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ORIGINAL PAPER

Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas

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Abstract Beta-blockers are a highly promising treatment modality for complicated infantile hemangiomas (IH). However, data on propranolol as first-line treatment, objective outcome measures and impact on hemodynamics in young infants is limited. We retrospectively evaluated a homogenous group of infants with proliferating complicated IH treated with propranolol (2 mg/kg/day). Outcome was assessed by blinded evaluation of clinical photographs by visual analogue scale (VAS), ultrasound examination and ophthalmological review (if appropriate). Tolerance and hemodynamic variables were recorded over time, including a 2-day in-patient observation at the initiation of therapy. Twenty-five infants (median age 3.6 (1.5–9.1) months) were included in the study. The median follow-up-time was 14 (9–20) months and 14 patients completed treatment at a median age of 14.3 (11.4–22.1) months, after a duration of 10.5 (7.5–16) months. In all patients, there was significant fading of colour (with a VAS of −9 (−6 to −9) after 7 months) and significant decrease in size of the IH (with a VAS of −8 (−3 to −10) after 7 months). Median thickness of the lesions assessed by ultrasound at baseline and after 1 month was 14 (7–28) mm and 10 (5–23) mm, respectively ($p<0.01$). In children with periocular involvement, astigmatism and amblyopia resolved rapidly within 8 weeks. The overall tolerance of propranolol was good, and no relevant hemodynamic changes were noted. *Conclusion*: Our report supports the excellent effect and good tolerance of this novel therapy, and we propose the use of propranolol as first-line treatment for IH.

Keywords Hemangioma · Infantile · Propranolol · Children · Betareceptor antagonist

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Introduction

Infantile hemangiomas (IH) are common, benign tumours, occurring in 4–10% of infants [9]. They are usually sporadic and show unique natural phases of proliferation and involution. The majority of IH can be left untreated and allowed to follow their natural course. However, a significant proportion of hemangiomas are associated with substantial morbidity in infancy and childhood [5]. IH that often require treatment include those involving the periorbital area, central face, airway, skin folds, anogenital area, sites at high risk for ulceration, dysfunction or disfigurement [6].

Systemic corticosteroids have been the mainstay of treatment for more severe IH; however, the response is variable, and side effects are insidious and difficult to monitor. Moreover, corticosteroids work best at stopping further growth, but actual shrinkage only occurs in approximately one third of patients [1]. Other treatment options for problematic IH include intra-lesional corticosteroids, vincristine, interferon-alpha, cyclophosphamide, laser, surgery or a combination of these therapies. However, each of these modalities has limited therapeutic benefit with its own side-effect profile and potential serious risks [2, 15].

In 2008, *Léauté-Labrèze* et al. reported the incidental finding that hemangiomas regress in children treated with propranolol, a nonselective beta-blocker used in treating infants with cardiac and renal conditions [12]. This report has been met with great interest and enthusiasm and physicians all over the world have started to use propranolol for the treatment of problematic IH. Several case reports and five published case series (including 23 to 58 patients each) have since supported the apparent efficacy of propranolol for IH [3, 10, 14, 17, 18]. The results of these observations are highly promising, consistently reporting propranolol to be effective and well tolerated for the treatment of IH, thus superior to oral corticosteroids. However, these are non-controlled studies, including heterogenous data regarding patient age, dose of propranolol, previous or concomitant treatment, monitoring and most of them lack objective evaluation. Moreover, no detailed information has been reported about the cardiovascular risks of propranolol in children treated for IH. We aimed to determine the effect of propranolol as first-line treatment for IH in a homogenous group of patients by blinded evaluation of clinical photographs and ultrasound examination at fixed time points. Using a standardised treatment protocol including a 2-day in-patient observation at the initiation of therapy we documented data on hemodynamic parameters during treatment.

Materials and methods

Patients

We performed a retrospective chart review of patients who were started on treatment with propranolol for problematic IH between December 2008 and December 2009 at the University Children's Hospital Zurich. Problematic IH were defined as hemangiomas with imminent impaired functional or cosmetic outcome if left untreated. These patients would have been treated with alternative methods (corticosteroids, laser or surgery) without the available knowledge of the efficacy of propranolol Only patients with proliferating IH up to the maximum age of 9 months and a complete 2-day in-hospital observation at the beginning of the treatment were included. Patients with ongoing or previous corticosteroid therapy were excluded. Consent to review patient case notes and for the treatment with propranolol (off-label indication) was received from all parents whose infants participated in this study in accordance with our institutional ethical standards.

