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Cardiac side effects of propranolol in infants treated for infantile haemangiomas

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Original Article

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Abstract

Objectives: This study aims to add proof to the safety profile of propranolol as first-line choice in treating infantile haemangiomas, in particular related to its cardiac side effects the main hindering reason for parents and physicians to start and comply with treatment. *Method:* This is a prospective observational and analytic study with a sample of 476 patients diagnosed with infantile haemangioma and treated with systemic propranolol during the time interval January 2011 to December 2021. We studied clinical propranolol adverse events experienced in hospital or outpatient and measured the impact of propranolol on blood pressure and heart rate. *Results:* This study showed that symptomatic adverse events caused by propranolol were mild and severe adverse events were rare. The most common clinical side effects were paleness, sweating, reduced feeding, and agitation. Only in 28 (5.9%) cases these symptoms were severe enough to review treatment, 1.8% had severe respiratory symptoms, 2.7% experienced hypoglycaemia, and 1.2% had heart-related symptoms. Mean blood pressure reduction with treatment was statistically significant only after achieving the maintenance dose 2 mg/kg body weight. Blood pressure under the 5th percentile was registered in 2.9% of cases, but only four patients had symptomatic hypotension. While heart rate reduction was noticed with the first dose, only two experienced symptomatic bradycardia. *Conclusion:* We conclude that propranolol is not only an excellent drug in treating infantile haemangioma, but it has also a very safe profile, with mild side effects and very rare severe cardiac adverse events, easily overcome with treatment interruption.

Infantile haemangiomas are vascular tumours characterised by an abnormal endothelial cell proliferation producing an aberrant vascular architecture.[1,2] Unlike other tumours, infantile haemangiomas have a proliferative and an involution phase. In most of the cases, there are found solitary lesions, but in 20% of them, they can be multiple and in multiple lesions is also increased the possibility of having visceral accompanying lesions. In 60% of the cases, the lesions are located on the head, but they are barely visible after birth and start to grow rapidly during the first weeks by achieving 80% of final dimension on the third month.[3] Infantile haemangiomas are the most common tumour of paediatric age with an incidence of 4–5%.[4,5,6]

Treatment is indicated in case of large haemangiomas that have tendency to complicate, affect organ function or have tendency to ulcerate, or cause scarring and disfigurement. If haemangiomas will be left on their natural course, it is observed in different studies that they will complicate in 10–20% of the cases.[6,7,8] Infantile haemangiomas started to be treated in 1960 at the beginning with steroids given systemically or by intralesional injection. In case of resistance to treatment, interferon α was added in 1980. However, both of these regiments if used for long time have undesired side effects, and efficacy was very variable.[9,10] In 2008, Leaute-Labreze and her collaborator noticed incidentally the effect of propranolol used for cardiac indications on reduction of infantile haemangiomas.[1] This led to initiation of large observational studies and randomised clinical trials that proved the efficacy and safety of propranolol for treating infantile haemangiomas and made it the first choice in treatment protocols.[6,11,12] Propranolol acts in haemangiomas through vasoconstriction, inhibition of angiogenesis, and promotion of apoptosis.[13,14,15,16,17] Through it β-non-selective blocking action (β_1 and β_2) propranolol reduces heart rate heart rate and blood pressure blood pressure, but many studies showed that these effects were not severe.[6]

The Consensus Conference of 2011 issued a protocol on how to use propranolol in treating infantile haemangioma as well as recommendations for each step, starting with pre-treatment investigation, treatment approach, the dosage and its escalation as well as the follow-up schedule.[5,12,18]

Propranolol was introduced for the first time to treat infantile haemangiomas in Albania in 2010 from the paediatric cardiologic team and while evidence of efficacy and safety was growing, it became the treatment of choice.

Table 1. BP and HR mean before, 2 hour, and 2 weeks after treatment in age groups.

