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Enhanced Percutaneous Delivery of Beta-Blockers Using Thermal Resurfacing Drug Delivery System for Topical Treatment of Infantile Hemangiomas

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Keywords
Beta-blockers · Enhanced percutaneous delivery · Infantile hemangioma · Pediatric dermatology · Tixel

Abstract
Background: Infantile hemangiomas (IHs) are the most common vascular tumors in children. In the past few years, topical beta-blockers (bBs) have been reported to be an effective treatment of superficial IHs. ***Objective:*** We sought to evaluate the clinical effectiveness and safety profile of enhanced percutaneous delivery of bBs for the treatment of IH. ***Methods:*** A retrospective study of all cases of IHs treated with enhanced percutaneous delivery of bBs between 2018 and 2019 was performed. Epidemiologic, clinical, and treatment data, including effectiveness score and safety, were reviewed. ***Results:*** The study included 11 patients with a total of 11 IHs. Of the total number of IHs, 7 (63.7%) showed a good response to treatment and 4 (36.3%) had a partial response; thus all patients (100%) had good or partial response to treatment. No systemic or local adverse effects were reported. ***Limitations:*** This is an uncontrolled retrospective study. ***Conclusion:*** Enhanced percutaneous delivery of bBs is a safe and efficient topical therapy for IH.

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors in children with an incidence of 4–10%, they are caused by proliferation of endothelial cells. Their natural history comprises of a rapid proliferation in the first months of life, followed by an involution phase that can take several years [1–3]. While most of the IHs does not require treatment, it is beneficiary and even obligatory in cases of IHs in high-risk distribution imposing dysfunction, disability, or disfiguration such as the eyes, nose, and throat. Treatment can also prevent post involution atrophy, telangiectasia, fibro-fatty tissue, and skin laxity which commonly occur in superficial hemangiomas [4–6].

Since the discovery of the effect of propranolol on IHs, oral propranolol is considered the first-line treatment for IHs [7]. In light of the possible adverse effects (AEs) profile of the systemic treatment, topical beta-blockers (bBs), namely propranolol hydrochloride and timolol maleate, are widely used for the treatment of superficial IHs [8–10], with an improvement in up to 90% of the cases, minor local AEs, and without any reported systemic AEs [11, 12]. The use of lasers, microneedles, as well as radio frequency waves, as topical drug delivery systems can en-

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Table 1. Patient and treatment characteristics

Patient	Sex	Age at the beginning, months	Size, cm	Color	Type	Location	Total treatment duration, months	No. of treatments	Interval, weeks	Drug	Score (0–3)	Satisfaction (0–3)
1	M	11	1.5×2	Bright red	Substantial thickness	Extremities	4	6	2–3	P	2	3
2	F	1.5	6×4	Bright red	Moderate thickness	Extremities	3.5	4	2–3	T	3	3
3	M	13	2×2	Purple/ dusky red	Minor	Head	2	3	2	T	3	3
4	F	7	3×5	Bright red	Substantial thickness	Neck	3	4	2–3	P	3	2
5	F	16	2×3	Purple/ dusky red	Moderate thickness	Extremities	3	5	2–3	P	2	3
6	F	12	1.5×4	Purple/ dusky red	Minor	Extremities	4	4	2–3	T	3	3
7	M	5	6×4	Bright red	Substantial thickness	Extremities	4	5	2–4	2P 3T	1.6	2
8	F	5	20×6	Bright red	Minor	Extremities	8	9	2–4	5P 4T	3	3
9	M	6	10×5	Bright red	Minor	Extremities	7	9	2–4	4P 5T	2.6	3
10	F	10	2×3	Bright red	Substantial thickness	Head	3.5	5	2–4	T	1.3	3
11	M	9	5×3	Bright red	Moderate thickness	Extremities	6	7	2–4	4P 3T	3	3

T, timolol; P, propranolol.

hance bBs bioavailability, and by that augment the response to the treatment; yet, it might be inapplicable in pediatric population due to their low pain tolerance [13]. We report our experience of applying topical bBs following treatment with a non-painful, non-laser novel thermal drug delivery system (Tixel-Novoxel) [13] in 11 patients with IHs.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000507808) [11–20] (Table 1).