Treatment protocol

Our centre for vascular anomalies defined a standardised protocol for the treatment of IH with propranolol in collaboration with the paediatric cardiology team. The following contraindications for the use of propranolol were applied: history or risk of asthma, reactive airway disease, impaired renal function, heart defects and arrhythmia with contraindication for the use of beta-blockers, children with central nervous system disorders, neonates under the age of 2 weeks and preterm babies before reaching a gestational age of 40 weeks. Before the start of treatment, the protocol included a clinical examination by a paediatric cardiologist, echocardiography, electrocardiogram (ECG), recording of baseline heart rate (HR) and blood pressure (BP), ultrasound examination (if possible due to the site of the lesion) and clinical photographs. Patients were admitted for a 48–72 h observation at initiation of treatment. On the first day, oral propranolol was administered at a dose of 1 mg/kg/day, divided in three doses, and increased to 2 mg/kg/day on the second day, if tolerated well. The children's HR and BP were monitored 1 h after administration of each dose of the medication and continuous HR monitoring was performed during their sleep. After completing the second day of treatment, the ECG, ultrasound of the lesion and photographs were repeated and the patients discharged, continuing on propranolol at 2 mg/kg/day, given in three doses per day. Follow-up visits were performed after 1 week, 1 month and every 2 months thereafter, including clinical examination, measurement of HR, BP and clinical photographs. Ultrasound examination was performed again after 1 week and 1 month. Patients with periocular IH additionally had regular ophthalmology reviews. The dose of propranolol was adjusted to weight during follow-up. Therapy was continued until the age of ≥12 months and weaned and stopped thereafter according to the clinical response by reducing the dose to 1 mg/kg/day for the last 4 weeks of treatment. Apart from the medication with propranolol no alternative or adjuvant therapies were performed.

Outcome measures

Digital photographs were taken by the same two hospital photographers who produced standardised images, using the same views and settings as in the baseline picture. The images were assessed by an independent board-certified dermatologist, who was unaware of the patient's age and

treatment at the time of each photograph. The observer documented changes in colour and size of the lesions on a visual analogue scale (VAS) ranging from −10 to +10 by comparing follow-up images to the baseline photograph pre treatment. On the visual analogue scale 0 represented the baseline photograph (pre-treatment), a decrease in colour or size resulted in a—number, an increase in colour or size in a + number.

If the location of the hemangiomas was amenable for ultrasound examination the maximal thickness of the lesions was measured by ultrasound (high resolution linear transducers with frequences from 5 to 17 MHz) at the above mentioned time points. The resistivity index as a measure of blood flow was very variable in relation to the activity of the patient and not consistently measured and therefore not included in this analysis.

For periocular IH, the outcome was reviewed by a board-certified paediatric ophthalmologist.

Adverse events were recorded by evaluation of the recorded hemodynamic variables in comparison to age-related normal values and the additional information in the patient's medical notes [8, 11, 16]. Hypotension was defined accordingly (systolic or diastolic blood pressure below the 5th centile for age) as follows [8, 11, 16]:

Age:	5th centile of systolic BP:	5th centile of diastolic BP:
0–3 months	57 mmHg	34 mmHg
3–6 months	71 mmHg	40 mmHg
6–9 months	85 mmHg	47 mmHg
9–12 months	87 mmHg	49 mmHg
12–36 months	90 mmHg	55 mmHg

Statistical analysis

Data collected from the patients' charts, ultrasound examination and evaluation of photographs by VAS were entered into a computerised database. Median and range were calculated for continous values. The figures show boxplots (without outliers and extremes). The Wilcoxon test was used to compare two related samples, the Friedman test was applied for repeated measures. The null hypothesis was rejected with a two-sided p value of <0.05.

Results

Patients and treatment

Twenty-five patients with IH were included in the study. The relevant epidemiologic and clinical characteristics of the patients and details about the individual treatment indication and duration are shown in Tables 1 and 2. The female-to-male ratio was 1.8: 1. The median age at start of treatment with propranolol was 3.6 (1.5–9.1) months. Three patients (numbers 2, 9, 23) were previously preterm infants born at 36 weeks of gestation and at initiation of treatment they were all older than 40 weeks of gestation. Patient number 3 was diagnosed with PHACE-syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities). He had a large plaque-type hemangioma on the left side of the face and a brain magnetic resonance imaging scan showed hypoplasia of the left internal carotid artery and an arachnoid cyst. Following review by the cardiology and neurology team, it was felt save to use propranolol in this patient.