Age group (nr)	Baseline			2 hours after			2 weeks after			p *BPs b- 2w*
	BP sys	BP dia	HR	BP sys	BP dia	HR	BP sys	BP dia	HR	
1–6 mo (341)	84.6 (±7.3)	46.9 (± 8.3)	138 (±15.4)	85.2 (± 8.5)	47.3 (± 11.5)	130 (±14.7)	81.1(±8.7)	44.5 (±7.9)	128 (±12.8)	**<0.0001**
6–12 mo (119)	88.4 (± 9.5)	51.3 (± 9.1)	131 (± 10.6)	89.7 (± 12.4)	51.9 (± 13.2)	124 (± 16.1)	84.3 (± 12.1)	50.2 (±14.1)	120 (±15.1)	**0.004**
12–24 mo (16)	91.2 (± 8.6)	54.7 (± 10.2)	118 (± 9.7)	91.9 (± 11.7)	55.5 (± 9.2)	106 (13.5)	87.6 (± 9.5)	51.7 (±11.8)	106 (±12.3)	0.2

BP = blood pressure; HR = heart rate.

Method

The purpose of this study is to investigate the safety profile of propranolol, when used in paediatric age to treat infantile haemangioma

Study type and population

This is a prospective observational and analytic study, that included a population of children 0 to 2 years old, diagnosed with infantile haemangioma at the cardio-pediatric department of the university hospital "Mother Theresa" in Tirana, during the time period January 2011 – December 2021 with indications to be treated. Data were recorded in a specific register designed for the study. From this study, all cases were excluded with missing data, whose parents refused or interrupted treatment prematurely or that showed treatment counterindications.

Treatment and studied variables

For every case were collected the following demographic data: gender, age, weight, height, and data related to treatment: blood pressure, heart rate before and during treatment, and symptomatic side effects recorded.

Propranolol was indicated to treat large infantile haemangiomas over 3 cm, fast growing, that have tendency to ulcerate or cause disfigurement, or for infantile haemangioma affecting organ function. Treatment was started as recommended in the consensus conference 2011, after a first thorough physical examination focused on cardiovascular and respiratory system. A basal electrocardiogram (ECG) and heart ultrasonography were performed to every child. Treatment was started with 0.5 mg/kg/day propranolol and was increased with 0.5 mg/kg/day every 3 days until achieving the therapeutic dose 2–3 mg/kg/day. It was given three times/day, with the meal to avoid hypoglycaemia.[4,5,19] The dosage form in our country is a suspension prepared from a licensed private drug store. Treatment was started on a hospital base in patients under the age of 8 weeks and ambulatory, but the first 3 hours monitored in hospital, in children older than 8 weeks.

We measured blood pressure and heart rate before starting treatment, 1 and 3 hours after giving the first dose, since the peak plasma concentration of propranolol and for instance the appearance of side effects is reached in less than 2 hours. Parents were instructed to recognise the symptoms of hypotension, bradycardia, hypoglycaemia and bronchospasm and report them. Treatment was continued for 9–18 months until full resolution was achieved, or regression stopped for several weeks.

Bradycardia was considered heart rate <80/min for children less than 12 months and <70/min for children over 1-year-old.

Hypotension was considered as recommended from consensus conference blood pressure a value under 5% percentile or <2 SD form mean for age, gender, and height calculated from the formula published on the fourth report on diagnosing, evaluation, and treatment of height blood pressure.[20,21]

Results

During this 10-year study period, January 2011 to December 2021, at the paediatric cardiology department were consulted and diagnosed with infantile hemangioma 611 children of the age of 1 month to 2 years. From this pool, 86 cases did not have systemic treatment indication. Only eight cases had counterindication to take propranolol, two of them had atrio-ventricular block, and the other six had severe previous bronchiolitis episodes. For 17 cases, data were missing in the register and in 24 cases parents

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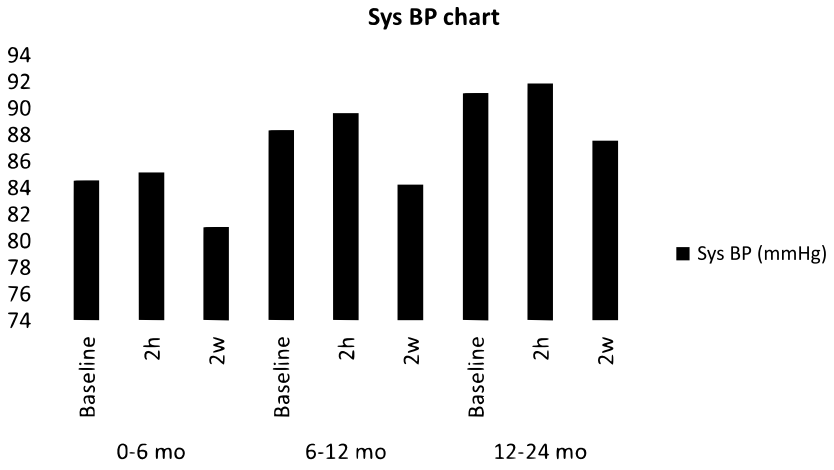

