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Monitoring oral propranolol for infantile hemangiomata

Jonathan Bar[1] | Efrat Bar-Ilan[1] | Roxana Cleper[2,3] | Eli Sprecher[1,3,4] | Liat Samuelov[1,3,4] | Jacob Mashiah[1,3,4]

[1]Division of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[2]Pediatric Nephrology Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Pediatric Dermatology Clinic, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Correspondence
Jacob Mashiah, Department of Dermatology, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Email: ymashiah1@gmail.com

Abstract

Treating infantile hemangiomas with oral propranolol may be initiated in accordance with various protocols some require hospitalization. However, different adverse events have been reported during treatment, thus it is of special importance to find a protocol which is both safe and feasible. We performed a retrospective cohort study of all cases of infantile hemangiomas treated with oral propranolol at our institute between January 2010 and February 2020. Pretreatment evaluation consisted of pediatric cardiologist evaluation including electrocardiography and echocardiography. The propranolol starting dosage was 0.5 mg/kg bid; 2 weeks later the dosage was escalated to 1 mg/kg bid. During the initiation and escalation visits, heart rate and blood pressure were measured before and every hour for a total of 3 h, and blood glucose level was measured within the first hour of treatment. A total of 131 children were treated during the study period. Scalp, facial and genital region infantile hemangiomas were more prevalent in regard to their relative body surface area. No symptomatic bradycardia, hypotension, hypoglycemia, or any other adverse events were documented; few patients had asymptomatic bradycardia and hypotension, which were more common in infants below 6-months of age. Only one patient had asymptomatic hypoglycemia, not requiring any intervention. Initiation and escalation of propranolol treatment for infantile hemangiomas proved to be safe, and without symptomatic adverse effects. However, considering the young age of the patients and the possible asymptomatic adverse reactions, we recommend the following simple protocol as presented, for pretreatment evaluation and short monitoring during treatment initiation and dose escalation.

KEYWORDS
beta-blockers, hemangiona, infantile hemangiomas, propranolol, therapy-systemic

1 | INTRODUCTION

Infantile hemangiomas (IHs) are benign vascular tumors, affecting up to 5% of the newborns.[1] Oral propranolol is considered today as a first line, effective and safe therapy for IHs.[2,3]

In light of the reported adverse events following propranolol administration, including bradycardia, hypotension, hypoglycemia, bronchospasm and sleep disturbance there is controversy regarding the method of monitoring during initiation and dose augmentation,

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with a diversity of monitoring protocols ranging from hospitalization of up to 48 h to virtual telemedicine.[3–11]

Furthermore, the primary debatable question in the literature lately is the necessity of repeated vital sign monitoring, with conservative methods suggesting monitoring on an outpatient basis, and more liberal approaches questioning the actual need of such monitoring.[5,12,13]

In this study, we aim to describe our experience adhering to a strict protocol of oral Propranolol administration including pretreatment evaluation and monitoring during initiation and dose augmentation, and verify the need for such monitoring.

2 | METHODS

2.1 | Patients

We performed a retrospective cohort study of all cases of IHs that underwent initiation and dose augmentation treatment with oral propranolol at the pediatric dermatology clinic at Tel Aviv Sourasky Medical Center, between January 2010 and February 2020. Inclusion criteria were cases of IHs that underwent initiation and dose augmentation treatment with oral propranolol. Exclusion criteria were (1) Cases that did not have full monitoring; (2) cases that changed treatment from propranolol to another beta-blocker. Epidemiological, demographic, and clinical data was collected.

2.2 | Ethics and consent

This study protocol was reviewed and approved by the institutional Helsinki research ethics committee in Tel Aviv Sourasky Medical Center. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Consent was not required as the information is anonymized, and the information did not include images, data or material that may identify any patient, this was approved by the institutional Helsinki research ethics committee in Tel Aviv Sourasky Medical Center.