At the time of initiation of treatment with propranolol, no patient was on any concomitant therapy. In two infants (numbers 13 and 19), laser therapy had been performed earlier without success and their IH continued to increase in size. All patients were treated with propranolol at a dose of 2 mg/kg/day. Fourteen patients completed treatment at median age of 14.3 (11.4–22.1) months and after a median treatment duration of 10.5 (7.5–16) months. Eleven patients had ongoing therapy with propranolol at the time of writing this paper (see Table 2). The median follow-up-time of all patients was 14 (9–20) months.

Treatment response

All IH stopped growing, faded in colour and became smaller (Fig. 1). VAS measurements of photographic documentation were available at time points 0 (baseline), 2 days, 1 week, 1, 3, 5 and 7 months for 25, 25, 22, 24, 17, 14 and seven patients, respectively. Figure 2a and b demonstrates the changes of VAS values for colour and size of the lesions over time. There was significant fading of colour and decrease in size of the IH during the follow-up period compared to the photographs at baseline. Of note, the VAS already decreased significantly within the first 2 days of therapy for both, colour and size. After 7 months fading of colour was reached with a VAS of −9 (−6 to −9) and shrinking of the lesions with a VAS of −8 (−3 to −10).

The two sub-groups of infants with deep (n=17) and superficial, plaque-type hemangiomas (n=8) were compared regarding their treatment response. The changes of VAS did not differ significantly either for size or colour at any of the time points between these two groups (data not shown).

Twenty-four patients were examined by ultrasound at baseline and during follow-up. The measurements of 11 patients were technically sufficient to be included for the analysis. The reasons for exclusion of other patients were difficulties in gaining reproducible readings due to the

Table 1 Clinical characteristics of all 25 patients

Patient no.	Gender	Type of hemangioma	Localisation of hemangioma	Age at start propranolol treatent (months)	Indication for treatment	Duration of propranolol treatment (months)	Age at end of propranolol treatment (months)	Relapse after propranolol treatment
1	Male	Plaque-type	Infraorbital/cheek	4.0	Functional risk	11.0	15.0	No
2	Female	Deep	Parotid region and forearm	3.3	Cosmetic risk	11.0	14.3	Yes
3	Male	Plaque-type	Left side of face, phace[a]-syndrome	1.5	Functional risk	16.0	Ongoing	.
4	Male	Deep	Infraorbital	2.2	Functional risk	16.0	18.2	No
5	Female	Deep	Nasal tip	5.3	Cosmetic risk	9.0	14.3	No
6	Male	Deep	Nasal tip	3.4	Cosmetic risk	11.0	Ongoing	.
7	Female	Plaque-type	Philtrum	4.0	Cosmetic risk	8.5	12.5	Yes
8	Female	Deep	Perianal	8.4	Functional risk	9.0	17.4	No
9	Female	Deep	Parotid region	4.9	Cosmetic risk	14.0	Ongoing	.
10	Male	Plaque-type	Periocular and forehead	3.9	Functional risk	7.5	11.4	No
11	Male	Deep	Nasal tip	4.3	Cosmetic risk	12.0	16.3	No
12	Male	Plaque-type	Complete right arm	3.2	Cosmetic risk	10.0	13.2	No
13	Female	deep	Genital	9.1	Functional risk	13.0	22.1	No
14	Female	Deep	Nasal tip	6.8	Cosmetic risk	12.0	18.8	No
15	Female	Deep	Nose and temporal region	3.3	Cosmetic risk	10.0	13.3	No
16	Female	Plaque-type	Nose	2.6	Cosmetic risk	10.0	Ongoing	.
17	Female	Deep	Ear	2.0	Cosmetic risk	11.0	Ongoing	.
18	Female	Deep	Upper eyelid	3.0	Functional risk	10.0	Ongoing	.
19	Female	Deep	Upper lip	7.1	Cosmetic risk	10.0	Ongoing	.
20	Female	Deep	Ear	2.9	Cosmetic risk	10.0	12.9	No
21	Female	Deep	Ear	2.0	Cosmetic risk	9.0	Ongoing	.
22	Female	Plaque-type	Forehead	5.5	Cosmetic risk	9.0	Ongoing	.
23	Male	Deep	Upper eyelid	2.3	Functional risk	12.0	14.3	No
24	Female	Deep	Head	8.3	Cosmetic risk	9.0	Ongoing	.
25	Male	Plaque-type	Perianal, genital	3.6	Functional risk	9.0	Ongoing	.

