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Topical Propranolol Therapy for Infantile Hemangiomas

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Abstract: **The nonselective beta-adrenergic receptor antagonist propranolol is an effective therapy for infantile hemangiomas. Systemic propranolol therapy shows a rapid therapeutic effect with good drug tolerability. We report on the efficacy of local application of propranolol ointment in superficial hemangiomas of the skin. In our outpatient department, 45 children with 65 hemangiomas were treated with 1% propranolol in a hydrophilic ointment topically applied twice a day. Before start of treatment and at each visit, clinical photographs were taken. If ultrasound did not confirm occult deeper components, children were included in the study. Treatment in the proliferative phase within the first 6 months of life (including seven preterm infants) induced regression in 59% and cessation of growth in 26% of the hemangiomas. No response or proliferation of subcutaneous components was observed in 15%. Clinically, no side effects caused by the beta-receptor blocker were noticed. Treatment of two ulcerated hemangiomas of the perineal region twice using a flash lamp pulsed-dye laser and propranolol ointment in the surrounding lesion led to healing of the ulcers in 3 and 6 weeks, respectively. In six patients, topical therapy was started between the ages of 7 and 33 months. Even in these hemangiomas, improvement was obvious after 2 or 3 months. Propranolol administered topically in 1% ointment could have a beneficial effect on superficial hemangiomas of the skin. The treatment was well tolerated without side effects even in preterm infants and in children with numerous or large lesions.**

The beta-adrenergic receptor antagonist propranolol is an effective therapy for infantile hemangiomas (IH) (1–5), even after therapy with corticosteroids or laser has failed (6). Systemic propranolol therapy shows a rapid onset of action, with good drug tolerability regardless of sex, age at onset of treatment, type of involvement, ulceration, or depth (7–9).

Therapy is often desired even in uncomplicated hemangiomas. The rationale for a therapeutic intervention in uncomplicated IH is usually to prevent

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slight functional impairment, scarring, or disfigurement that might lead to psychosocial stigmatization of affected children (5,9,10). Hence, a therapy easy to administer, cost-effective, and with minimal potential side effects would add to existing treatment options. Bonifazi et al (11) reported on six cases treated with 1% topical propranolol in a oil based cream. We have further tested the efficacy of a local application of propranolol ointment in 45 patients with IH.

METHODS

We treated 45 children (27 female, 18 male) with a total of 65 hemangiomas using topical propranolol from September 2008 to June 2010. They were divided in two groups; group 1 ($n = 39$) were 6 months old or younger (mean 2.6 months), and group 2 ($n = 6$) were aged 7–33 months. In group 1, seven infants were low-weight preterm infants (gestational age < 37 weeks) seen in the neonatal intensive care unit. All parents gave written informed consent to participate in the study.

In all seven preterm infants, blood pressure and heart rate were monitored once a day during their in-patient treatment in the hospital. Further laboratory studies to monitor drug toxicity were not performed.

Before start of treatment, clinical photographs were taken. The maximal thickness of the lesions was measured using ultrasound (high-resolution linear transducer with a frequency of 10 MHz) in 24 patients. Color-coded duplex sonography was performed in 20 patients. If ultrasound confirmed no subcutaneous components, children were included in the study. The first follow-up visit was performed after 2–4 weeks of treatment. Further visits were scheduled at 1 month and every 2 months thereafter. IH severity was assessed according to the color of the surface, the texture on palpation, and its visible volume. At each visit, clinical photographs were taken.

The hospital pharmacy prepared the propranolol ointment propranolol-hydrochloride at a 1% concentration in a hydrophilic ointment (Deutsches Arzneibuch DAB 2009; Deutscher Apotheker Verlag, Stuttgart, Germany). Parents were advised to apply the ointment twice a day in a thin layer ($\sim$1.5 mg/cm^2, or $\sim$15 μg propranolol/cm^2) to the hemangioma.

