Topical treatment with propranolol gel as a supplement to the existing treatment of hemangiomas

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Background: **Systemic treatment with propranolol is proven to be effective for patients with hemangiomas with less side-effect. We used a propranolol gel for topical use on hemangiomas.**

Methods: **In this retrospective study, we analyzed 148 patients who had been treated topically with propranolol gel for 12 weeks. We analyzed the data of patients and clinically gave each hemangioma a "hemangioma score" to determine the treatment success.**

Results: **In 147 of the 148 patients, strong signs of resolution under treatment included lightening, paling, and less vascularization. The hemangioma score showed a significant decrease during the treatment. Relevant serum levels of propranolol were not found. Adverse effects were rare and not related to propranolol.**

Conclusion: **Topical treatment with propranolol gel is suitable for specific hemangiomas in addition to cryotherapy and systemic treatment with propranolol.**

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Key words: **hemangioma;**
hemangioma score;
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Introduction

Systemic treatment with propranolol for hemangiomas has been available since 2008. This milestone caused a revolution in the existing treatment concept for hemangiomas.[1,2] Our experience in treating more than 500 patients with oral propranolol at Children's Hospital Heilbronn as well as others have demonstrated the impressive response of hemangiomas to the treatment with propranolol.[3-6] Systemic treatment has been proven as an extremely effective treatment with less side-effect.[1,2,7]

In addition to systemic treatment with propranolol, cryotherapy at -32 °C has proven to be valuable. It is a rapid and effective measure, especially for early treatment of hemangiomas. Further treatments for hemangiomas are laser therapy and, in exceptional cases, surgery.

Topical beta-blockers were successfully used in China, i.e., the use of timolol eye drops for a hemangioma of the eyelid.[8] Following this report, we have used a propranolol gel topically in specific patients since April 2011. In the meantime, more than 140 patients have been treated with this gel. Several reports[9-15] support the topical treatment of hemangiomas using beta-blockers such as timolol and propranolol. Those studies were performed in small groups of patients and did not show any side-effects.

Methods

Patients

The procedures performed in this study were in accordance with the ethical standards of the responsible committee and with the *Helsinki Declaration*. Informed consent was obtained from the study participants.

Treatment protocol

Propranolol gel is composed of propranolol hydrochloride (1%), sodium hyaluronate (3%) and aqua conservans (96%). Local treatment with propranolol gel was introduced at Children's Hospital Heilbronn, Germany.

The propranolol gel was placed on hemangioma until the entire tumor and its margins on the initial portion of healthy skin were covered with a 1- to 2-mm-thick layer of propranolol gel. The tumor region was covered with a commercially available adhesive plaster. The gel remained on the hemangioma for about 2 hours. Then the adhesive plaster was removed and

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gel residues were wiped off. The gel was applied twice daily for 12 weeks. Post-treatment follow-up was made after 4 and 12 weeks. The follow-up contained clinical investigation of the patient, photographic examination and, if necessary, an ultrasound investigation of the hemangioma.

A total of 148 patients who had been treated with propranolol gel were included in this study. The data of these patients were analyzed retrospectively and each hemangioma was given a score based on the "modified hemangioma score" at each follow-up. This score for hemangioma was used in other studies (not yet published) and was modified according to the parameters important for local treatment of hemangioma (Table 1).

Hemangiomas of the entire body including the genital region were treated locally with propranolol gel if they were growing rapidly (Table 2). Topical treatment was indicated for the following hemangiomas: 1) Proliferating hemangiomas that can no longer be treated with cryotherapy (flat, extensive hemangiomas with >1 cm in diameter and deep hemangiomas with a maximum depth of 6 mm on ultrasound); 2) Extensive hemangiomas that need to be treated and for which systemic treatment with propranolol is not yet indicated; 3) Localized and segmental hemangiomas with the exception of the face, especially those in the gluteal and genital region or at the hands and feet; 4) Hemangiomas in patients with renewed growth after cryotherapy or laser therapy; 5) Rapidly proliferating hemangiomas in preterm infants.

We did not use propranolol gel on the face (eye, mouth, and nose) because an adhesive plaster cannot be easily placed at this site, and the substance of the gel is unlikely to be effective in the cartilaginous portion of the nose. In these cases, we used systemic propranolol or cryotherapy according to the size and vascularization of hemangiomas. The characteristics of hemangiomas treated with propranolol gel are shown in Table 2.

Table 1. Modified hemangioma score, used to analyse each hemangioma at each clinical evaluation visit. Score range: 0-10.

