial finding	Sex	GA (weeks)	BW (g)	Age at diagnosis (days)	Diagnostic procedures	Size (mm)	Localization	US characteristics	Laboratory tests	Complications	Therapy	Follow-up findings
1	Multiple skin hemangiomas	M	37	4,170	17	US Doppler, MRI with contrast, cardiac ultrasound	20×20, 17×17, 10×10 mm	Multifocal, plus spleen and pancreatic hemangioma	Hypoechogenic, well-defined	Elevated GGT and bilirubin	Cholestasis	Ursodiol	Normalization of laboratory tests after 3 mo, complete regression within 18 mo
2	Incidental finding during US	M	38	2,780	2	US	13×9 mm	Focal, R	Hypoechogenic, with peripheral vessels	N	/	/	Complete regression within 6 mo
3	Incidental during US	M	34	2,830	2	US	17×21×10 mm (after diagnosis increase, max 24×17×26 mm)	Focal, R	Hypoechogenic, lobulated, well-defined, with peripheral vessels	Elevated GGT	/	/	Complete regression within 18 mo
4	Palpable abdominal mass, feeding difficulties, pain, tachypnea	M	41	3,440	17	US Doppler, needle biopsy, MRI with contrast	27×38×48 mm	Focal, L	Well-defined, highly vascularized lesions	N	Feeding difficulties due to stomach compression	Propranolol	Complete regression within 12 mo
5	Incidental finding during US	M	39	3,000	1	US	33×30 mm (after diagnosis increase, max 41×30×26 mm)	Focal, L	Hyperechogenic	Thrombocytopenia (PLT 104 $\times 10^9$/L)	/	/	Complete regression within 12 mo
6	Incidental finding during US	F	40	3,590	4	US	8 mm	Focal, L	Hyperechogenic	Thrombocytopenia (PLT 114 $\times 10^9$/L)	/	/	Complete regression within 6 mo
7	Incidental finding during US	F	32	2,160	4	US	20 mm	Focal, L	Hypoechogenic, lobulated, with calcinations	N	/	/	Complete regression within 6 mo
8	Incidental finding during US	M	29	990	93	US	do 10 mm (after diagnosis slight increase 13×13 mm)	Multifocal, R	Hyperechogenic	N	/	/	Complete regression within 12 mo

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Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Table 1. (Continued) Clinical characteristics of neonates with hepatic hemangiomas hospitalized at the Department of Neonatology, University Children's Hospital, Ljubljana, between 2010 and 2020

No.	Initial finding	Sex	GA (weeks)	BW (g)	Age at diagnosis (days)	Diagnostic procedures	Size (mm)	Localization	US characteristics	Laboratory tests	Complications	Therapy	Follow-up findings
9	Incidental finding during US	M	33	2,760	5	US	26×15×20 mm	Focal, R	Non-homogeneous echostructure	N	/	/	Regression with residual calcinations within 30 mo
10	Pallor, petechiae, hematoma of the back, cephalohematoma	M	40	3,710	1	US Doppler, MRI, cardiac ultrasound	65×45×35 mm (after diagnosis increase, max 77×67×47 mm)	Focal, L	Non-homogeneous echostructure, small necrotic parts	Anemia (1st day of life min Hb 9.5 g/dL), thrombocytopenia (min PLT 7×10^9/L), elevated D-dimer (max 40,227 µg/L), abnormal coagulation tests (APTT: max 43.6 s; TT: max 70 s; fibrinogen: min 0.4 g/L),	Persistence of thrombocytopenia and hypofibrinogenemia up to 2.5 months of age	Thrombocyte, erythrocyte and plasma transfusion, propranolol	Complete regression after 12 mo of therapy
11	Incidental finding during US	M	40	3,800	5	US	7 mm	Focal, R	Hyperechogenic	N			Complete regression within 6 mo
12	Incidental finding during US	M	40	3,260	5	US	7 mm	Focal, R	Hyperechogenic, well-defined	N	/	/	Complete regression within 6 mo
13	Incidental finding during US	M	41	3,470	10	US	7 mm	Focal, R	Hyperechogenic, well-defined	N	/	/	Complete regression within 6 mo
14	Palpable abdominal mass, anemia	F	36	2,610	10	US Doppler, US and MRI with contrast, cardiac ultrasound	35×45×48 mm (after diagnosis increase, max 33×57×60 mm)	Focal, L	Non-homogeneous, mostly hyperechogenic	Anemia (min Hb 8.8 g/dL)	/	Propranolol	Partial regression till 24 mo (5×15 mm)
15	Palpable abdominal mass, hyperdynamic precordium, petechiae	M	39	3,720	0	US Doppler, US and MRI with contrast, cardiac ultrasound	32×60×62 mm (after diagnosis increase, max 29×72×73 mm)	Focal, L	Non-homogeneous, highly vascularized lesions, small necrotic parts	Thrombocytopenia (min PLT 23×10^9/L), abnormal coagulation tests (APTT: >160 s, TT: >150 s; min fibrinogen: 1,0 g/L), elevated CK-MB (max 52,9 µkat/L) and NT-proBNP (max 23,150 ng/L).	High-output cardiac failure	Thrombocyte transfusion, propranolol	After propranolol therapy recovery of cardiac function and partial regression of hemangioma.