In two ulcerated hemangiomas, only the components of the hemangioma surrounding the ulceration were treated using propranolol ointment. In these cases, the propranolol treatment was combined with two sessions of flash-lamp pulsed-dye laser (V Beam; Candela Laser GmbH, Neu-Isenburg, Germany) (spot size 7 mm, pulse duration 0.45 ms, fluence 5 J/cm^2). After application of an antiseptic lotion (Octenisept, Schülke & Mayr GmbH, Norderstedt, Germany), the ulcerated hemangiomas were covered using a lipidocolloid dressing (Urgocell non-adhesive; URGO GmbH, Sulzbach, Germany).

RESULTS

None of the treated hemangiomas was located in a life-threatening area. The distribution of the 65 hemangiomas was as follows: 20 (31%) on the head and neck, 25 (38%) on the trunk, 13 (20%) on the extremities, and 7 (11%) in the anogenital region.

Topical application of 1% propranolol ointment was well tolerated in all children, even in all low-weight preterm infants. The treatment did not affect blood pressure and heart rate monitored in preterm infants (results not shown). None of the parents reported wheezing, and food intake was regular. No local irritation was observed in any patient. One girl with a large segmental hemangioma of the hip and lower limb had recurrent itching, but no erythema or skin induration was noticed.

In group 1, 39 children (including seven preterm infants) with 57 hemangiomas were treated. Overall, initiation of regression was observed in 23 IH (59%) (Fig. 1), cessation of growth in 10 (26%), and no response or proliferation of newly developed subcutaneous components of the hemangiomas in six (15%) (Table 1). In 5 of these 6 patients, subcutaneous parts of the hemangiomas developed in the head area after initiation of the topical propranolol therapy. Nevertheless, the cutaneous parts of the hemangiomas showed signs of regression such as grayish color and softening. In these patients, systemic propranolol treatment was initiated.

Seven preterm infants with 15 hemangiomas were treated using topical propranolol ointment starting in the neonatal intensive care unit (Fig. 2). Clinically, no side effects caused by the beta-receptor blocker have been noticed. Even in children with multiple lesions, blood pressure and heart rate did not change after initiation of topical propranolol therapy.

Two boys, ages of 6 and 7 months, had ulcerated hemangiomas in the perineal region. In these cases, treatment of the ulcers with flash-lamp pulsed dye laser administered on two occasions, and propranolol ointment in the surrounding lesion led to healing of the ulcers in 3 and 6 weeks, respectively. During the continuing therapy with topical propranolol, no new ulceration occurred.

In group 2 (6 children older than 7 months of age), treatment was initiated because the IH did not change in the weeks before treatment. Signs of improvement were obvious after 2 or 3 months of propranolol therapy in all lesions ($n = 10$) (Fig. 3), and the parents continued therapy up to 9 months.

