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Propranolol for infantile haemangioma: Striking effect in the first weeks

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ABSTRACT

Objective: Discuss effect and dynamics of propranolol (PR) treatment in infantile haemangioma (IH) of head and neck in children during follow-up.
Methods: Between 2010 and 2011, 22 children with head and neck infantile haemangioma (IH) treated by PR were recruited into the study. In a retrospective chart review clinical data were analyzed at 5 consecutive, different check-up time from 1 week to 12–14 months. Effectiveness of PR treatment was assessed by a symptom score method.
Results: In the whole series a significant regression was observed in 13 patients (59%) in the first week of the therapy. Further five patients showed this time a marked, two mild improvements, and two children did not respond initially to the PR therapy. In one of them (case #8) later on a mild improvement could be seen too. At the second check-up (1 month after initiating PR therapy) 50% of children showed definitive improvement compared to the first visit. Difference between first and second check-ups was significant, and between the 4th and 5th visits the improvement showed the lowest rate. Comparison of IH regression between the 2nd and the 5th check-ups resulted in a p value a little larger than 0.05.

There was not significant correlation between the initial IH severity and the treatment effectiveness at the follow-ups ($p > 0.05$). No significant differences were found in treatment effectiveness concerning the IH localizations, too.
Conclusion: PR treatment is highly effective in children with IHs. The most striking effect is seen at the first week of treatment; later improvement is much slower, sometimes with periods of stagnations. The cause of this is probably the spectacular early effect of vasoconstriction, though other impacts of PR to the individual molecular markers of IH seemed to be less impressive clinically. However, treatment should be continued for at least 6 months because early cessation can cause a relapse.

1. Introduction

Infantile haemangiomas (IH) are the most common tumors of infancy with an incidence of >2% of infants in general, and of 10% of Caucasian children, in particular. IH typically presents few a weeks after births, and occur more frequently in girls [1]. In most cases they are limited to cosmetic, esthetic or certain functional defects; however, although benign, severe IH can also be life threatening if it affects the airways. Despite their tendency to undergo spontaneous regression, their management can be challenging. Various modalities have been applied for treating of IHs: (a) watchful waiting, (b) administration of a high dose of corticosteroids, vincristine or interferon alpha, or (c) use a "cold knife", laser surgery and cryosurgery. Each of these options involves significant drawbacks and/or side effects [1].

Recently Léaute-Labréze et al. described their serendipitous observation of an antiproliferative effect of propranolol on IH [1]. Since the original publication of their finding in 2008, several papers emphasized the effectiveness of PR on IH. During the last four-year-period, PR became the first-line treatment of children with IH. Although the correct mechanism of the drug is not quite clear, a possible molecular effect of PR to different target points in IHs has been published [2]. Minimal or no side effects have been reported, and the regression rate has been near to 100%.

Nevertheless, there are few data in the literature on the dynamics of IH improvement, especially in long-term follow-up. Sans et al. reported PR treatment of 32 cases in which recovery was achieved after 2 months, treatment being continued for a mean duration of 6.1 months [3]. Others have recommended PR treatment for 6–18 months [4,5]. However, these studies did not

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specially address the issue of the temporal dynamism of regression, and evaluated only the long term outcome.

We have therefore conducted a study focused on the dynamic changes in IHs of the head and neck region in children with a view, during the follow-up period of 6–14 months of PR treatment. A further aim of the study was to assess the effectiveness of PR treatment concerning the initial severity and localization of IH during the treatment course. Data were collected in order to establish the need for continuing or terminating the treatment.

2. Material and methods

Between 1st October 2010 and 31st December 2011, 22 consecutive patients (17 females and 5 males), aged 1 month to 8 months (mean: 3, 7 months) were recruited into the study. All of them had IH in the head and neck region. The patients had been admitted for treatment to the departments of otorhinolaryngology, pediatrics and dermatology in a tertiary level children's hospital in Budapest, Hungary. Prior to commencing the study all patients had undergone thorough clinical examination by a dermatologist, pediatrician, ENT surgeon and a cardiologist. In cases involving cutaneous IHs a photo had been taken, the initial status had been scored and recorded. In cases with pharyngeal, glottic, subglottic and tracheal IHs whole airway endoscopy had been carried out. In patients with periorbital and orbital involvement ophthalmologic check-ups had been performed with ultrasonograhpy.