[a] *PHACE*, posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities

location of the IH, poor cooperation of the patient and different examiners. Measurement of the thickness of the IH proved to be the most reliable indicator for regression. There were no changes of echogenicity observed during regression. Figure 3 shows the decrease of hemangioma thickness within the first month of treatment as assessed by ultrasound examination. Median thickness of the lesions at baseline and after 1 month were 14 (7–28) mm and 10 (5–23) mm, respectively ($p<0.01$). All five ulcerated hemangiomas healed completely within 2 weeks after start of treatment with propranolol.

Six patients (numbers 1, 3, 4, 10, 18 and 23) had periocular involvement of their IH. Four of them (numbers 3, 10, 18 and 23) presented with partial obstruction of the visual axis and amblyopia in the preferential looking test. In two children (numbers 4 and 10), unilateral astigmatism of −1.5 and −2.0 diopters was noted due to the IH. After baseline examination, standard occlusion therapy of the unaffected eye was initiated in the four children with amblyopia. At the same time, the children were started on propranolol. Fast resolution of the visual axis obstruction was noted in all of them and occlusion therapy could be stopped after 1 to 6 months with no signs of amblyopia. Astigmatism as well improved rapidly to −0.5 and −0.75 diopters with equal refraction in both eyes within a few weeks to maximum 2 months.

In two of the 14 patients who completed treatment with propranolol, mild re-growth and darkening of colour was noted in their IH at 8 weeks after discontinuing therapy. These patients (number 2 and 7) had been treated with propranolol for a total of 11 and 8.5 months, and therapy was stopped at the age of 14.3 and 12.5 months, respectively. They were both re-started on propranolol and their IH rapidly improved again.

Table 2 Summary of baseline characteristics and treatment of children with hemangiomas

Patient characteristics and treatment	$n=25$
Female-to-male ratio	1.8:1
Type of hemangioma	
superficial/plaque-type	8
deep	17
Localisation of hemangioma	
head	21
nose	7
periocular involvement	6
parotid area/ear involvement	5
perianal area	3
PHACE[a]-syndrome	1
Ulcerated hemangiomas	5
Echocardiogram pre-treatment	
normal	21
persistent foramen ovale	4
Electrocardiogram pre-treatment	
normal	23
abnormal	2
Age initiation of propranolol (months)	
median (range)	3.6 (1.5–9.1)
Duration of propranolol treatment (months), $n=25$	
median (range)	10 (7.5–16)
Age at end of propranolol treatment (months), $n=14$	
median (range)	14.3 (11.4–22.1)
Duration of propranolol treatment until stopped, $n=14$	
median (range)	10.5 (7.5–16)

[a] *PHACE*, posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities

Hemodynamics and adverse events

As shown in Table 2, echocardiography performed at baseline revealed a persistent foramen ovale in four patients. Pre-treatment ECG was normal in all children except for two patients, whose QT duration was mildly prolonged (corrected QT interval of 455 and 456 ms, respectively).

We evaluated hemodynamic variables during the 2-day in-patient observation at initiation of treatment. Baseline values of HR, systolic and diastolic BP were compared with the minimal values measured during the 2-day in-patient stay, as shown in Fig. 4. At baseline, the HR was 121 (108–150) bpm, systolic BP 86 (70–116) mmHg and diastolic BP 49 (30–71) mmHg compared to 100 (58–125) bpm, 76 (64–110) mmHg and 45 (31–69) mmHg as minimal values during the 2-day observation, respectively ($p<0.05$). Transient bradycardia was noted in four patients. These episodes occurred at night during sleep and were all self-limiting without necessitating stimulation of the infant. Other vital parameters (e.g. BP, oxygen saturation) were unremarkable at the same time. In three infants with repeat short bradycardia the dose of propranolol was increased slower and in-patient observation prolonged up to 3 to 4 days. With this regimen, bradycardias ceased in all patients, and they were discharged at the intended propranolol dosage of 2 mg/kg/day. In six children, low blood pressure was recorded during the first 48 h of treatment while the infants were asleep. All six of them had a decreased diastolic BP but only three of them had low systolic values. However, these BP values were usually only 2–10 mmHg below the normal age range and no patient showed any concomitant symptoms.

ECG changes compared to baseline ECG were noted in seven patients before discharge. All of these seven infants had a mild prolongation of the PQ duration (PQ interval of 122 to 140 ms;). The prolonged corrected QT interval noted as baseline remained unchanged in one patient and resolved in the other.