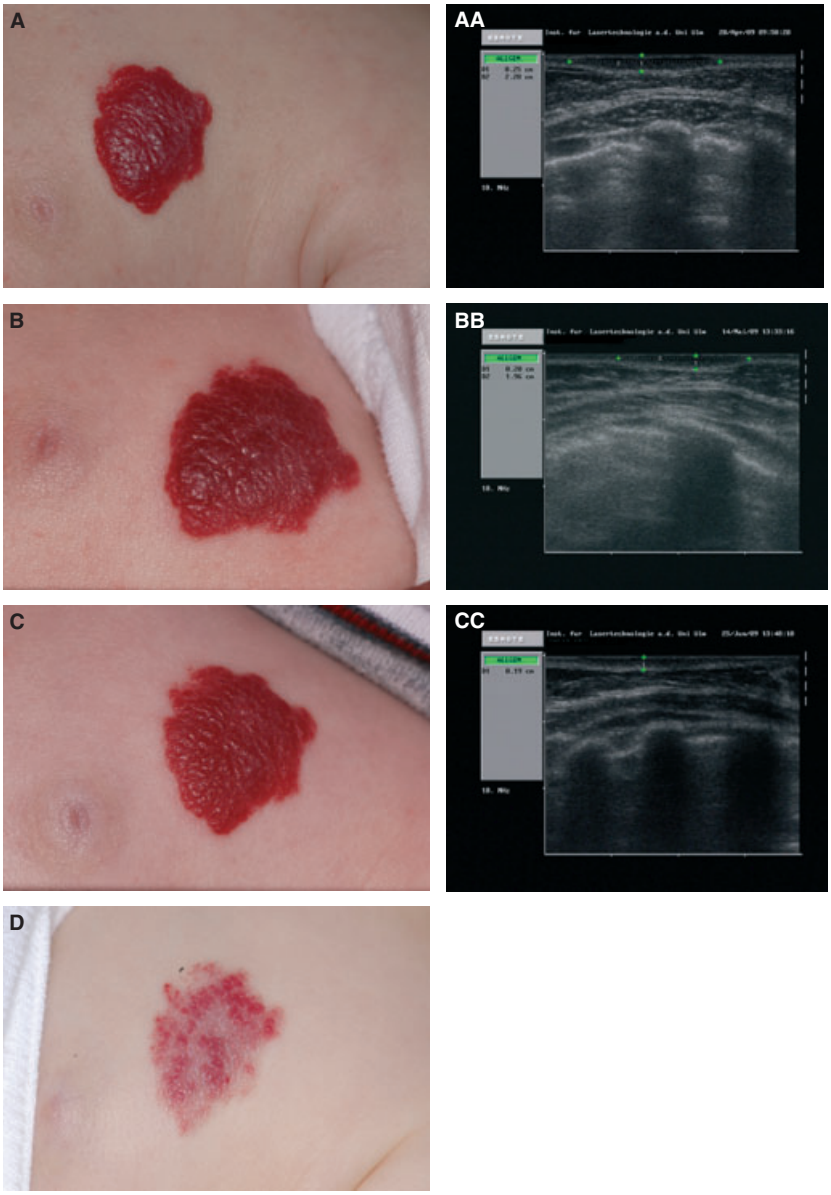

Figure 1. Superficial hemangioma on the breast of a girl (Patient 1 in Table 1) (**A**) at the age of 10 weeks, before starting topical propranolol therapy. (**AA**) Matched ultrasound picture, maximum thickness of the hemangioma 2.5 mm. (**B**) After 17 days topical propranolol treatment. (**BB**) Ultrasound measurement showed flattening of the lesion, maximum thickness 2.0 mm. (**C**) Minimal change after 8 weeks of therapy. (**CC**) Maximum thickness 1.9 mm. (**D**) After 6 months of topical propranolol therapy.

DISCUSSION

No large clinical trials exist in support of any highly effective topical therapy in the management of hemangiomas (5). For the treatment of superficial lesions, topical therapy with corticosteroids and imiquimod has been reported. Topical potent corticosteroids can improve thin superficial hemangiomas but not their deep component (12). Adverse reactions include atrophy and hyperpigmentation. Topical imiquimod has also been reported to be safe and effective in treating small superficial lesions (13), but crusting and ulceration are possible complications (14). Recently, topical application of timolol maleate, a hydrophilic nonselective beta-blocker was reported to treat periocular hemangiomas successfully without adverse events (15–17).

In cases of early intervention in the proliferative phase, we were able to induce regression or stabilize growth in 85% of the hemangiomas within the first 6 months of therapy. In five patients, subcutaneous

TABLE 1. *Clinical Characteristics of the Patients of Group 1 (Treatment was initiated less or equal to 6 months)*