Nine patients had received steroid treatment – oral prednisolon was given in a dose of 1 mg/kg/day – before the administration of PR, for the mean duration of 1.5 weeks (5–14 days), without any significant effect. In four children CO_2 laser surgery had been carried out after 7–8 months of PR treatment because of severe skin involvement. The other nine children had been treated with PR only.

After cardiac examination, oral PR therapy was initiated in all children in a dose of 2 mg/kg/day in 3 divided doses a day and ECG and blood glucose level monitoring were continued in the first 48 h of PR therapy. For this period the children were admitted to the ward, for subsequent therapy the treatment was continued as an outpatient basis. The blood glucose level, blood pressure and pulse rate were checked at all controls. Ten children with large skin lesions, received local PR treatment as well, twice-a-day (2% cream). This local therapy was given during the whole treatment period. The oral PR therapy for all children was continued for at least 6 months and was terminated when no further improvement could be detected.

The medical records of the patients were evaluated retrospectively. The following variables were taken into consideration in the assessment: IH color, extension, stiffness with palpation, local complications such as bleeding and ulceration.

The initial severity of IHs was scored as follows: a score of 1, 2, 3 and 4 if the diameter of the IH was $<$2 cm, 2–3 cm, 3–4 cm or $>$than 4 cm, respectively. The color of IHs was scored at the same way: score 0 for mild, 1 for moderate an 2 for severe grade of the symptom. The stiffness was scored as 0 or 1 (soft or hard) by palpation. The summarized highest score was 5. Score 5 was given if a complication of IH (ulceration or bleeding) was detected, independently of the extension of IH.

In patients with subglottic lesions the stridor, dyspnea and the endoscopic findings were considered as variables (this affected a total of 2 patients). The scores were the following: score 0, 1 or 2 according to the degree of the stridor, 0 or 1 as dyspnea was observed or not, and 0, 1, or 2 according to the degree of subglottic stenosis caused by IH compared to the age-matched normal lumen (0 if lumen was $>$70%; 1 if 70–50%; and 2 if the lumen was less than 50%). The possible highest score was 5 in this group, too.

In four patients with periorbital IHs the extension and thickness was measured by ultrasound.

The IH status was checked five times during the follow-up: first after 1 week of therapy, secondly after 1 month, then 2–3 months, 4–6 months and the fifth was at 12–14 months of therapy or observation.

The regression, stagnation or progression of IH was analyzed on each occasion through assessing its changes in diameter, stiffness, color and possible complications. Regression (improvement of IH) or progression (worsening of IH) received a value of one, two or three "+" sign according to the degree compared to the previous visit status, while stagnation was marked with an "s" letter.

The final result was deemed as excellent, when the IH regression showed marked reduction both in color and

Table 1
Clinical data on 22 children at five consecutive check-ups.

