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ORIGINAL ARTICLE

Recurrence rate of infantile hemangioma after oral propranolol therapy

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Abstract

Oral propranolol is the treatment of choice for infantile hemangiomas. The growth relapse rate following oral propranolol therapy is not well established in the literature. The present study aimed at determining predictors of growth relapse of infantile hemangiomas after discontinuation of oral propranolol therapy. A retrospective analysis was performed of all cases of infantile hemangiomas aged ≤ 12 months undergoing oral propranolol therapy in a 6-year period. Of the 198 cases, regrowth after oral propranolol therapy was observed in 35 patients (18%). Facial hemangiomas showed a higher ($p = 0.003$) relapse rate as compared with other hemangiomas (27 out of 107 facial cases vs. 8 out of 91 with other location, respectively 25% and 8.8%). Of 35 growth relapses cases, 66% of cases (23 in total, 18 facial and 5 otherwise located hemangiomas) underwent a second cycle of oral propranolol therapy (median length of treatment 3 months, interquartile range 2–3). All cases had a successful outcome, either after a single cycle oral propranolol therapy (163 cases, 82%), or in case of regrowth, after a second therapy cycle (23 cases, 12%) or further conservative management (12 cases, 6%).

Conclusion: Facial infantile hemangiomas relapse earlier and more frequently after oral propranolol therapy. We suggest to closely monitor these patients, as a second cycle of propranolol may be indicated. Prolonged oral propranolol therapy might be considered for facial infantile hemangiomas.

What is Known:
- *Oral propranolol is the treatment of choice for infantile hemangiomas.*
- *The growth relapse rate following oral propranolol is not well established.*

What is New:
- *The present study points out that facial infantile hemangioma relapse earlier and more frequently after oral propranolol therapy.*
- *Patients with facial infantile hemangiomas should be monitored after propranolol therapy discontinuation.*

Keywords Infantile hemangioma · Propranolol · Recurrence · Relapse

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Abbreviations

IH	Infantile hemangioma
OPT	Oral propranol therapy
HIF-1α	Hypoxia-inducible factor-1-α
VEGF	Vascular endothelial growth factor
IGF-2	insulin-like growth factor 2
GLUT-1	Glucose transporter 1

Introduction

Infantile hemangioma (IH) is the most common benign tumor of infancy, with a prevalence of up to 10% in the first years of life [1, 2]. The IH incidence is indirectly proportional to gestational age (23% in preterm infants of < 1000 g birth weight

vs. 1–4% in term infants [2]). The pathogenesis is not fully understood, but several studies show a link between IH and hypoxic stress in early life, which is supported by the association between IH and hypoxia-triggered factors like HIF-1α, VEGF, IGF-2, and GLUT-1 [3, 4]. Female gender and a light skin type are considered to be predisposing factors [5].

The vast majority of early proliferative IH growth occurs before age 5 months, and overall growth, including late proliferative growth, is nearly always complete by 9 months of age [6]. An involutions phase typically begins at 1 year of age and continues for the first several years of life [6].

Because IHs are benign, 90% of all cases can be monitored actively without intervention [4]. However, in 10% of cases, IHs lead to serious complications, such as ulceration, impairment of anatomic orifices (such as eyes, ears, and genitals), major cosmetic disfigurement, and life-threatening airway compression or heart failure due to its size or location. These IH require active intervention [5, 7]. Until 2008, possible treatments included corticosteroids, vincristine, interferon alfa-2a, cyclophosphamide, pulsed dye laser therapy, cryotherapy, and surgery [3]. Although associated with serious side effects [6], corticosteroids were the first-line treatment until Léauté Labrèze et al. reported IH regression following propranolol treatment [8]. Since this report was published, oral propranolol therapy (OPT) has replaced corticosteroids as the treatment of choice for IH because it is safer and more effective [9, 10] and surgical procedures for IH have decreased by about 90% since the introduction of the OPT [11]. OPT is successful in the majority of cases, but some patients present rebound after stopping treatment. The reasons for post-treatment relapse have not been sufficiently described [12–15]. The present study aimed to identify prognostic factors for post-OPT relapse and to investigate the long-term outcome of OPT in a pediatric cohort with IH.

Methods

Study design

All children aged 12 months or younger undergoing OPT for IH at our university center for pediatric surgery between January 1, 2009, and June 30, 2015, were included in the study. Study exclusion criteria were patients that were cared for elsewhere after OPT initiation at our clinic and therefore had incomplete follow-up data. Electronic medical charts were retrospectively evaluated. Ethical approval was obtained from the institutional review board (University of Heidelberg, Germany). The study was performed in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 2013. Informed consent from the patients and their parents was not necessary because of the retrospective character of our study.