Results

The study included 11 patients (6 girls and 5 boys) with an average age of 8.6 months (range: 1.5–16 months) and a total of 11 IHs. The initial size range of the examined IHs was from 3 to 120 cm^2 with an average of 24.5 cm^2. The color distribution at presentation was as follows: 8 (72.72%) were bright red, 3 (27.27%) were purple or dusky red. Four (36.3%) of the IHs had minor thickness, 3 (27.4%) had moderate thickness, and 4 (36.3%) had substantial thickness. Three (27.3%) hemangiomas were located on the head and neck area and 7 (63.7%) on the extremities. None of the IHs were ulcerated. The mean duration of treatment was 4.36 months (range: 2–8 months). Four (36.3) patients were treated with timolol with an average of 4 treatment (range: 3–5), three (27.3) patients were treated with propranolol with an average of 5 treatments (range: 4–6), and 4 (36.3) patients received propranolol at the beginning and were switched to timolol with an average of 7.5 treatments (range 5–9). Eight patients were treated only with the Tixel drug delivery system once every 2–4 weeks, followed by topical beta-blocker application immediately and once every hour for 3 h, while 3 patients received additionally topical propranolol 4% PLO gel over the IHs twice daily without occlusion for the first month of treatment; however, in light of the good response after each Tixel treatment, the daily treatment was ceased.

Of the 11 IHs, 7 (63.7%) showed good response to treatment, and 4 (36.3%) demonstrated a partial response. Altogether all patients had good or partial response to treatment (Fig. 1, 2). No recurrence was recorded in the 2-month posttreatment follow-up period. No systemic or topical AEs were reported. Although the Tixel treatment