Components	Quality	Score
Color of the hemangioma	Bright red	2
	Pale	1
	Skin color	0
Surface consistency	Markedly raised	2
	Raised	1
	Flat	0
Firmness	Firm	2
	Softer	1
	Not firm or much softer	0
Depth	Maximal (90-100%)	2
(if ultrasound, otherwise "0")	Less deep (50-89%)	1
	No depth or much less deep (<50%)	0
Size	>2% body surface	2
	1-2% body surface	1
	<1% body surface	0
		Total score (0-10)

Table 2. Characteristics of the treated patients

Variables	Count	Percentage (%)
Gender		
Female	100	68
Male	48	32
Age at beginning		
1 mon	39	26
2 mon	32	22
3 mon	34	23
4 mon	24	16
5-8 mon	19	13
Location		
Head	24	16
Thoracic/abdominal	46	31
Arm/leg	48	32
Genital area	13	9
Gluteal	17	12
Adverse events		
Over all	12	8
Ulceration	5	3
Eczema	4	3
No effect, growth	2	1
Others	1	1

Statistical analysis

Statistical analyses were made to evaluate effectiveness of treatment with propranolol gel and to find differences between the treatment at varying body regions and the age of patients at the start of the treatment. Means and standard deviations were calculated at the same time. The Shapiro Wilk test was used, and the data were classified as they were not normally distributed. The Mann-Whitney test and Wilcoxon's rank-sum test were used to determine the effect in 1 month and 1-3 month treatment, respectively. The Kruskal-Wallis test and one-way analysis of variance were used to determine the differences between localization of hemangiomas and age of children.[16]

Results

In the 148 patients, 147 had hemangiomas ceased to grow within a few days after topical treatment with propranolol gel. Only one patient showed growth of hemangioma. In this patient, a systemic therapy with propranolol was prescribed instead of local treatment. In most patients, we observed typical signs of resolution such as lightening and paling of hemangioma after four weeks. We also observed a reduced size of the hemangioma. In cases of deeper lesions, ultrasound revealed less vascularization of hemangioma and reduced depth of penetration. After 12 weeks of treatment, we found a residue of hemangioma, which did not grow further even after discontinuation of the treatment. Spontaneous and progressive resolution was

also observed after the treatment. Cessation of growth was "only" seen in some cases. However, hemangiomas might be well resolved spontaneously in these cases. Further clinical evaluation was performed after discontinuation of the treatment. No relevant rebound was found after the treatment with propranolol gel in our patients. The hemangioma score showed a further reduction of the treated hemangioma after treatment in each patient without re-growing.

Local treatment with propranolol showed significant effects by comparison of the scores at the start of the treatment and after 1 month of the treatment (the Mann-Whitney *U* test, Wilcoxon's rank-sum test, $P \leq 0.001$). Significant effects were also observed when the scores of 1 month of the treatment were compared with the scores after three months of the treatment ($P \leq 0.001$) (Fig. 1).

The gender (female n=100, male n=48; the Mann-Whitney *U* test, Wilcoxon's rank-sum test; at beginning of the treatment P=0.513, after 1 month of the treatment P=0.789, and after 3 months of the treatment P=0.471) and localization of the treatment (arm/leg n=48, genital area n=13, gluteal n=17, head n=24, thoracic/abdominal n=46; the Kruskal-Wallis test, one-way analysis of variance, the log-rank test; at the beginning of the treatment P=0.25; after 1 month of the treatment P=0.293; after 3 months of the treatment P=0.579) were studied (Figs. 2-4). The age of patients at the beginning of the treatment (1 month n=39, 2 months n=32, 3 months n=34, 4 months n=24, 5-8 months n=19) did not show any significant difference (the Kruskal-Wallis test, one-way analysis of variance, the log-rank test; at the beginning of the treatment P=0.467, after 1 month of the treatment P=0.910, after 3 months of the treatment P=0.910) (Fig. 1).

Serum levels of propranolol were determined in 20 patients (including pre-term infants) to rule out clinically relevant serum levels of the substance due to topical use. The patients always had propranolol levels below the measurable range (<20 ng/mL; therapeutic range: 50-300 ng/mL). Based on serum levels of propranolol, we conclude that topical use does not lead to systemically relevant serum levels. No side-effects such as those associated with systemic use of propranolol (bradycardia, hypotension, hypoglycemia) were observed in these patients. Other side-effects included ulceration in 3% of the patients and eczema in the areas of the adhesive plaster stripes in 3%. In cases of ulceration, treatment with propranolol gel ceased.