2.3 | Treatment regimen and monitoring

Treatment was commenced at 0.5 mg/kg bid, administered 12 h apart. Two weeks later the dosage was augmented to 1 mg/kg bid, again 12 h apart. The morning dose given at each monitoring visit was administered in the pediatric dermatology day-care center. At each monitoring visit, lasting 3 h, heart rate and blood pressure were measured before treatment and every hour, while the patient was at rest or asleep, and the mean of at least three measurements was recorded. Blood glucose level was measured within an hour after treatment initiation, at each monitoring visit. The parents were instructed to continue treatment at home and asked to report any adverse events.

We used reference ranges for heart rates, blood pressure and glucose levels based on international guidelines.[7,14–17] Body surface area assessment was conducted according to the Lund and Browder chart.[18]

2.4 | Statistical analysis

Continuous variables were compared using Student *t*-test and Welch *t*-test. All statistical tests were two-sided. p Value <0.05 was considered as statistically significant. SPSS was used for all statistical analyses (IBM SPSS Statistics, ver. 26, IBM Corporation, Armonk, NY, USA).

3 | RESULTS

One hundred and thirty-one patients with a total of 182 IHs (of whom 35 were multiple IHs), had started treatment at our pediatric dermatology outpatient day-care center between January 2010 and February 2020 and had followed the treatment protocol mentioned above. Eighty-nine were females (68%) with a mean age of 7.3 months (range 7.5 weeks to 4.5 years) and a mean weight of 7.34 kg.

Pretreatment cardiac assessment (including cardiologist evaluation, ECG and echocardiography) did not reveal any contraindication for propranolol treatment across the cohort. All patients were treated in accordance with the above-described protocol except for a single

TABLE 1 Demographic and clinical data of patients

Parameter	Number (percentage)
Number of patients	131
Age, mean (SD), months	7.3 (6.8)
Sex (female, male), no. (%)	89 (68%), 42 (32%)
Weight upon treatment start, mean (SD), kg	7.34 (2.1)
Week of birth, mean	37.7
Preterm, no. (%)	19 (25%[a])
Weight of birth, mean (g)	2900
Low Birth Weight, no. (%)	14 (23%[a])
Previous therapy with topical propranolol, no. (%)	20 (15%)
Complications prior to treatment, no. (%)	
Ulceration	8 (6%)
Multiple IHs[b]	12 (9%)
Respiratory tract[c]	4 (3%)
Ocular[d]	3 (2%)
LUMBAR[e] syndrome	1 (1%)

Abbreviation: IHs, infantile hemangiomas.
[a]As this data was missing for some patients, the percentiles are calculated from the available data.
[b]Warranting an abdominal ultrasonography.
[c]Including lip, tongue, subglottic, oral mucosa, larynx, buccal mucosa, parotid.
[d]Causing ptosis, ocular compression or astigmatism.
[e]With hypospadias.

patient that had his treatment switched to Atenolol on the second visit due to sleep disturbances. None of the patients received any other medications from treatment initiation until treatment augmentation at the second visit. Demographic and clinical data are presented in Table 1.

Data regarding heart rate, blood pressure and glucose levels were obtained for 127 patients on their first visit, and for 125 patients on their second visit, as presented in Figure 1. There was a small decrease in systolic and diastolic blood pressure and heart rate following treatment initiation (as compared to prior treatment values and values measured every hour following treatment initiation, Table 2). Diastolic pressure reduction and heart rate reduction were lower during the second visit as compared with the first visit ($p < 0.02$ and $p < 0.01$, respectively).

The number of recorded adverse events was small. No participant had symptomatic bradycardia; non symptomatic bradycardia was documented in 5 (4%), with an average reduction of 3.8 beats/min and a maximum reduction of 7 beats/min from cutoff range; or 15 patients (11%), with an average reduction of 5.3 beats/min and a maximum reduction of 17 beats/min from cutoff range, depending on the reference score used.[7,14]

Furthermore, there was no evidence of symptomatic hypotension. Nonsymptomatic hypotension was documented in 16 children (12%), with an average reduction of 4 mmHg and a maximum reduction of 11 mmHg from cutoff range; or 7 (5%), with an average reduction of 3 mmHg and a maximum reduction of 12 mmHg from cutoff range patients, again depending on the reference scores as mentioned above.[7,14]

A single patient had asymptomatic hypoglycemia with a glucose level of 48 mg/dl 1 h after propranolol administration. The rest of the patients had a normal glucose level of at least 65 mg/dl 1 h following treatment initiation or dose escalation.