	Hemangioma				Treatment		
Patient	*n*	Location	Size	Subtype	Age at initiation, months	Duration, months	Response
1	1	Breast	Focal	Superficial	2.5	9.5	Regression
2	4	Head	Focal	Superficial	1.5	16.5	Stop of proliferation*
3	2	Trunk	Focal	Superficial	4	6	Stop of proliferation
4	1	Trunk	Large	Superficial	2	10	Regression
5	1	Leg	Large	Superficial	1	6	Stop of proliferation
6	1	Anogenital	Focal	Superficial	2	10	Regression
7	1	Trunk	Large	Superficial	1.5	10.5	Stop of proliferation
8	2	Trunk	Large	Mixed	3	6	Regression
9	1	Trunk	Focal	Superficial	6	6	Regression
10	1	Trunk	Focal	Superficial	2	10	Stop of proliferation
11	1	Trunk	Large	Superficial	2.5	8	Stop of proliferation
12	2	Leg, head	Focal	Superficial	2.5	6	Regression, stop
13	1	Trunk	Focal	Superficial	2	6	Regression
14	1	Leg	Segmental	Superficial	3	17	Regression
15	1	Head	Large	Superficial	1.5	10.5	No response
16	1	Head	Focal	Superficial	2	5	Stop of proliferation*
17	1	Leg	Large	Superficial	2	4	Regression
18	1	Anogenital	Focal	Superficial	6	4	Regression*
19	1	Head, neck, plantar	Large	Mixed	1.5	1	Progression†
20	1	Trunk	Focal	Superficial	6	4	Regression
21	1	Head	Focal	Mixed	2	10	Stop of proliferation*
22	1	Hand	Focal	Superficial	4	4	Regression
23	1	Head	Focal	Superficial	1	3	Regression
24	1	Neck	Large	Superficial	6	8	Regression
25‡	2	Head, anogenital	Large	Mixed	1.5	1	Progression,† ulceration
26‡	2	Head, leg	Focal	Mixed	1.5	1	Progression†
27‡	2	Head, arm	Large	Mixed	1.5	1	Progression,† ulceration
28	1	Leg	Large	Superficial	2.5	10	Regression
29	1	Anogenital	Focal	Superficial	2	10	Regression
30	1	Head	Large	Mixed	1	1	Progression†
31	2	Head	Focal	Superficial	4	3	Stop of proliferation
32	1	Head	Focal	Superficial	3	3	Stop of proliferation
33§	1	Arm	Large	Superficial	2.5	6	Regression
34§	1	Head	Large	Superficial	2.5	7	Regression
35§	1	Arm	Large	Superficial	1.5	5	Regression
36§	1	Anogenital	Focal	Superficial	1.5	2	Regression
37§	5	Trunk, arm	Focal, large	Superficial	2	3	Regression
38§	4	Head, trunk	Focal	Superficial	2	2	Regression
39§	2	Head, anogenital	Focal	Superficial	3	3	Regression

*Additional sessions of flash lamp pulsed-dye laser therapy.
†Switch to systemic propranolol therapy.
‡Triplet.
§Preterm infant.

components of the hemangioma developed after initiation of therapy. Nevertheless, the superficial components of these hemangiomas indicated signs of regression such as grayish color and softening during topical propranolol therapy. Even in low-weight preterm infants, topical propranolol was effective and devoid of local or systemic side effects. Topical propranolol was also effective for IH beyond the proliferative phase, as is the case for oral propranolol treatment (9,18).

The mechanisms of action of propranolol in IH are unknown. Our results indicate that the beta-blocker acts transdermally in the hemangioma. This fact requires skin penetration of the active ingredient. After oral administration, propranolol-hydrochloride has a pronounced first-pass metabolism, resulting in poor bioavailability (15–23%) from oral formulations. Maximal plasma levels are obtained after 1–2 hours, and the half-value period of renal elimination is approximately 3–4 hours. Because of variable absorption profiles and therefore a high incidence of adverse effects after oral administration, attempts have been made to develop novel drug delivery systems for beta-blockers, including transdermal delivery systems. In vitro studies in human skin demonstrated that between 10.4% and 36.6% of the applied