GA: gestational age, BW: birth weight, US: abdominal ultrasound, M: male, F: female, MRI: magnetic resonance imaging, R: right, L: left, GGT: gamma-glutamyl transferase, N: normal, min: minimum, max: maximum, PLT: platelet, APTT: activated partial thromboplastin time, TT: thrombin time, Hb: hemoglobin, CK-MB: creatine kinase-MB, NT-proBNP: N-terminal pro-brain natriuretic peptide.

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propranolol was continued, and regression of the tumor was noted after 6 months of life. At 12 months, total regression of HH was confirmed.

Case 3

The third patient was a female neonate who was evaluated for anemia (Hb 10.3 g/dL at 24 hours of life) after birth. At 10 days of age, a painless abdominal mass was palpated below the lower left costal arch, which was clinically diagnosed as splenomegaly. Abdominal US and MRI showed a hypervascular lesion (5×4.5×3.5 cm) bulging from the left hepatic lobe. Coagulation tests and thrombocyte counts were normal. The anemia could not be explained by extended evaluation; therefore, treatment with propranolol (max 3.5 mg/kg/day) was started at the age of three weeks. Abdominal US showed gradual regression after 2 months. Anemia resolved at 4 months of age, and at 18 months of age the size of HH was reduced to 2×1 cm.

Case 4

The fourth patient was a male neonate who presented with hypotonia, petechiae, tachypnea, and hyperdynamic precordium at birth. The thrombocyte count was significantly reduced (platelet count, 23×10^9/L), and the coagulation tests were pathological. Newly formed petechiae and suffusions appeared within the first 24 hours after birth, and platelet transfusion was indicated. Abdominal US showed a HH (6×6×3 cm) with an arteriovenous fistula, which was confirmed by contrast-enhanced US. Signs of high-output cardiac failure were present, and an echocardiogram showed a dilated right atrium and right ventricle, and mild dilatation of the left ventricle. N-terminal pro-brain natriuretic peptide (NT-proBNP) was elevated. At two days of age, propranolol was started (2 mg/kg/day), hemodynamic improvement was noticed with normalization of the results of clinical and echocardiographic examination, and proBNP levels decreased. A gradual reduction in the size of the HH was noticed over several months, and at 12 months of age, the HH lesion was 5.5×3.5×3 cm in size but showed no vascularization on Doppler US.

DISCUSSION

Liver hemangiomas are classified as CHH or IHH [1,2]. Clinically, they are distinguished by their presentation and clinical course; presence of the histopathological marker glucose transporter type 1 (GLUT-1) is characteristic of IHH [5]. Current treatment algorithms are based on the clinical picture and pattern of HH presentation. Historically, steroids were the most commonly used medication for hemangiomas, but since the introduction of propranolol in 2008 for the treatment of cutaneous IH, it has become an important treatment modality for IHH as well [8,9,14-16]; IHH is thought to present as multifocal or diffuse HH, while focal HH is supposed to be CHH.