In order to determine whether age is a covariate for the blood pressure or heart rate reduction, a correlation analysis was performed on age and the difference between the "before treatment" vital sign measurement and the mean of the "after treatment" measurements. Spearman correlation between age and vital signs was found as statistically significant only for the first visit's heart rate and systolic blood pressure ($\rho = -0.22$ and -0.30 respectively, both $p < 0.01$); This implies that younger patients have greater reduction in blood pressure and heart rate after treatment, regarding their first visit; The lack of significant reduction in the second visit perhaps implies that the

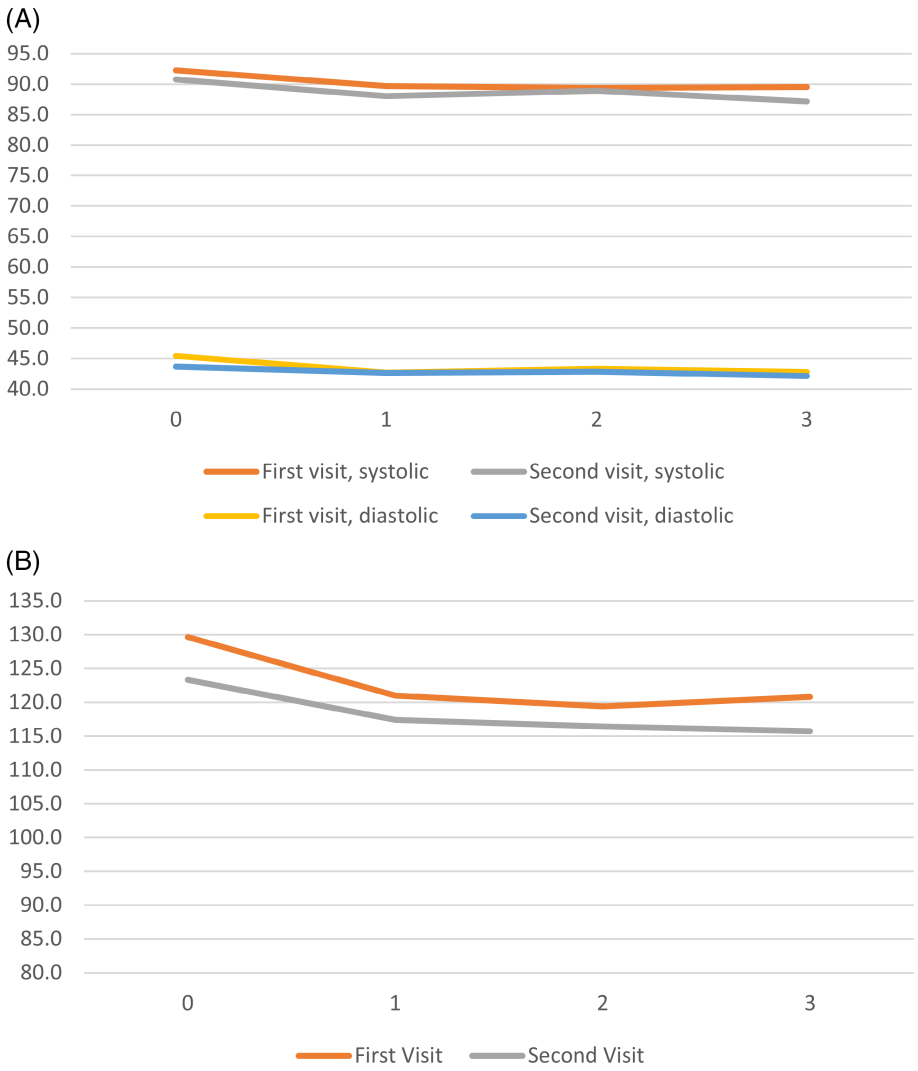

FIGURE 1 Vital signs monitoring values by treatment hours, in first and second clinic visits. The *X* axis represents the number of hours from treatment initiation, whereas "0" represents the measurement performed before treatment. The *Y* axis is the vital sign measurement: (A) Blood pressure in mmHg (B) Heart rate in beats per minute (Image was created with Microsoft Excel 2019)