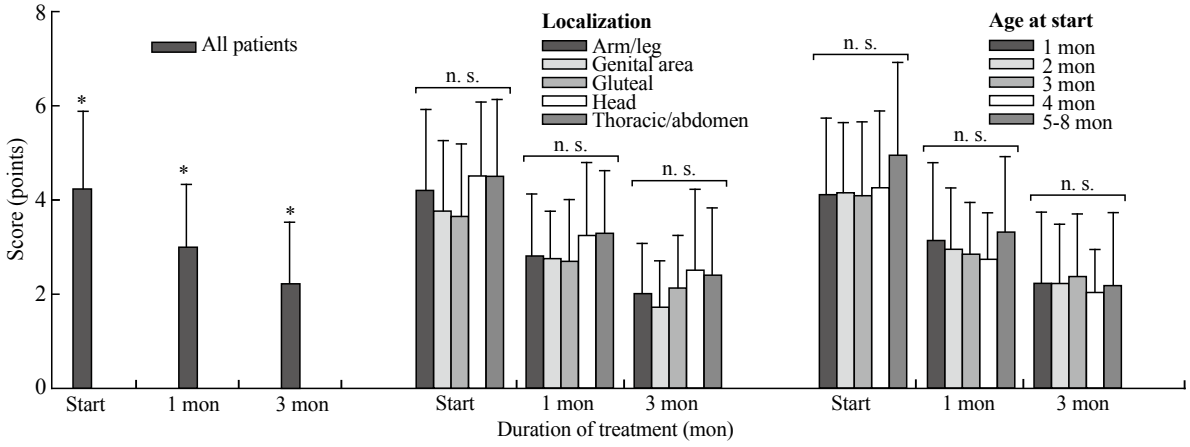

Fig. 1. Treatment scores at start, after 1 month and 3 months of treatment for all patients and distributed to localization and age at start of treatment. *: $P \leq 0.001$, when score at start was compared with score after 1 month, and score after 1 month was compared score after 3 months of treatment. No significant differences were found when the different localizations of hemangiomas were compared each other. n.s.: No significant differences were found when the different ages at start of treatment of hemangiomas were compared each other.

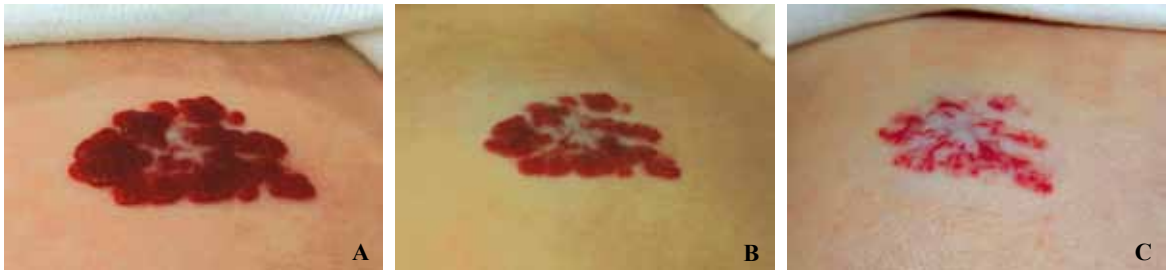

Fig. 2. Patient LB 26, abdominal hemangioma. **A:** before treatment, score 5; **B:** after 4 weeks, score 3; **C:** after 12 weeks (end point), score 1.

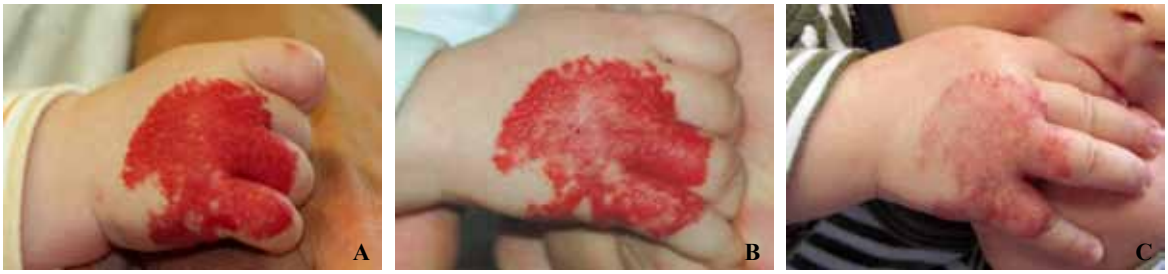

Fig. 3. Patient JA04, hemangioma of the right hand. **A:** before treatment, score 2; **B:** after 4 weeks, score 1; **C:** after 12 weeks (end point), score 0.