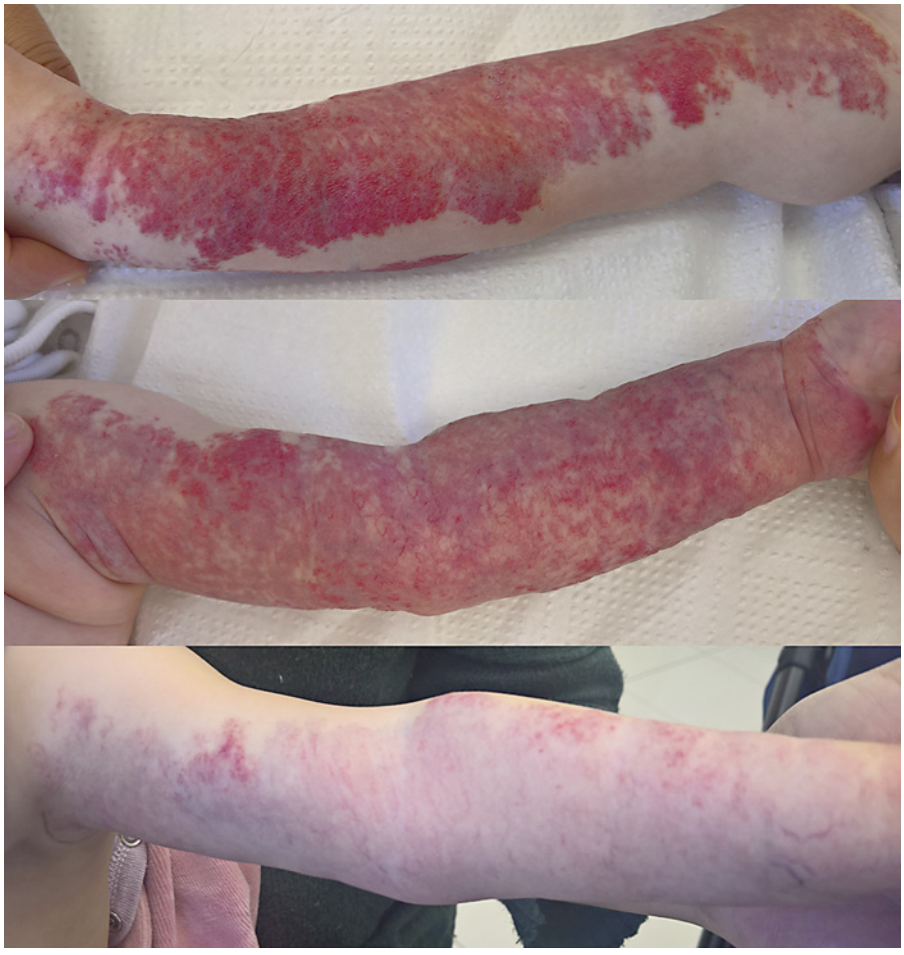
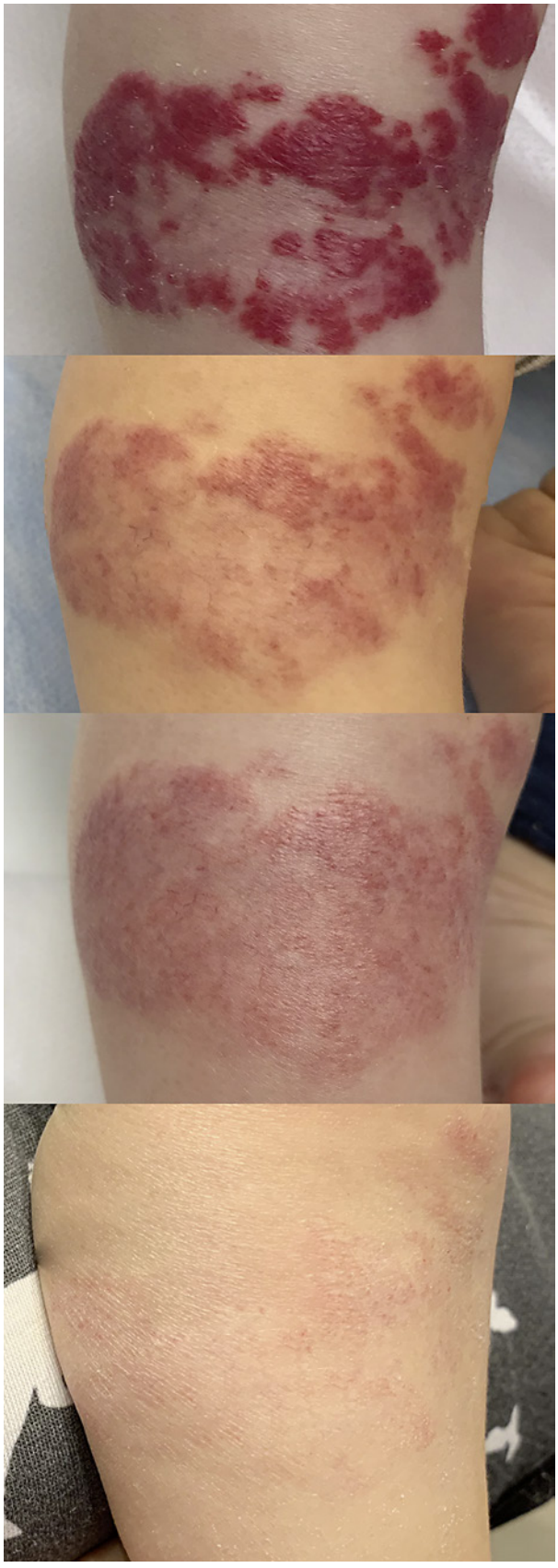


Fig. 1. Patient No. 8 is a 5-month-old girl with a large hemangioma on her left hand, measuring 6 × 20 cm before, during, and after the final treatment.

causes discomfort and even slight pain, the pain is bearable, remains only during the treatment time, and did not influence the decision of continuing or not the treatment.

Discussion

In the past decade, treatment of IHs has changed dramatically and oral propranolol has become the first-line treatment [7, 8]. The commonly reported AEs of oral propranolol are sleep disturbances and acrocyanosis. Rare but possible serious ones include bradycardia, hypotension, bronchospasm, and hypoglycemia [8, 9]. In light of the possible AEs profile of the systemic treatment, its length and the young age of the patients, a topical regimen of bBs, having a significant lower AEs rate, is used as an alternative treatment modality, mainly for superficial IHs [11, 12]. There is no commercial topical bBs medication registered, nor a consensus protocol for the treatment of superficial IHs with topical bBs [8] which is applied off-label, using various concentrations, vehicles, dosages, and application frequencies, of compounded propranolol or timolol eye drops solutions, with relatively good results [11, 12, 15]. Nevertheless, topical bBs treatment, usually requiring up to 16 months (average 5–7.5 months) in several studies) [11, 12] is not sufficiently efficacious for widespread or deep IHs. The major conflicting points regarding the topical treatment are as follows: (1) Which is the most suitable bB molecule for topical drug delivery? (2) What is the appropriate vehicle? (3) How can we enhance the percutaneous delivery? (4) What is the best treatment regimen – the easiest, least painful, shortest, and with best final cosmesis? The efficiency of topical treatment depends on the drug potency and its ability to penetrate the skin. Lasers, microneedles, radio frequency, and ultrasound have all been used to increase drug bioavailability in the skin [21]. Ma et al. [22] have reported the use of fractional carbon dioxide (CO_2) laser for assisted drug de-