TABLE 2 Changes in vital signs before and after treatment

	Visit	Mean before treatment	Mean after treatment	Absolute difference	Relative difference (%)	*p* Value
Systolic BP	1	92.3 mmHg	89.5 mmHg	2.7 mmHg	3	<0.01
Systolic BP	2	90.8 mmHg	88.0 mmHg	2.7 mmHg	3	<0.01
Diastolic BP	1	45.4 mmHg	43.0 mmHg	2.5 mmHg	5.5	<0.01
Diastolic BP	2	43.7 mmHg	42.6 mmHg	1.1 mmHg	2.5	>0.05
Heart rate	1	129.6 BPM	120.4 BPM	9.2 BPM	7.1	<0.01
Heart rate	2	123.3 BPM	116.5 BPM	6.8 BPM	5.5	<0.01

Abbreviations: BP, blood pressure; BPM, beats per minute.

patients had adjusted well to the treatment. There was no statistically significant correlation between age and glucose levels, in both visits. Furthermore, there was no statistically significant correlation between low-birth weight history and blood pressure or heart rate mean reduction, and neither between preterm history and blood pressure or heart rate reduction.

Additionally, patients were split into four age groups (0–3 months, 3–6 months, 6–12 months, 12+ months), and a paired *t*-test was performed, comparing the first visit's "before treatment" and mean "after treatment" measurements. All patients had a statistically significant reduction in heart rate ($p < 0.01$); Patients aged 0–3 months had a mean reduction of 12.5 beats/min, those aged 3–6 months had 11.4 beats/min reduction, whereas older patients aged 6+ months had milder reductions. Similarly, younger patients aged 0–3 months and 3–6 months had a statistically significant systolic blood pressure reduction of −6.2 mmHg and −3.9 mmHg, respectively ($p < 0.05$), but no statistically significant reductions for the older patients.

4 | DISCUSSION

IHs are benign prevalent vascular tumors, affecting up to 5% of the newborns.[1,9] Since the first report in 2008, oral propranolol is considered first line, effective and safe therapy for IHs.[2]

In light of the reported adverse events following propranolol administration, including bradycardia, hypotension, hypoglycemia, bronchospasm and sleep disturbance,[6] meticulous guidelines for close monitoring during initiation and dose augmentation were recommended.[3]

However, during the last several years controversy emerged regarding the need for such monitoring,[5,7–10,12,13] and according to a survey conducted by Kumar et al most pediatric dermatologists nowadays do not rigorously adhere to these recommendations.[19]

The aim of this retrospective cohort study comprising 131 cases of IHs was to ascertain the necessity for long monitoring at the beginning and dose escalation of oral propranolol treatment, by adhering to a strict administration protocol with almost no protocol deviations, thus making our conclusion more robust.

IHs characteristics in our cohort are in accordance with previous data.[1]

One of the common protocols, which is also part of current recommendations[3] is 2-h blood pressure and heart rate monitoring after treatment initiation and at substantial dose escalation of oral propranolol treatment, thus detecting side effects in infants whose cardiologic pretreatment evaluation did not reveal any potential contraindications to the treatment.[3,20]

Similarly to previous studies,[5,7,12,13] no symptomatic bradycardia, hypotension, hypoglycemia, or any other major adverse events were documented, while few non-symptomatic adverse events, not necessitating treatment discontinuation or dose decrease were recorded, including hypoglycemia (one patient) and asymptomatic bradycardia or hypotension in 5 or 15 patients and 7 or 16 patients respectively, depending on the chosen reference criteria.[7,14] As shown (see Table 2), diastolic pressure and heart rate reduction were lower during the second versus the first visit, which suggests an adaptive sympathetic response to the treatment.