No.	Name	Sex	Age (mo)	IH location	IH score	Check-ups					Late outcome
						1	2	3	4	5	
#1	K.K.	F	2	Parotideal, retro-auricular, occipital	4	r+++	s	s	r+	p++	Fair
#2	S.A.	F	1.5	Subglottic, face, upper arm	5	r+++	r+	s	r+	r+	Good
#3	B. R.	F	1	Nasal peak	5	r+	r+	s	s	s	Good
#4	S. R.	M	7	Occipital	3	r+	p+	s	s	r+	Fair
#5	K.V.	F	1	Face	3	r++	r+	r+	s	r++	Good
#6	S.D.	M	2	Parotideal	4	r+++	r++	r+++	r+++	r+++	Excellent
#7	N.N.	F	7	Occipital, retro-auricular, chest	5	r+++	r+	r+	r+	r+	Excellent
#8	P.E.	F	2	Face	2	p+	s	r+	s	r+	Fair
#9	K.K.	F	2	Face, eyelid	3	r+++	r++	r+	s	s	Good
#10	V.Z.	F	8	Periorbital	2	r++	r+	s	s	r+	Good
#11	B.N.	F	4	Labial, tongue, face	4	s	s	p+	p+	s	no change
#12	S.Z.	F	7	Face	3	r+++	p+	s	s	s	Fair
#13	K.D.	M	2	Midface, nasal, lower arm	2	r+++	r+++	r+++	r++	r++	Excellent
#14	S.L.	F	4	Face	4	r++	r++	r++	r++	r+	Excellent
#15	H.R.	F	3	Face, chest	3	r++	r+	r+	s	r+	Good
#16	L.R.	F	4	Face, periorbital	4	r+++	r++	s	r+	r+	Good
#17	S.Z.	M	5	Face, periorbital, labial	3	r+++	r++	r+	r+	r+	Excellent
#18	H.V.	F	3	Subglottic	5	r+++	r++	r+	r+	r+	Excellent
#19	P.L.	M	1	Eyelid, buccal	3	r+++	r+++	r++	s	r+	Excellent
#20	V.L.	F	2	Labial, parotideal, earlobe	3	r+++	r++	r+++	r+	r++	Excellent
#21	C.E.	F	8	Parotideal	3	r++	r++	s	r+	p+	Good
#22	T.L.	F	1	Nasal peak	2	r+++	r+++	r+++	r+	s	Excellent

The distribution of patients by gender, age, hemangioma localization. The extent and clinical course of IH during the five medical check-ups as measured in IH scores (see in the text).
Abbreviations: p: progression; r: regression; s: stagnation; +: mild; ++: definite, +++: significant.

extension, good when a definite improvement was achieved and no additional treatment was necessary and fair when there was only mild improvement and laser surgery had to be carried out.

For statistical evaluation the SPSS 15.0 program version was used. As IH is an ordinal variable rank procedures were used to evaluate changes and relationships. Changes in the IHs at the different control check-ups were compared by means of the *Friedman test* (for more than two samples) and *Wilcoxon signed rank* test (for comparing two samples), applied on related samples. $p = 0.05$ was regarded as the threshold for statistical significance. The possible relationship of the effects of PR treatment at different control check-ups with the initial severity scores and the localization of IHs were assessed. The *Spearman-correlation* was used to explore the relationship with initial IH score and *Kruskal–Wallis test* (comparing more than two groups) to analyze the relationship with the localization.

The study received the approval of the Institutional Review Board of the hospital. Informed consent was received from the parents of all children.

3. Results

We analyzed the data collected throughout the period of treatment and observation for the 22 children at five check-up times. Relevant data relating to the age, the sex, the localization and the extension of the IH and its clinical outcome are presented in Table 1.

Eight children had only one IH in the head–neck region, while 14 exhibited multiple IHs. In seven cases IHs in the orbital–periorbital, nasal, airway or oral regions posed the risk of functional complications.

All but one of the children responded positively to the PR treatment. As an early outcome excellent regression was achieved in nine patients (41%), a definitive improvement in further eight patients (36%). In case #1 a rapid regression was observed at the first week of therapy, but after a subsequent 14 weeks period of stagnation, marked progression was detected despite of continuous PR treatment. In case #11 the diagnosis was reassessed as venous malformation since PR was ineffective, and CO_2 laser surgery was carried out with some improvement. The most frequent locations of IH were on the face, in the parotid and periorbital regions. Two children (case #2 and #18) in this series presented an airway compromise caused by IH. Both of them responded promptly and very well to the PR therapy, but in case #2 a stagnation of the symptoms was observed in the follow-up after 6 months. However, despite the severe initial condition no surgery was necessary.

In the overall series a significant regression was observed in 13 patients (59%) during the first week of the therapy. A further five patients exhibited a marked improvement and two cases a mild improvement during this time, whereas two children failed to respond initially. However, in one of these 2 cases (case #8) a mild improvement was seen later. By 2–3 months after the start of PR therapy 50% of the children displayed a definitive improvement relative to the first control. Subsequently, only less than 30% showed noticeable or marked improvement compared to previous check-ups. After completion of the course of PR therapy, cases #1, #4, #8 and #12 participated in CO_2 laser surgery.