Values of HR, systolic and diastolic BP at the time points 1 week, 1, 2, 5, 7 and 9 months were available in 24, 24, 17, 12 and eight patients, respectively. Figure 5 shows the mean values of HR and BP during 7 months of treatment with propranolol.

During follow-up, the following additional symptoms were reported by the children's parents: sleepiness ($n=1$), sleep disturbances ($n=1$) and increased level of anxiety ($n=1$). All of these symptoms were only reported at a single follow-up visit and self-limiting thereafter. Overall adverse events were all mild and transient and there was no treatment drop-out of patients due to adverse events. Neurologic follow-up of patient number three with PHACE-syndrome revealed a global developmental delay of 5 month at the age of 16 months. This was felt to be related to the PHACE-syndrome and the detected brain abnormalities.

Discussion

Problematic hemangiomas require intervention to control growth and reduce the likelihood of imminent functional and cosmetic deformities [6]. Since the report of *Léauté-Labrèze* et al. in 2008 propranolol has been widely used for the treatment of problematic, although randomised controlled studies have not been finished yet [12]. Propranolol is a non-selective beta-receptor antagonist which has previously been used in young infants for a variety of indications, such as hypertension, supraventricular tachycardia, congestive heart failure and thyrotoxicosis [4]. Although widely used now for the treatment of complicated IH, a generally accepted concept of how propranolol works in IH is lacking. *Storch* et al. recently summarised the current