livery of topical timolol solution for the treatment of deep IHs. The fractional CO_2 laser was applied once weekly on the IHs of 9 patients followed by an application of a cotton pad saturated with 2–5 drops of topical ophthalmic solution of timolol 0.5% under occlusion for 30 min immediately after the laser treatment, as well as 4–5 times a day for the whole treatment period, with an average number of laser treatments of 11.6 and average treatment duration of 14.2 weeks. A total of 88% of patients demonstrated excellent and good regression. There were no systemic AEs or significant changes in vital signs and blood glucose level measured after the first timolol application. Pinpoint bleeding as well as erythema and edema which appeared after the laser treatment ceased 1–3 days later and the dot crusting resolved in 1 week [22]. The disadvantages of the CO_2 laser as enhanced drug delivery method of topical bBs in young children are the pain it causes, the need to protect the eyes during the treatment, and the high cost of the device. We used the Tixel drug delivery system once every 2–4 weeks with an average of 5.5 treatments and average treatment duration of 17 weeks. All patients, except 3 who additionally applied bBs twice daily for the first month, were treated solely with topical bBs, 4 times 1 h apart, after the Tixel drug delivery application without occlusion, and did not receive any treatment between the Tixel sessions, meaning that they were treated only 5.5 (range: 3–9) days during the whole treatment period. All patients showed good or partial response to treatment without systemic or local AEs. Another advantage of the drug delivery system used in our study over the CO_2 laser is the substantially lower pain during the treatment as well as lack of healing time, lasting few days after the treatment. Both enhanced drug delivery methods show better results, with shorter treatment period, than the reported results of the accepted regimen of topical bBs treatment for IHs, comprising of twice or three daily applications during the treatment period which varies between several weeks up to 16 months (average 5–7.5 months in several studies) [11, 12]. Propranolol and timolol have been used with similar efficacy and AEs profile for topical treatment of IHs [12]. We used a topical monotherapy of propranolol 4% gel or timolol 0.5% eye drops solution (in 3 and 4 patients each) and both agents (in 4 patients) with similar results but with a smaller number of treatments in the timolol group, probably due to its better ability to permeate the viable epidermis

Fig. 2. Patient No. 2 is a 1.5-month-old girl with a hemangioma on the anterior surface of her right shin, measuring 6 × 4 cm before, during, and after the final treatment.

and dermis as a hydrophilic molecule. Nevertheless, the small number of cases does not allow us to draw a solid conclusion. As in every topical treatment, treating bigger lesions, requires the use of substantially larger amounts of the drug, and enhances the risk of systemic AEs due to higher plasma concentration, thus requiring special considerations and precautions. The hydrophilic molecule of timolol gained a better penetration rate through the distorted and dehydrated SC, while the enhanced penetrating rate of propranolol can be attributed to the emulsion properties and appropriate viscosity of the PLO gel that does not block the micro-channels made by the Tixel. An explanation to the absence of systemic AEs, despite the penetration enhancement, can be that the bBs have enough retention time and its diffusion rate through the viable epidermis and dermis is appropriate and not too high.

The main limitation of our study is the small cohort. There is a need for a randomized double-blind, placebo-controlled study, with a much bigger cohort of patients treated for superficial, mixed, and deep IHs, with a longer follow-up period, in order to compare between topical treatment alone, or assisted drug delivery, and to establish the safety profile and the best treatment regimen.

Conclusion

We have demonstrated for the first time that Tixel-assisted percutaneous drug delivery of topical bBs shows promising results in the treatment of IHs. This approach seems effective as well as safe and should be further studied.

Key Message

Tixel assisted percutaneous drug delivery of topical beta-blockers shows promising results in the treatment of infantile hemangiomas.

Acknowledgment

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Statement of Ethics

The parents or guardians of all patients gave their written informed consent. The study protocol was approved by the institute's Helsinki committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have contributed significantly, and are in agreement with the content of the manuscript.

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