Figure 1. Graphical presentation of systolic BP means for each age group before and after treatment.

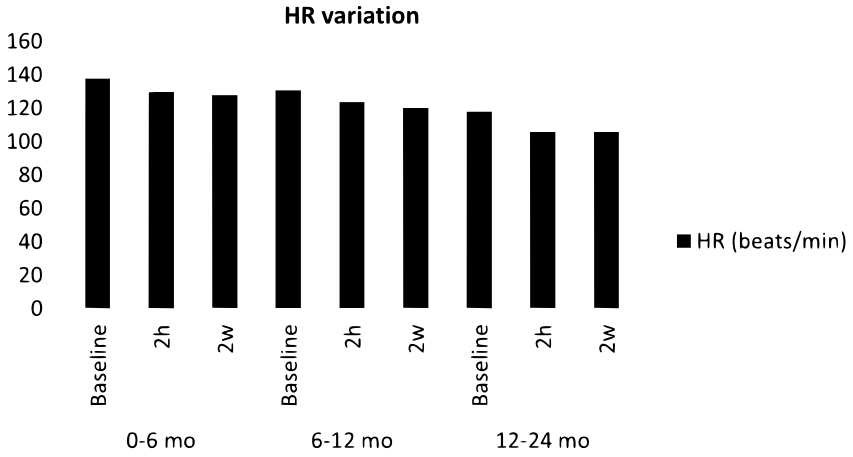

Figure 2. Graphical presentation of HR means before and after treatment for each age group $p < 0.0001$ per (1–6 mo), <0.0001 (6–12 mo), and 0.04 (12–24 mo).

had denied the treatment because of fear from propranolol heart side effects. At the end Only 476 patients were included in this study, 269 females and 207 males with a rate of 1.3:1. The age distribution was as following: 341 on the age group of 1–6 months, 119 on the age group of 6–12 months, and only 16 cases over 1-year-old. Median age at the presentation was 3 months.

In our sample, the main presentation were solitary lesions and during the pre-treatment investigation, less than 5% of cases were found to have multiple lesions or organ involvement. On heart ultrasound as part of pre-treatment investigation, 26 (5.6%) cases of Congenital Heart Defect (CHDs) were found. They were mainly Patent Ductus Arteriosus (PDA), Atrial Septal Defect (ASD) or Venticular Septal Defect (VSD), but not any one of them was considered a treatment counterindication.

Treatment effect was noticed from the first doses with colour fading, softening and decrease of lesion size and has further continued in the first months with growth arrest and slow involution. Afterwards, the involution was slower as found in literature through apoptosis.[17] Treatment was stopped usually after complete resolution or after achieving a stable and no further involuting lesion.[2,22] Recurrence in our study after stopping treatment happened only in 32 cases, that makes 7% of the study sample, less common than mentioned in the literature.[23,24]

Concerning the propranolol treatment side effects in this 10-year period, it was as following. In the first hours of hospital monitoring immediately after the first dose, no major side effects were noticed. Adverse side effects were reported mostly from parents when they reached the dose 1.5–2 mg/kg body weight on the second week of treatment. The most common complain were paleness, sweating and cold extremities, agitation and restless sleep, reduced feeding, fatigue, and somnolence, and some have reported cough and wheeze. But only in 28 (5.9%) cases, these symptoms were severe enough to review the treatment, with 9 patients (1.8%) having moderate respiratory symptoms, 13 patients (2.7%) experienced hypoglycaemia, although in 7 cases hypoglycemia happened in the condition of another acute infection and only 6 patient (1.2%) had symptomatic hypotension or bradycardia. In most of cases, these symptoms were overcome only by stopping treatment for several days or stepping down to the previous tolerated dosage. The second dose increase was tolerated well.[25] There was only one deceased patient, an infant with a large hepatic haemangioma and concomitant heart failure.