OPT treatment protocol

An IH was indicated for OPT if the following conditions were met: (1) obstruction of an orifice or compression of vital structures, such as the eye, nasopharynx, or anus; (2) risk of long-term disfigurements, such as large hemangiomas in the face; and (3) presentation with other complications, such as ulcerations [16]. OPT dosage was based on the patient's weight and started from an initial dose of 1 mg/kg/day for the first day followed by 2 mg/kg/day (in three single doses/day), with further dose adjustments according to the body weight. Before OPT, blood pressure was measured in all patients, and ECG and ECHO were performed. Blood pressure was also measured 1 h and 2 h after each administration, and capillary glucose concentration was measured 1 h after the first and final doses were administered. Continuous device–assisted heart rate monitoring was performed for 48 h. Patients were re-assessed 3–6 weeks following the initiation of OPT, or earlier in the case of complications. OPT dosage was increased to 3 mg/kg/day in cases the IH had not responded clinically such as by discoloration, growth arrest, regression, or if complications, such as ulcerations, occurred. OPT treatment was carried out at least up to the 9th month of life to ensure that a possible late proliferative phase has also been completed. A pediatric surgery medical staff team, consisting of four residents and two senior physicians specialized in pediatric surgery, treated and evaluated the children here reported.

Study data

Patient demographics and OPT-related data were recorded. These included pre-OPT ECG and ECHO findings, location, number, and depth of soft tissue involvement of IH. Hemangiomatosis cases with more than ten cutaneous IH were recorded. Adverse events during and after OPT were also recorded. Common complaints of sleep disturbance, cold extremities, and diarrhea were classified as mild adverse effects, whereas possibly life-threatening complications such as hypotension, hypoglycemia, and bradycardia were defined as severe adverse effects [16]. Reductions in IH color, surface/volume, and texture were regarded as signs of treatment success. No visible change in or further growth of IH was regarded as signs of treatment failure. Hemangioma relapse was defined as increased IH color, surface/volume, or texture after OPT cessation. Missing variables were handled using the hot deck imputation method by which each missing value is replaced with an observed response from a "similar" unit.

Data analysis

Statistical analysis was performed using SPSS® version 21 (SPSS® Corp., Chicago, IL, USA).

The Shapiro-Wilk test was used to test for normal distribution of the data. Normal distribution of data was assumed in cases the p value of the Shapiro-Wilk test was above 0.05. Frequency distributions were determined for categorical variables and continuous variables were presented as mean values ± standard deviation and range in case of normally distributed variables and as median and interquartile range (IQR, first quartile–third quartile) in case of non-normally distributed variables. Categorical data were compared using a two-sided Fisher exact test, and continuous variables were compared using a two-sided t test. Odds ratios with 95% confidence intervals were calculated to quantify the strength of the association between IH location and the occurrence of an IH regrowth after OPT. A $p < 0.05$ was considered significant for all analyses.

Results

Patient's characteristics

In total, 198 patients were included in the present study. Among those nineteen (9.6%) patients were born prematurely (week 32 ± 3, range 25–36), and 149 (75%) of the patients were female. The median age at the start of OPT was 2 months (IQR 2–4) and the median bodyweight of the patients was 6 kg (IQR 4.5–6.3). Cardiac screening by ECG and ECHO was performed before OPT initiation and no contraindications for OPT were detected.

Hemangioma characteristics

The median number of IH was 1 IH (IQR 1–2), 129 patients (65%) had one IH, and 29 (14%) had 2 IH, while the remaining 20% had more than 2 IH. Most IH were located in the facial area (54%) and had both cutaneous and subcutaneous components (Table 1). Hemangiomatosis > 10 IH was noted in five (2.5%) patients, and 16 (8.1%) patients had IH ulcerations before OPT started.

Table 1 Infantile hemangiomas characteristics. Data is reported as number of patients (%)

Localization	**Number (%)**
Scalp	12 (6.1%)
Face	107 (54%)
Neck	9 (4.5%)
Trunk	18 (9.1%)
Extremities	41 (20%)
Diaper area	11 (5.6%)
Growth pattern	***n* (%)**
Cutaneous	69 (34%)
Subcutaneous	32 (16%)
Mixed	85 (42%)
Segmental	12 (6%)

Adverse effects during OPT

During hospitalization and initiation of therapy, no adverse effects were observed. There was no significant drop in blood pressure, heart rate, or blood glucose revealed in the 48-hour monitoring. During outpatient treatment, no severe adverse events were observed. Minor adverse effects under OPT were experienced by twenty patients (10%). These included nine (4.5%) cases of vomiting and/or diarrhea, four (2%) cases of fatigue, and seven (3.5%) cases of cold extremities. Although these adverse effects did not indicate treatment discontinuation, in two cases of fatigue the parents wished to stop that treatment. After medical consultation and discussion, treatment was continued in those cases in accordance with parents. There were no adverse events during follow-up after OPT completion.