Table 2
Mean ranks at different visits.

	Mean rank
Follow-up 1	4.39
Follow-up 2	3.20
Follow-up 3	2.68
Follow-up 4	2.18
Follow-up 5	2.55

The dynamics of IH change considering the mean ranks is featured in the table. The improvement was the most expressed at the first and second consecutive check-ups, but slowed later. A slight acceleration in the regression of the IH can be seen at the time of the last follow-up. The result was significant for the 5 different check-ups applying the Friedman test (chi-square = 32.079, df = 4, $p < 0.0001$).

The dynamics of IH changes represented by rank means is shown in Table 2. Improvement was striking at the first visit after which the IH regression rate slowed down. A slight, not significant acceleration of IH average regression could be seen again at the final examination.

The *Friedman test* indicated significant differences between the results of five follow ups (chi-square = 32.079; df = 4; $p < 0.0001$).

The changes in the clinical appearance of IH at the five consecutive visits are featured in Table 3. The difference between the findings at the first and second follow-up was significant ($p = 0.002$) while that between the fourth and fifth check-ups was the least expressed ($p = 0.592$) (*Wilcoxon signed rank test*).

The *Friedman test* did not reveal a statistically clear and significant difference between the results of the last four consecutive controls, only a borderline statistical significance (chi-square = 7.196; df = 3; $p = 0.066$).

There was no significant correlation between the initial severity of IH and the effectiveness of treatment at the various controls (k1: $r_s = 0.087$, $p = 0.7$; k2: $r_s = -0.231$, $p = 0.3$; k3: $r_s = -0.340$, $p = 0.12$; k4: $r_s = 0.163$, $p = 0.46$; k5: $r_s = -0.131$, $p = 0.56$) and no significant differences in treatment effectiveness were observed for IH localizations (k1: $p = 0.34$; k2: $p = 0.09$; k3: $p = 0.56$; k4: $p = 0.17$; k5: $p = 0.93$) either.

In two cases, (case #12 and #21) the dose of PR had to be temporarily reduced from 2 mg/kg/day to 1 mg/kg/day for 2 weeks, because of temporarily decreased pulse rate. No changes in blood glucose level had been detected. No other side-effects of the therapy were observed. The patients with extensive skin lesions benefited from topical PR cream in addition to oral administration of the drug.

4. Discussion

In the last 3 years, the oral administration of PR has become the first-line treatment of IHs [6]. PR has progressively replaced steroids from the therapeutic regimen because of its effectiveness and low side-effect rate. There have been reports of excellent effects on IH in the airway, trachea, and mediastinum and on the skin throughout the whole body, especially in the head and neck region [7–9]. The result of the present cohort of 22 children with head and neck IHs confirms the high efficacy of PR therapy.

Despite the communications on the positive experiences with PR therapy, the mechanism of its effect is still not clear. It is thought that vasoconstriction may be responsible for the initial color change [1,2,10]. The pathway leading to resolution may involve down-regulation of proangiogenetic factors such as basic fibroblast growth factor and vascular endothelial growth factor and triggering apoptosis of capillary endothelial cells [1,2,10]. There are data on the effect of PR in selectively inhibiting the expression of MMP-9 (angiogenic and extracellular matrix degrading enzyme) and human brain microvascular endothelial cells, which cells are playing an essential role in tumor angiogenesis [2,10,11].

In our series, all of the IH patients responded to PR therapy. In 13 (59%) of children excellent regression was detected in the first week, and in further 7 patients (36%) the improvement was good or acceptable. After the follow-up of 6–8 months, the late outcome

Table 3
Changes in clinical appearance if IH at consecutive visits.