The main target of this study was assessing the effects of propranolol used for treating infantile haemangioma, on infant's blood pressure and heart rate as these are the main concerning side effects that refrain parents from starting treatment. The data are summarised on Table 1 and are illustrated visually on Figures 1 and 2. The whole sample was stratified in three age groups: 1–6 months, 6–12 months, and 1–2 years. The measurements were performed at three time points, before starting treatment, 2 hours and 2 weeks after starting it, and were summarised as mean values for each group. The significance of propranolol effect on these parameters was studied by comparing the means of blood pressure and heart rate of each age group before and after treatment through statistical tests look at Table 1.

By simply observing the graphs and reading the means before and after treatment, it is easy to notice the reduction of blood

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pressure in the second week of treatment at each age group, but surprisingly immediate after the first dose of treatment the blood pressure is slightly increased, as you can see it in Figure 1. The blood pressure reduction after the second week is statistically significant for the first two age groups with p-values, respectively, $p < 0.0001$ for the age group of 1–6 months and $p = 0.04$ for the age group of 6–12 months as seen in Table 1, but this difference was not significant for the age group of 12–24 months with $p = 0.2$. The comparison of means was performed with SPSS.

In our study sample, propranolol decreased the mean blood pressure, and the reduction was statistically significant, but hypotension episodes under the 5th percentile, calculated for age and gender with the formula from *The forth report on diagnosis, evaluation and treatment of blood pressure*, were registered only in 14 cases (2.9%), and all of them were found only after reaching the therapeutic dose of 2 mg/kg body weight/day.[20] Nine of these cases had also low diastolic blood pressure under the 5th percentile, but only four (0.8%) of all them experienced hypotension symptoms with excessive sweating, paleness, and somnolence. Blood pressure values for the four symptomatic patients were respectively: P1 – 2 mo and BP – 60/32 mm Hg; P2 – 2.5 mo and blood pressure – 58/ 25 mmHg; P3 – 3.5 mo and blood pressure = 64/ 36 mm Hg; and P4 – 3 mo and blood pressure = 56/ 28 mm Hg. Hypotension under the 5th percentile were recorded only on the age group of 1–6 months. All the symptomatic cases were hospitalised and observed. Three of them were clinically improved only by interrupting temporarily propranolol and being supported with IV fluids, while one of them required adding inotrope drugs to recover until propranolol effect weaned.

Propranolol effect was also statistically significant even on heart rate. It was studied through comparing heart rate means before and after treatment and resulted in a significant difference in all age groups with p values $p < 0.05$ as you can see in Table 1. However, bradycardia under the reference value for the age was found only in nine cases (~2%), eight of them were at the age group of 1–6 months (~2.3%), and only one in the age group of 6–12 months (~0.8% of that group age). Symptomatic bradycardia was reported only for two patients. One of them was lethargic, reduced breastfeeding, and looked pale, while the other had syncope. The patient that experienced syncope had a mild aortic stenosis on ultrasound that was not considered counterindication for systemic treatment with propranolol.

Discussion

Even in our country, infantile haemangiomas are the most common benign tumour lesion in paediatric age. The mean birth rate during the last 10 years in Albania was around 27 000 per year and from 2011 to 2021 476 infantile haemangioma patients were treated with systemic propranolol. This is less than that was expected in our calculations based on disease incidence and treatment rate,[11] probably because of system leak or resistance to treatment. The first medical consultation was mainly realised within the first 3 months of life.