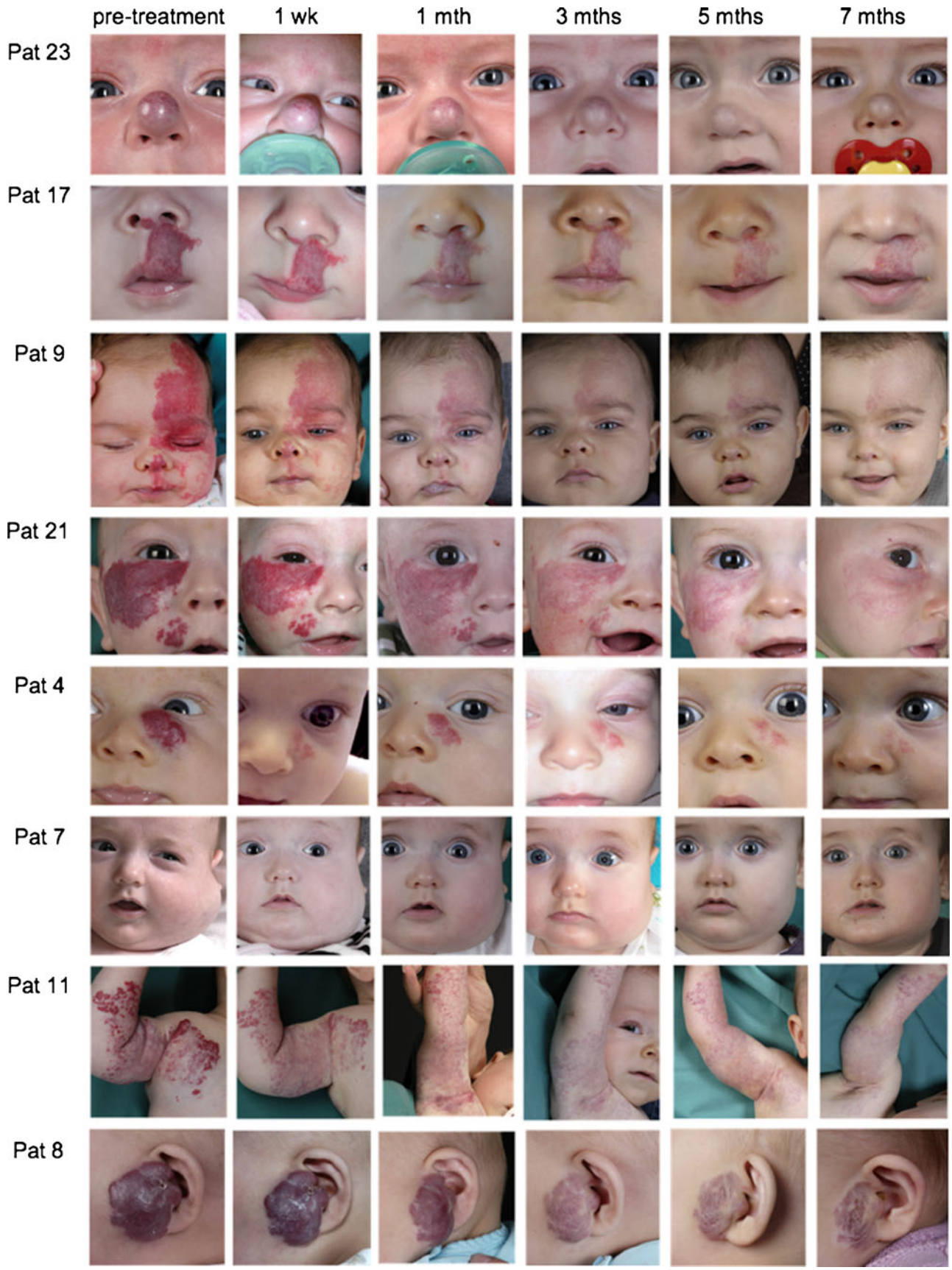

Fig. 1 Photographic documentation of eight infants with problematic infantile hemangiomas during treatment with propranolol

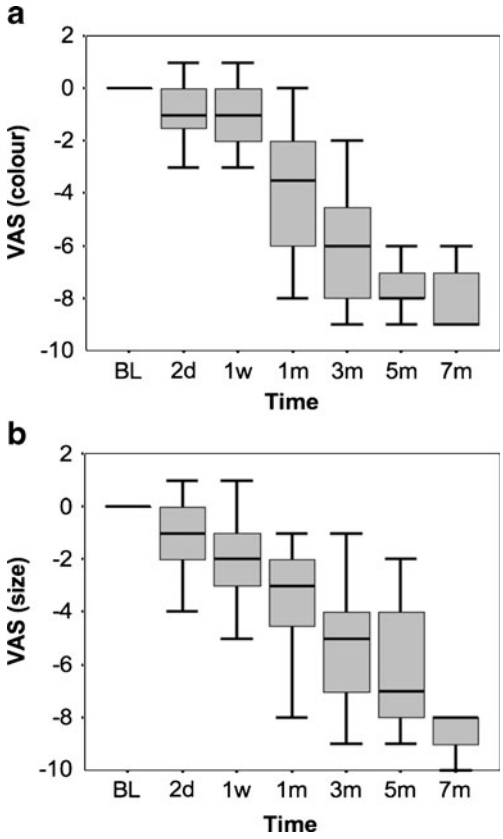

Fig. 2 Changes of VAS regarding colour (**a**) and size (**b**) of the hemangiomas during follow-up and treatment with propranolol (*BL* baseline; *d* days; *w* weeks; *m* months); $p<0.01$ for both parameters

knowledge on the molecular mechanisms involved [19]. The striking effect of propranolol on growing IH can be attributed to three molecular mechanisms: vasoconstriction, inhibition of angiogenesis, and induction of apoptosis. They correspond to early (brightening of hemangioma surface),

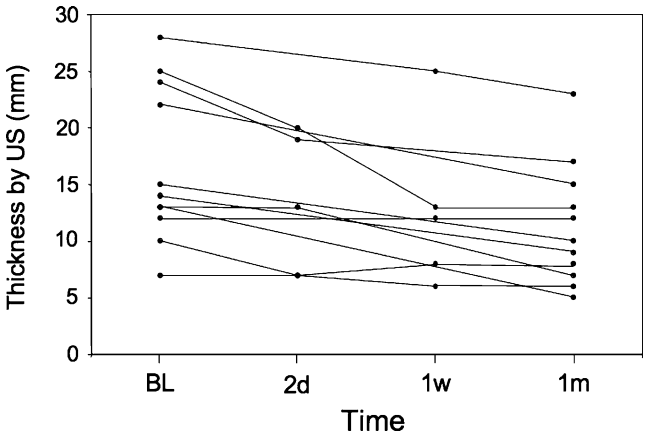

Fig. 3 Change of hemangioma thickness measured by ultrasound (US) in 11 patients during the first month of treatment (*BL* baseline; *d* days; *w* week; *m* month); $p<0.01$

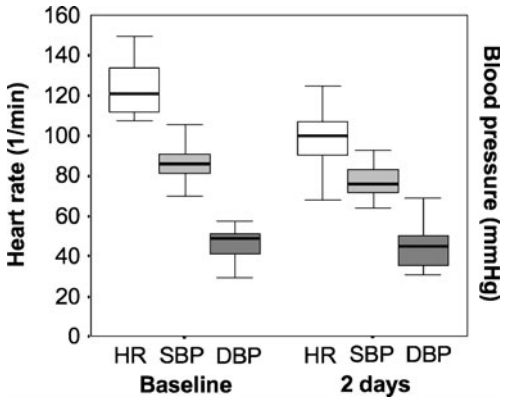

Fig. 4 Hemodynamic variables during the 2-day in-patient observation at initiation of treatment with propranolol. Baseline values of heart rate (HR, *white boxes*), systolic (SBP, *light grey boxes*) and diastolic blood pressure (DBP, *dark grey boxes*) are shown in comparison with the minimal values recorded ($p<0.01$ for HR and SBP, $p=0.03$ for DBP)

intermediate (growth arrest), and long-term (regression) clinical observations.