Course of treatment

The median first treatment duration was median 6 months (IQR 5–7); the median follow-up duration was median 8.5 months (IQR 7–12.9). OPT was successful and stopped IH growth in 192 (97%) patients. The OPT dosage was increased to 3 mg/kg in five patients (3%) because further IH growth was observed, after which the long-term outcome was successful. The 16 (8.1%) ulcerations detected before treatment disappeared under OPT. No topical medication, apart from disinfection, was applied on ulcers. Scars occurred following ulcers; however, we do not have reliable data providing evidence that the start of treatment had an impact on the rate of sequelae following ulcers. During outpatient treatment, OPT was temporarily suspended in 30 cases for the following reasons: respiratory tract infection in 15 (7.6%) cases, gastrointestinal infection in nine (4.5%) cases, fever in two cases (1%), and parental non-compliance in nine (4.5%) cases. In all cases, OPT was resumed in median after 1 week (IQR 1–2). The overall rate of IH regrowth after initial OPT was 18% (35 patients). The median time between the end of therapy and regrowth was 1.5 months (IQR 1–3.1), and the mean age at second therapy circle was 11.6 ± 2.8 months (range 7–17). Of the 35 cases with regrowth of IH after OPT, 27 (77%) patients had an IH located in the face. The rate of regrowth was significantly higher in cases the IH was located in the face compared with IH located in other regions (77% vs. 49%, $p = 0.003$) (Table 2). An IH located in the face had an OR 3.46 (95% confidence interval 1.48–8.07, $p = 0.004$) of undergoing a regrowth after OPT discontinuation compared with IH located elsewhere. The time from OPT discontinuation to IH regrowth was not significantly different

Table 2 Comparison between children with regrowth and without regrowth of infantile hemangioma (IH) after oral propranolol therapy. Data is reported as number of patients (%), and median [interquartile range, first quartile–third quartile]

After OPT discontinuation	IH regrowth	No IH regrowth	*p* value
Patients ($n = 198$)	35 (18%)	163 (82%)	
Sex (female)	29 (82%)	111 (68%)	0.102
Full-term birth	35 (100%)	144 (88%)	0.028
Number of IH	1 [1–2]	1 [1–2]	0.166
Start age at OPT (months)	2.5 [2–6]	3 [2–4]	0.441
End age at OPT (months)	9 [7.5–11]	10 [8.5–10]	0.907
OPT duration (months)	5.5 [4.5–6]	6 [5.5–7]	0.183
Localization			
Face	*27 (77%)*	*80 (49%)*	*0.003*
Scalp	1 (2.8%)	11 (6.7%)	0.742
Neck	2 (5.7%)	7 (4.3%)	0.291
Trunk	1 (2.8%)	18 (11%)	0.939
Extremities	3 (8.6%)	37 (22%)	0.977
Diaper area	1 (2.8%)	10 (6.1%)	0.742
Hemangiomatosis > 10 IH	0 (0%)	6 (3.3%)	0.593
Depth of soft tissue involvement			
Cutaneous	5 (14%)	33 (20%)	0.487
Subcutaneous	3 (8.6%)	18 (11%)	1.000
Mixed	26 (74%)	101 (62%)	0.181
Segmental	1 (2.9%)	11 (6.7%)	0.696

The rate of regrowth was significantly higher in cases the IH was located in the face compared with IH located in other regions (77% vs. 49%, $p = 0.003$)

between cases with facial IH and cases with IH located elsewhere (1.8 ± 1.5 vs. 2.8 ± 2.1 months, $p = 0.167$). Patients with and without relapse showed no significant difference in gender distribution, prematurity rate, or the average number of IH. Furthermore, the start, end, and mean durations of OPT were similar in both groups. The depth of soft tissue involvement did not influence the growth relapse rate. Of the 35 patients with IH regrowth after initial OPT, 23 (66%) underwent a second cycle of OPT for a median treatment length of 3 months (IQR 2–3).

All 198 evaluated IH cases had a successful outcome, either after a single cycle oral propranolol therapy (163 cases, 82%), or in case of regrowth, after a second therapy cycle (23 cases, 12%) or further conservative management (12 cases, 6%).

No surgical treatment was performed due to a failure of previous treatment. However, in the later course, a surgical treatment at the IH location was performed in 13 cases (7%) to resect a residual finding, excessive skin, scar tissue, or skin discolorations.