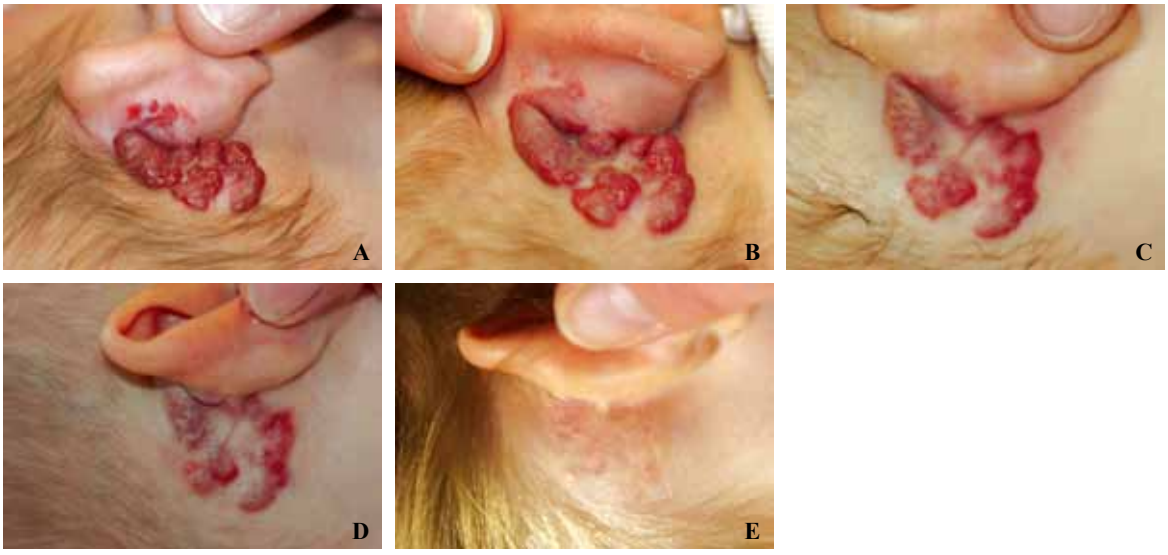

Fig. 4. Patient EV18, hemangioma of the ear. **A:** before treatment, score 6; **B:** after 4 weeks, score 3; **C:** after 12 weeks (end point), score 1; **D:** 5 weeks after end point; **E:** 14 months after end point.

Discussion

When the treatment of hemangioma is indicated for infants, one must realize that a large percentage of hemangiomas tend to resolve spontaneously and do not need any treatment at all. However, some hemangiomas are prone to progress significantly. As the final scar-like alterations are as large as the maximum dimensions of the hemangioma itself, there is a good reason to establish the indication for the treatment of selected hemangiomas.

Our patients from a markedly transregional population constituted a pre-selected group referred by pediatricians. About 40% of them required no treatment after their parents were informed the condition of their children. Regular clinical evaluation is necessary to monitor the spontaneous development of hemangiomas in these patients.

The treatment of hemangiomas at Children's Hospital Heilbronn is as follows: cryotherapy at -32 °C, systemic treatment with propranolol, and topical treatment with propranolol gel. This treatment is complemented by laser therapy and surgery. According to our experience, propranolol gel is suitable for topical treatment of the hemangiomas that are not amenable to cryotherapy because of their size (>1 cm diameter), depth (>3 mm depth on Doppler ultrasound) or location. The propranolol gel is used in competition to laser treatment as a first line treatment and, in some cases, to systemic propranolol treatment. In some cases, propranolol gel is timely used instead of systemic treatment with propranolol. Hemangiomas in the extremities, genitals, and especially the gluteal region can be successfully treated.

Topical use of propranolol gel is a viable therapy even in preterm infants with rapidly proliferating hemangiomas in the trunk and extremities. In three preterm infants (born in the 28th to 36th week of gestation) who were undergoing in-hospital treatment for other reasons, propranolol gel was used for topical treatment of their hemangiomas. Continuous monitoring including continuous measurement of heart and respiratory rate, 2-hourly measurement of blood pressure, and close clinical observation revealed no effect on the cardiovascular system.

As in systemic propranolol therapy, laser treatment and cryotherapy, topical treatment of gluteal hemangiomas

rarely leads to ulceration. However, this often occurs even when a hemangioma is not treated. Ulcers can be managed by an aseptic wound dressing. Thus, they cannot be regarded as a specific side-effect of topical treatment with propranolol gel. Other side-effects of topical treatment have not been observed so far.