As described in the literature, lesions were mostly solitary, superficial, and localised mainly on the head area that unfortunately is more prone for disfigurement and by consequence requires treatment.[3,4,26] Organ involvement was present in less than 5% of the total sample, with only one case of massive liver involvement, complicated with heart failure.[27] CHDss had a higher incidence between infantile haemangioma patient. In our sample, they were encountered in 5.6% of cases but none of them was counterindication to treatment, while in other studies they were reported up to 20% of cases.[28]

Treating infantile haemangioma with propranolol has shown a great success from the first incidental observation on 2008 from Leaue-Labreze and her collaborator to the further large studies and metanalysis conducted to prove this observation. In a metanalysis performed from Agency for Healthcare Research and Quality (AHRQ) on 2016, the efficacy of systemic propranolol was 88–99%, much higher compared with other earlier treatments as steroids or interferon.[1,5,6,29] Our clinic has been using propranolol as first-line treatment for infantile haemangioma for 10 years now and states its high efficacy in the resolution of IH with a success rate of 88% in 1-year treatment, even though different studies have reported a cure rate from 60 to 95%.[6]

Propranolol is used now for more than a decade as first-line treatment for infantile haemangioma, but there is still hesitancy in starting treatment, and not only from the parents but even from the medical staff, mainly because of side effect concerns, especially on heart. For this reason, we decided to share our experience and add prof to the current literature that propranolol is a very effective and safe choice and that side effects are very rare and easily manageable. We decided to measure the effect of propranolol in the main heart parameters, blood pressure, and heart rate.

What was the effect of propranolol on blood pressure? As it can be easily distinguished on the upward summary Table 1 and the graph in Figure 1, the mean blood pressure 2 hours after taking the first dose has a tendency to be mildly increased compared to the base level, and this can be explained with the vasoconstriction that propranolol causes as non-selective β-blocker by blocking β_2-receptors, but on the following days this effect wanes and will be overcome by the negative chronotropic and inotropic effect which result in blood pressure reduction.[14]

In our study sample, we had only 4 out of 476 cases with symptomatic hypotension, and all of these episodes were registered when it was achieved the therapeutic dosage of 2 mg/kg/day. These events were easily overcome only with a brief time interruption of treatment and were registered mainly in infants that had been sick on the previous days. One case was after vaccination, and only one case required inotropic support.[11,30]

In contrary to blood pressure, heart rate decrease was noticed immediately after the first dose as may be noticed on Figure 2 graphs. By looking to the mean numbers and the graphs, the decrease was more prominent with the first dose and slower with the consequent dose increases. This reduction was statistically significant for our sample, but reduction under the bradycardia threshold of 80 bpm was registered only in nine cases (around 1.8%) for the whole sample, all of them under the age of 1 year. In literature, there were reported in 0–4% of sample cases.[31,32] Registered bradycardias were mostly asymptomatic findings, except for two cases who experienced symptomatic bradycardia, one only with paleness, sweeting, and decreased activity and the other had syncope as presenting symptom with a heart rate of 58 bpm when examined in hospital. Both cases were observed for 24 hours in the hospital and were weaned of treatment for 1 week. Treatment was reintroduced on the following week with the lower dose under strict hospital monitoring and was tolerated well.

We concluded on our experience that the dose of 2 mg/kg/body weight has a very good therapeutic result and is safe, with very rare and mild side effects, without significant risk of life threat. Even when side effects did happen, they were easily managed, mostly only with dose reduction to the previous dose or through stopping

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the treatment temporarily. The following dose increase has been almost always very well tolerated, what makes us suppose that these side effects may be precipitated by external factor as an infectious disease, miscalculated dosage, or errors of administration. As for the right therapeutical dose we are pleased with the success rate of 2 mg/kg, even though many other studies have proved safety for higher doses too.

The long-time experience now with propranolol and its very safe profile has given as the confidence to shorten the observation period in clinic or even to start the first treatment doses at home, without having to monitor heart rate and blood pressure during the first dose, but only relying on symptom report remotely from parents using telemedicine. Treatment reassessment was considered only in case of symptomatic side effects.

Our study has its own weak points mainly related to the long study period, where the staff in charge has changed several times, the variable measurements are prone to equipment and staff bias, especially blood pressure measurement since children are not cooperative. Overall this was a long-term study with a large sample that makes it a good representative of the study population. On the other side, the results are compatible with those of other studies also.

In summary, this study demonstrates that propranolol is a very good choice in treating infantile haemangiomas, with a very good clinical results in haemangioma resolution and with minimal and not life-threatening cardiac side effects.

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Conflict of interest. None.

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