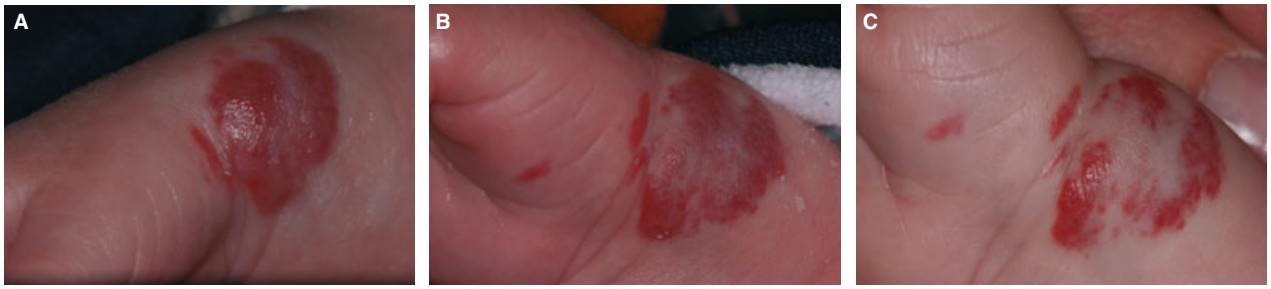

Figure 2. Preterm patient (birth 27 + 5) with a cutaneous hemangioma at his right wrist (Patient 35 in Table 1). (**A**) Two weeks after initiation of topical propranolol treatment. (**B**) After 2 months of treatment, color changed from intense red to purple and gray, and the surface became more velvety. (**C**) Further improvement after 4 months of treatment.

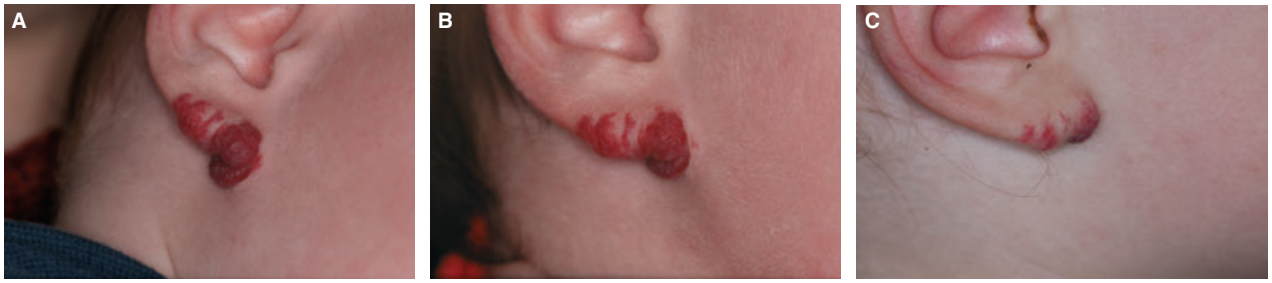

Figure 3. Hemangioma of the right earlobe (**A**) at the age of 14 months. (**B**) Status at the age of 19 months, start of topical propranolol therapy. (**C**) After 3 months of topical treatment.

dose accumulated in the skin, but only a small amount (4.1–16.1%) of the dose permeated through the skin into the blood system (19). Mishra et al (20) showed that in vivo, in rats, maximum plasma concentrations of propranolol hydrochloride were low (25 ± 5.0 ng/mL) 24 hours after topical administration of 200 μL of 0.4% drug solution on 1 cm^2 of the dorsal skin. Cumulative skin irritation studies in guinea pigs indicated that propranolol caused skin irritation but no sensitization, phototoxicity, or photosensitization (21). Skin irritation increased with increasing propranolol dosage and application times. In these studies, propranolol was administered under adhesive patches, and the development of erythema was considered to be mainly due to physical factors such as peeling (22). Skin permeation studies using terpenes as chemical penetration enhancers (23) showed no apparent skin irritation (erythema, edema) in rat and human skin, although terpenes enhanced the absorption by extraction and disruption of lipid bilayers and by keratin denaturation of the stratum corneum.

If propranolol is applied topically onto the skin on the hemangioma twice a day, the concentration can accumulate near the vessel walls without metabolic changes. High local concentration of propranolol at the capillaries of the hemangioma without high systemic concentration is an advantage of topical therapy. Further research is needed to examine the transdermal penetration of the propranolol ointment and to optimize the optimal propranolol concentrations and formulations.

This preliminary study shows that topical propranolol therapy appears to have a beneficial effect on superficial IH of the skin. Randomized studies are needed to confirm the efficacy and safety of the topical therapy.

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