There is a difference between local treatment with propranolol gel and contact cryotherapy at -32°C or systemic treatment with propranolol. As the three treatments complement each other and are not competitors, a comparison of their advantages and disadvantages would be limited in nature. The topical use of propranolol may be indicated for hemangiomas.

In contrast to systemic use of propranolol, systemic side-effects such as hypoglycemia, bradycardia or hypotension are unlikely to occur during topical treatment. Serum levels of propranolol are not achieved after topical treatment. The duration of local therapy is 12 weeks, which is much shorter than that of systemic treatment with propranolol. The latter is usually conducted for at least 6 months.

The success of systemic treatment is definitely impressive in a short period. However, two treatments are almost equivalent in a long period. It should be noted that the indications for systemic and local treatment with propranolol are significantly different. It is very important to distinguish hemangiomas that are still amenable to local treatment from those that require systemic treatment. Thus, a comparison of the two treatments is of limited value.

In the present study, the positive effect of topical treatment with propranolol was seen in a large number of patients. For the first time, we used a modified hemangioma score to evaluate the efficacy of topical treatment and found a significant reduction of the score.

We believe that topical treatment with propranolol gel fills the "gap of therapy options" between cryotherapy and systemic treatment with propranolol in an ideal way, and is therefore an important adjunct for the treatment of hemangiomas.

Relevant side-effects have not been observed so far. If it is indicated, treatment with propranolol gel has a positive effect in most patients. Further investigations on this subject will follow.

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Ethical approval: The Ethical Committee of Heidelberg University approved this study (no.S-020/2013). The treatments in this study were in accordance with the ethical standards of the committee and with the *Helsinki Declaration*. Informed consent was obtained from the study participants.

Competing interest: None declared.
Contributors: Schneider M and Ruef P proposed the project and wrote the paper. They are the guarantors.

References

1 Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649-2651.
2 Sans V, de la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009;124:e423-e431.
3 Cremer HJ, Kachel W, Kosel C. Propranolol for the treatment of complicated haemangiomas. Kinder- und Jugendarzt 2009;40:457-460. [In German]
4 Cremer HJ, Bause H, Mangold C, Elsesser-Glaab S, Schneider M. Hämangiome im Kindesalter: Neue Klassifikation/ Diagnostik/bewährte und neue Therapieformen, 2009. www.hautnet.de (accessed January 27, 2013).
5 Schiestl C, Neuhaus K, Zoller S, Subotic U, Forster-Kuebler I, Michels R, et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. Eur J Pediatr 2011;170:493-501.
6 Manunza F, Syed S, Laguda B, Linward J, Kennedy H, Gholam K, et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. Br J Dermatol 2010;162:466-468.
7 Love JN, Sikka N. Are 1-2 tablets dangerous? Beta-blocker exposure in toddlers. J Emerg Med 2004;26:309-314.
8 Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using β-blocker solution. Arch Ophthalmol 2010;128:255-256.
9 Chantasart D, Hao J, Li SK. Evaluation of skin permeation of beta-blockers for topical drug delivery. Pharm Res 2013;30:866-877.
10 Oranje AP, Janmohamed SR, Madern GC, de Laat PC. Treatment of small superficial haemangioma with Timolol 0.5% ophthalmic solution: a series of 20 cases. Dermatology 2011;223:330-334.
11 Kunzi-Rapp K. Topical propranolol therapy for infantile hemangiomas. Pediatr Dermatol 2012;29:154-159.
12 Moehrle M, Léauté-Labrèze C, Schmidt V, Röcken M, Poets CF, Goelz R. Topical Timolol for small hemangiomas of infancy. Pediatr Dermatol 2013;30:245-249.
13 Xu G, Lv R, Zhao Z, Huo R. Topical propranolol for treatment of superficial infantile hemangiomas. J Am Acad Dermatol 2013;67:1210-1213.
14 Zhai YN, Song HT, Chen SQ, Zhang MX, Li CJ, Xia Y, et al. Effect of propranolol gel on infantile hemangiomas. Zhonghua Zheng Xing Wai Ke Za Zhi 2013;29:25-28. [In Chinese]
15 Niu JN, Xu GQ, Lü RR, Huo R. Treatment of superficial infantile hemangiomas with topical propranolol. Zhonghua Zheng Xing Wai Ke Za Zhi 2013;29:100-103. [In Chinese]
16 Glantz SA. Alternatives to analysis of variance and the t-test based on ranks. In: Glantz SA, eds. Primer of biostatistics, 6th ed. New York: McGraw-Hill, 2005: 363-412.

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