We describe successful treatment with propranolol in 4 neonates with symptomatic focal HH. However, histopathological analysis was not performed in any of the cases, and the exact subtypes (CHH or IHH) could not be verified. In two patients (cases 1 and 3), HH was diagnosed later after birth (at 10 and 17 days of life). In both cases, HH grew postnatally, which is characteristic of IHH. In case 1, clinical improvement and size reduction were noticed soon after the introduction of propranolol treatment, whereas in case 3, size reduction was more gradual.

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In two patients (cases 2 and 4), HH presented at birth, and this feature is characteristic of CHH, which does not react to propranolol. Despite this typical characteristic of CHH, an increasing size (more pronounced in case 2) after birth was noted, and this feature is a characteristic of IHH. Interestingly, severe thrombocytopenia was observed in both cases. After the introduction of propranolol, gradual regression in size was detected in both cases. We cannot claim that the reduction in size was an effect of propranolol or the HH's clinical course alone, as a naturally occurring reduction in size in the case of CHH may be expected [17]. However, we can certainly confirm that hemodynamic improvement and thrombocyte normalization in case 4 were observed after the introduction of propranolol, while the severity of thrombocytopenia decreased after propranolol treatment in case 2.

According to our experience and reports of successful treatment of focal HH with propranolol in the literature, limiting propranolol treatment to only multifocal and diffuse HHs seems too restrictive.

Data from the LHR showed that no focal HHs expressed GLUT-1 (n=0/8); therefore, they were classified as CHH, which does not respond to propranolol treatment [5]. According to these data, medical treatment for focal HHs is not rational. The findings of Ernst et al. [10], who reported 7 cases of HHs, disagree with data from the LHR. Their data showed that 2 of the 5 focal HHs were positive for GLUT-1, reflecting the characteristics of IHH. These two hemangiomas were diagnosed in newborns three days after birth, which is a typical clinical feature of CHH. If histopathological staining was not performed, the clinical information about the early presentation in these two cases could lead to the wrong conclusion that they were CHH. Although some of the reported successful medical treatment of focal HHs may not be entirely attributed to treatment, since some focal HHs may actually be rapidly involuting CHHs, which feature naturally occurring involution [17], the data from German research suggest reasons for propranolol treatment of symptomatic focal HHs.

With new insights into the biology of IH, our understanding of the mechanisms of the action of propranolol has improved. The proposed mechanisms of action involve modulation of the renin-angiotensin system, vasoconstriction, inhibition of angiogenesis, and promotion of endothelial cell apoptosis [18]. Although these mechanisms have not been evaluated in congenital hemangiomas, some of the successes of propranolol treatment in symptomatic focal HHs, such as improving the hemodynamic condition of the neonate, may be attributed to them.

CONCLUSION

Many studies have confirmed the efficiency and safety of propranolol treatment for IH in infants, while congenital hemangiomas are said to be unresponsive to propranolol. Despite some typical clinical characteristics of CHH and IHH, the occasional overlap in clinical presentation makes exact subtype classification possible only through histopathological examination. Since biopsy carries the risk of bleeding, this diagnostic procedure is seldom performed, and subtype verification is missing in clinical settings. According to the LHR, focal HHs are considered CHHs, and propranolol treatment is not recommended. In addition to our case series, there are many other reports of the successful treatment of focal HHs with propranolol. These reports, in addition to those of focal HHs expressing GLUT-1, a typical marker of IHs, suggest reasons for questioning the proposed treatment algorithms. We believe that although subtype verification is not confirmed in cases of symptomatic focal

HHs, propranolol may be used as a first-line treatment in these neonates, as the minor risk of side effects of propranolol is outweighed by its possible benefits. The goal of propranolol treatment in symptomatic cases is not only tumor size reduction but also hemodynamic and hematological normalization. More studies are needed to confirm the treatment efficacy of propranolol in symptomatic focal HHs in neonates, and the development of noninvasive markers for better differentiation between IHHs and CHHs would be appreciated.

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