Following the observation of *Léauté-Labrèze* et al., several case reports and five case series (including 23 to 58 patients each) have described the excellent effect of propranolol for the treatment of IH [3, 10, 14, 17, 18]. However, in most of these series, propranolol was not used as single therapy and a proportion of the reported patients received concomitant systemic or intralesional steroids and laser treatment [3, 14, 18]. In addition, varying age groups of children and thus different stages of hemangiomas were included in these studies and objective outcome measures were limited or lacking. *Sans* et al. report the efficacy of propranolol (dose 2–3 mg/kg/day) to be 100% in 32 patients, based on the individual judgement of the treating physicians in most cases and additional ultrasound examination in 11 patients (34%) [18]. Based solely on the clinical and photographic evaluation by the treating physicians *Laforgia* et al. and *Manunza* et al. reported an excellent response of propranolol (dose 2 mg/kg/day) for IH in 23 and 30 children, respectively [10, 14]. *Qin ZP* et al. in China treated 58 children with propranolol (dose 1.0–1.5 mg/kg/day) for IH [17]. The overall treatment response was evaluated with the use of a four-point scale by the treating physicians. The outcome was excellent in 17.2%, good in 60.4% moderate in 20.7% and poor in 1.7% of cases. Most recently, *Buckmiller* et al. evaluated 32 patients treated with propranolol (dose 2 mg/kg/day) by clinical examination (treating physicians) and assessment of photographs by blinded physicians, revealing 50% of patients to be excellent responders, 47% partial responders and 3% non-responders [3].

In our study, we included only infants with proliferating hemangiomas who were exclusively treated with propranolol

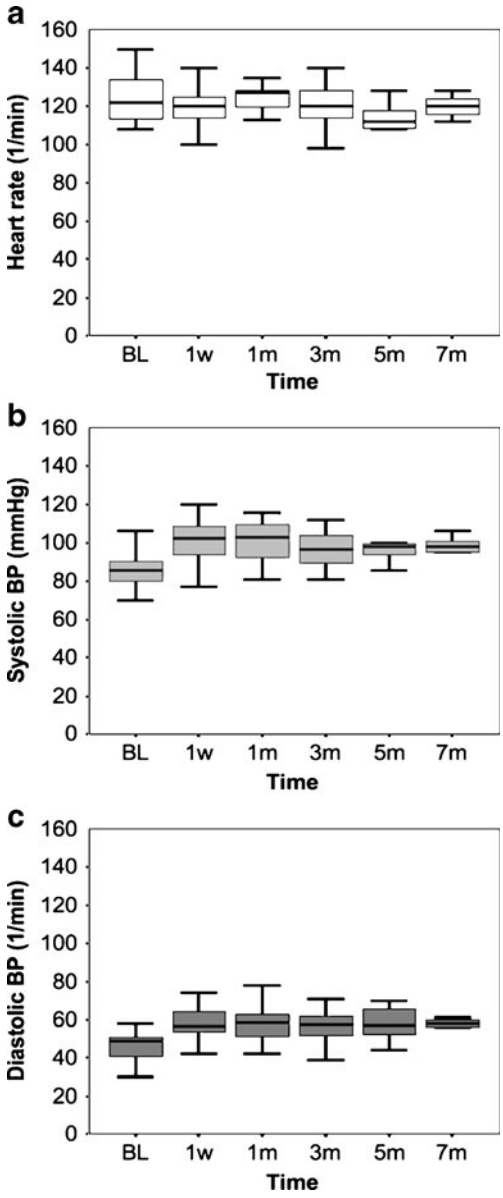

Fig. 5 Heart rate (**a** *white boxes*, $p=0.04$), systolic (**b** *light grey boxes*, $p=0.09$) and diastolic blood pressures (**c** *dark grey boxes*, 0.15) during 7 months of treatment with propranolol (*B*L baseline; *w* week; *m* months)

at a consistent dose of 2 mg/kg/day, according to a standardised protocol. Blinded evaluation of digital photographs revealed significant fading of colour and decrease in size of all IH. Unlike *Qin* et al., we did not find a significant difference in response between deep and superficial haemangiomas in our small cohort [17]. However, it is our impression that superficial hemangiomas in particular seem to reach a certain plateau of response after approximately 7 to 8 months of treatment with characteristic residual telangiectatic skin changes, whereas deep hemangiomas (e.g. parotid hemangiomas) more likely completely resolve.