	Check-up 2 to check-up 1	Check-up 3 to check-up 2	Check up 4 to check-up 3	Check-up 5 to check-up 4
z	−3.077	−1.538	−1.567	.535
p	.002	.124	.117	.592

Comparison of the results considering IH changes is indicated here at the time of the 5 consecutive check-ups. A significant difference in IH improvement was seen between the first and second visits ($p = 0.002$) as measured in IH scores. The improvement was least expressed between the fourth and fifth check-ups ($p = 0.592$) (*Wilcoxon rank test*).

was excellent in 9 children, good in 8, and fair in 4. These results are in accordance with those of Buckmiller et al. [12] who reported an improvement in quality of the IH during PR therapy in 97% of 32 children; 50% were excellent responders, 47% partial responders and only 1.3% was non-responder. The partial and non-responder children received other therapies (laser surgery or steroid injections). In our cohort four children necessitated CO_2 laser surgery after 6–8 months of PR therapy. Steroid treatment was initiated in 9 patients, but after the introduction of PR, steroid was abandoned.

The limitation of this study (as for similar studies) is the lack of objective measurement for the therapeutic effect of the treatment. Even ultrasound assessment, which was applicable in certain cases, could give data on the thickness of IH only. However, in our opinion the visual analog scale with symptom scores and photographs allowed us to sufficiently detect the changes of IH during therapy.

Only minimal side effects were noted: the dose of PR had to be reduced and suspended for 2 weeks in two patients because of lower pulse rate and lower blood pressure. These findings are similar to those of others [13].

Gou and Ni [14] were the first to describe the benefit of topical timolol solution (a β-blocker) for treating a large eyelid IH in a 4-month-old infant. We also applied locally a 2% PR cream to 10 children with large skin lesions, twice-a-day together with oral PR administration. All of these children benefited from this therapy.

From the aspect of differential diagnostics congenital vascular anomalies are not well understood because of the lack of uniformly accepted classification and the poor level of understanding the natural history of these lesions [15]. This is the reason why their diagnosis is sometimes (as in our case #11) difficult. Although such anomalies do not demonstrate rapid growth as IHs do, their distinction from IHs can be challenging. The management and treatment of malformations differ from those of IHs: the steroid or PR treatment of malformations is useless [16]. In our practice, CO_2 laser treatment lead to some improvement.

IHs of the airway poses a special, life-threatening problem in infants. The range of subglottic narrowing generally extends from 10% to 99%. Various tools have been proposed for surgical excision, including the CO_2 laser, KTP laser, and the microdebrider [17]. In a series of 116 subglottic IH patients at 3 pediatric ENT centers 32 tracheostomies were performed. PR treatment resulted in spectacular effect in this population [4].

We observed 80% and 70% subglottic stenosis due to IH respectively in our cases #2 and #18. Rapid response could be detected after 1 week of treatment in both children. During the 15 months follow-up, the improvement became slower with periods of stagnation, but finally PR treatment could be ceased and surgery was not necessary at all.

In this study we focused in particular on the dynamics of the therapeutic effect of PR treatment of IH. In accordance with the relevant literature findings [6], the most dramatic effect in the regression of IH was observed in the first weeks, in which PR was introduced in the proliferating phase. The regression was rapid in all cases, was manifested in decolouration, softness and decrease in extent. The improvement continued but subsequently slowed down and a slight acceleration of IH regression was observed at the last visit.

No significant relation could be proved between the efficacy of PR treatment and the location and initial severity of IH. It is difficult to answer the question as to how long the treatment should last. Many authors suggest that the therapy has to be continued until no further improvement is seen, and then should be tapered over a period of 1–2 weeks. If a rebound effect occurs patients have to be placed back on propranolol [11]. We gave PR to patients at least for 6 months, with no significant adverse event.

In conclusion, PR has become the first-line treatment of IH, because of its effectiveness and low rate of side-effect. Relapse is rare, but after the striking improvement in the first weeks of therapy later the effect is not as dramatic as it was initially. The cause of this is probably the spectacular early effect of vasoconstriction, though other impacts of PR to the individual molecular markers of IH seemed to be less impressive clinically. However, treatment should be continued for at least 6 months because early cessation can cause a relapse. In extended skin lesions the application of local PR cream and CO_2 laser treatment can be considered as an adjuvant therapy.

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