In one 9-month-old patient, the initial IH was located in the face, whereas secondarily evident finding after the OPT was located at the neck, possibly being a deep IH that was not detected at the beginning of the therapy. It occurred 3.5 months after OPT discontinuation, and the patient did not undergo a second cycle of OPT, as this was declined by parents.

Discussion

Since its discovery as a treatment for IH a decade ago, OPT has become the treatment of choice for IH, and its safety and efficacy are well documented [9, 17–24]. However, the reasons for IH regrowth after OPT discontinuation are not sufficiently described [25–34]. Here, we investigated these factors in a cohort of 198 children undergoing standardized OPT for IH over a 6-year period.

In our study population, the IH regrowth rate was 18% after OPT, which is slightly higher than reported rates of 8 to 17% [23, 26]. This could be explained by our follow-up of median 8.5 months (IQR 7–12.9) compared with 6–9 months in other studies [12, 13].

Three studies [12, 13, 27] identified subcutaneous or segmental hemangiomas as risk factors for IH regrowth after OPT. However, we could not confirm these findings in our study. Completing OPT before the age of 12 months has also been described as a risk factor for IH regrowth [26], but our findings did not confirm this.

In the present cohort, the regrowth rates in the facial region (25%, 27 out of 107 facial IH cases) were similarly high as in the neck region (22%, 2 out of 9 neck IH cases). However, of the 35 regrowth IH cases, 27 cases had a facial IH (77%) while only 2 cases had neck IH (5.7%) cases, and the difference within each group regarding the regrowth rate was statistically significant only in the facial IH group ($p = 0.003$). The lack of statistical significance in the neck IH group might be explained by the low number of patients in this group ($n = 9$) compared with the face IH group ($n = 107$). Although it has been shown that initial hemangiomas are more common in the facial area [27], higher IH regrowth rates in this region have not been reported before. We showed that IH regrowth was more frequent in the facial region (77% of all IH regrowth cases). This regrowth in the facial area was successfully treated by either a higher dosage or a prolonged treatment in our study. However, the restricted overall number of included patients limits our findings, and further validation is needed. Prolonged monitoring of facial IH after OPT might be necessary to detect IH regrowth early on and to initiate further therapy. We suggest more regular post-treatment monitoring in the first 2 months after OPT, as we observed the highest regrowth rates during this period. OPT may need to be adapted for IH in the facial region as severe complications (like impaired vision, hearing, eating, or breathing) can occur. Adaptations of the treatment protocol might include prolonged OPT for facial IH; this has been shown to reduce long-term IH regrowth [14]. In the present study, OPT

treatment was carried out at least up to the 9th month of life to ensure that a possible late proliferative phase has also been completed. Thus, recurrences unlikely occurred due to too short treatment time. As in our cohort the duration from OPT discontinuation to IH regrowth was 2 months, for facial we suggest prolonging the conducted average 6 months long initial OPT for another 2 months to an overall average 8-month-long initial OPT duration. OPT for facial IH could be prolonged to the 11–12th month of life to reduce the rebound probability. Gradual reduction in propranolol administration might be a valid option for early rebound identification [25]. However, the present study does not allow us to evaluate the effectiveness of these suggested adaptations to OPT treatment and monitoring.

The present study is limited by its retrospective nature and potential bias, such as undetectable confounding factors. IHs vary widely in type, size, number, and localization, so comparing treatment outcomes in a standardized manner is difficult. Our assessment of OPT success was based on subjective assessments of the doctors and parents. Our treatment protocol is also not comparable with those used in other studies; therefore, the advantages and disadvantages of our protocol over others cannot be determined. Furthermore, we only considered a circumscribed study population treated at one center, so we cannot exclude referral or selection bias. The limited number of patients may have restricted the number of complications and IH regrowth, and the true effects may not have been fully validated. Further studies including more patients are needed to evaluate risk factors for IH regrowth, and the effectiveness of the suggested adaptations to OPT treatment and monitoring.

Conclusion

In conclusion, the present study points out that facial IH relapse more frequently after oral propranolol therapy. We suggest to closely monitor patients with facial IH, as they might need extended or repeated oral propranolol therapy.

Authors' contributions Study conception and design: Giovanni Frongia.
Data acquisition: Giovanni Frongia, Ji-Oun Byeon.
Analysis and data interpretation: Giovanni Frongia, Ji-Oun Byeon.
Drafting of the manuscript: Giovanni Frongia, Ji-Oun Byeon.
Critical revision: Arianeb Mehrabi, Patrick Günther.
Accountable for all aspects of the work: G. Frongia.

Data availability N/A

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The local ethics committee approved this study. Ethical approval was obtained from the institutional review board.

Consent to participate Not necessary, in accordance with institutional ethic review board, due to retrospective study design.

Consent for publication N/A

Code availability N/A

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