As an objective outcome measure, we included ultrasound examination of the IH. Reduction in IH thickness proved to be the most reliable indicator for regression. However, gaining reproducible ultrasound data of IH in this cohort of young infants is challenging, depeding on size and location of the lesion and cooperation of the patient. The resistivity index as a measure of vascularity has been used in the study by Sans et al., however we observed a great variability of the resistivity index related to the activity of the patients and therefore did not include this variable [18]. The overall value of ultrasound assessment for recording treatment response of IH remains unclear at this stage.

For infants with periocular IH, ophthalmologic examination is an important and helpful monitoring measure during treatment. In our opinion, the resolution of visual axis obstruction, astigmatism and initial amblyopia was substantially quicker than what we usually observed with corticosteroid treatment. The general observation that propranolol may induce a more rapid and greater clinical improvement of IH than corticosteroids is supported by a small recent retrospective comparative study (Powell J et al., oral communication at the 18th Workshop of the *International Society for the Study of Vascular Anomalies (ISSVA)*, Brussels, 2010) but needs to be confirmed in larger comparative trials.

The true frequency of recurrence of IH after stopping treatment with propranolol cannot be addressed by our limited data. However, recurrences seem to occur in approximately 20–40% of cases [10, 18] (Phillips R et al. and Pope E et al., oral communications at the 18th Workshop of the *International Society for the Study of Vascular Anomalies (ISSVA)*, Brussels, 2010). Most interestingly, re-growth of IH's after stopping propranolol is also observed in children older than 12–14 months, thus at a time when the natural proliferation phase is believed to be well completed. This unexpected phenomenon raises the question whether treatment with propranolol may delay the natural growth phase of IH. Predictors of regrowth after stopping treatment remain to be identified. However, as in our group, recurrences of IH are usually mild and the patients respond well to re-treatment with propranolol.

Although we found a significant decrease in HR and BP during the 48-h in-patient observation at the start of therapy, these changes were mild and not associated with any symptoms. Of note, these values are probably also explained by the children's activity level at the time of measurement and represent physiological differences. Whereas baseline values originated from alert children during daytime, the recorded minimal values were detected at night during sleep. Regarding the blood pressure values it needs to be considered that automated measurement of diastolic BP often is inaccurate in this young age group.

This may limit adequate assessment of adverse effects. A prolongation of the PQ duration, as noted in the ECG of seven infants after starting treatment, represents the expected effect of beta-blocking agents on the atrio-ventricular node. Overall, no critical hemodynamic changes occurred during treatment with propranolol. Frequency and nature of adverse events observed in our cohort were similar to other reports and overall considered to be minor [3, 10, 14, 17, 18].

During 40 years of clinical experience no serious cardiovascular event was recorded for children on chronic beta-blocker therapy [13]. Hypoglycaemia may occur due to beta-blocking therapy and has recently been reported in four infants treated for IH [7, 11]. We did not observe any hypoglycaemia in our cohort; however, blood glucose levels were not routinely measured. Of note, two of the cases reported by Holland et al. had been on long-term propranolol therapy before the episode of hypoglycaemia occurred, without any known previous abnormalities of blood glucose levels. Although hypoglycaemia seems to be a rare adverse event physicians must be aware of the potential for hypoglycaemia and propranolol should be discontinued during inter-current illness, especially in the setting of restricted oral intake. Overall adverse events during propranolol treatment appear minor as compared to the serious side effects of previous modalities for the treatment of IH such as systemic corticosteroids and interferon-alpha, which is associated with spastic diplegia in up to 25% [13]. However, as propranolol evolves as a new medical indication, careful monitoring is warranted.

This study is subject to a number of limitations: small cohort of patients, retrospective and uncontrolled study design, limited ultrasound values as objective outcome measure. However, we believe this report adds further data to demonstrate the high efficacy of propranolol as first-line treatment for problematic IH. In addition, our detailed analysis of cardiovascular variables supports the good overall tolerance of this therapy in young infants. Randomised-controlled studies with a large collective will be helpful to more accurately investigate the efficacy and safety of propranolol and reveal further information on appropriate treatment dose and duration in particular.

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