During the last years, several studies have addressed the need for monitoring. In a study of 220 children with IHs,[13] in which propranolol dosage was escalated from 0.5 to 2 mg/kg/day, divided into three doses/day, over 3 days, no severe treatment-related adverse events were documented, hemodynamic changes were clinically asymptomatic and did not require intervention. Nevertheless, a statistically significant reduction in systolic BP and HR was recorded. Blood glucose level remained stable. In another study of 279 children with IHs,[5] propranolol was initiated and dosage was increased in either an in-person or virtual telemedicine settings. All patients were asymptomatic without immediate adverse episodes, yet 46 patients experienced clinically significant drops in vital signs. Puttgen et al[12] published a retrospective multicenter cohort study of 783 children with 1148 episodes of monitoring of at least 1 h after initiation or escalation of propranolol for IHs. Immediate intervention or drug discontinuation were not warranted, and symptomatic bradycardia or hypotension were not recorded during any monitoring episode. There was a mean HR and BP change from baseline one to 2 h post-treatment administration. Several earlier studies, initiating and escalating propranolol treatment either during hospitalization or in outpatient clinic settings, yielded similar results with mostly asymptomatic decrease in BP and HR.[4,6,10,21–24]

According to the results of our study, as well as previous ones, close ambulatory monitoring during initiation and dose augmentation of propranolol for IHs proved this treatment to be safe and well tolerated, without clinical hemodynamic compromise. Taking the initiation protocol one step further, in the effort to facilitate the treatment of IHs, thus promoting its use and decreasing costs, the question of the

real necessity of prolonged monitoring is brought up in several studies.[5,12]

As noted in our study and in all other cited studies, decrease in BP and HR have been recorded. The existence of such adverse effect, despite being asymptomatic in almost all cases, still suggests the possibility of clinically relevant adverse events. Of note, alterations in BP and HR in infants pose a non-dismissible risk, especially in high-risk situations such as preterm and very low weight infants, those with a history of hypoglycemia, or possibly those with segmental hemangiomas. This is further supported by our particular findings, as younger patients (<6 months) especially have higher reduction in both systolic blood pressure and heart rate compared to older ones, which might stress further the need for monitoring in this subpopulation. Though not without disadvantages, delaying the treatment for younger patients might be an alternative option—as our results demonstrate that having a history of prematurity or low-birth weight are not associated with reduced HR and BP.

In summary, we recommend ambulatory short-term monitoring of propranolol treatment for IHs. The results of this retrospective study warrant larger prospective and confirmatory studies.

AUTHOR CONTRIBUTIONS

Jonathan Bar: Conceptualization (equal), methodology (equal), project administration (equal), data curation (lead), literature review (lead), writing—original draft (lead), formal analysis and investigation (lead). **Efrat Bar-Ilan:** Conceptualization (equal), methodology (equal), project administration (equal), literature review (equal), writing—review and editing (equal). **Roxana Cleper:** Conceptualization (equal), methodology (equal), writing—review and editing (equal). **Eli Sprecher:** Supervision (equal), writing—review and editing (equal). **Liat Samuelov:** Supervision (equal), writing—review and editing (equal). **Jacob Mashiah:** Conceptualization (lead), methodology (equal), supervision (lead), project administration (equal), writing—review and editing (lead). All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study protocol was reviewed and approved by the institutional Helsinki research ethics committee in Tel Aviv Sourasky Medical Center, approval number 0106-20TLV. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Consent was not required as the information is anonymized, and the information did not include images, data or material that may identify any patient, this was approved by the institutional Helsinki research ethics committee in Tel Aviv Sourasky Medical Center.

ORCID

Efrat Bar-Ilan https://orcid.org/0000-0003-1260-3960
Jacob Mashiah https://orcid.org/0000-0002-9417-2932

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