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A novel topical nano-propranolol for treatment of infantile hemangiomas

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Abstract

Topical propranolol has been used for the therapy of superficial infantile hemangiomas (IH). A retrospective investigation was conducted in 50 patients to evaluate the clinical effect of a new type of topical nano-propranolol-dispersed hydrogel. Participants were treated 3 times per day for 2 weeks to 11 months. 68% of patients were female and 12% had received other treatments before therapy. The nano-propranolol 0.5% hydrogel was initiated at a mean age of 5.010 months and for a mean duration of 3.610 months. The response rate was 86%. No recurrence and rebound growth occurred after withdrawal of hydrogel. Slight side effects (application site itching, erosion and crusting) were observed in only 2 cases. All the local irritations were evaluated as mild and were tolerated without discontinuing the medication. We suggest that topical nano-propranolol hydrogel could be an alternative option for the treatment of uncomplicated superficial IH with satisfactory tolerability and optimal effectiveness.

Key words: Propranolol; Infantile hemangioma; Beta blocker; Topical therapy

Background

Infantile hemangiomas (IH) are the most common congenital vascular tumor of infancy with a reported incidence of 5%-10%.[1] The incidence is higher (20%-30%) in extreme low birth weight babies.[2] IH are most prevalent in Caucasian children and are three times more common in female infants than male. The head and neck region is the most frequently involved area (60%), followed by the trunk (25%) and the extremities (15%), and these tumors display a non-random distribution largely correlating with regions of embryological fusion.[3] The natural history of the hemangioma characteristically goes through a rapid proliferating phase in the first several months of life followed by a spontaneous involution stage, with slow resolution spanning years. These lesions are usually not present at birth but instead are noted within the first few weeks of life. Precursor lesions are common but often subtle; findings may include telangiectasias, pallor, a bruiselike appearance, and, rarely, ulceration. A residual fibrofatty mass often persists after spontaneous involution of IH.

Because of the spontaneous regression and the majority of lesions produce no long-term scarring, most cases require no treatment. However, 10% of IH require treatment during the proliferating phase,[4] for the reason of life-threatening locations, local complications, or cosmetic/functional risks.[5] Since the serendipitous discovery of the efficacy of propranolol in the treatment of IH by Léauté-Labrèze et al,[6] the effectiveness of propranolol for IH of all types has been demonstrated in multiple publications.[7–10] Subsequently, the off-label use of this molecule became the first-line treatment for IH. Hemangeol (propranolol hydrochloride), an oral solution specially developed for safe and effective use in children, was FDA approved in the USA on March 17th, 2014 and marketed as the first and only FDA-approved treatment for proliferating IH requiring systemic therapy currently (http://www.pierre-fabre.com/en/fda-approval-market-hemangeoltm).

Conflict of interest: None.

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Table 1
Summary of baseline characteristics and treatment of IH.

Patient characteristics and treatment	n = 50
Female-to-male ratio	34:16
Type of hemangioma	
Superficial	50
Deep	0
Mixed	0
Location of hemangioma	
Head and neck	26
Limbs	9
Trunk	5
Periocular	8
Mouth	2
Indication for treatment	
Cosmetic risk	50
Functional risk	0
Life-threatening	0
Local complication	0
Previous treatment	
Laser treatment	4
Radiation treatment	2
Other invasive treatment (embolization, surgical excision)	0
Other agents (corticosteroids, vincristine sulfate, cyclophosphamide, interferon)	0
Other topical agents (imiquimod, timolol)	0
Age at initiation of nano-propranolol treatment (months), median (range)	5.010 ± 3.940
Duration of nano-propranolol treatment (months), median (range)	3.610 ± 2.522
Age at end of nano-propranolol treatment (months), median (range)	8.620 ± 4.327

Nanotechnology is the latest and fast emerging technology wherein dimension of particle of material is reduced nearly to that of individual molecule or their aggregates.[11] Recently, advances in nanotechnology have provided great opportunities for strategies in tumor treatment.[12–14] To improve the efficacy of drug delivery, nanotechnology-based drug-delivery systems are gaining considerable attention, as they have the potential to reduce side effects, minimize toxicity, and improve antitumor treatment efficacy.

We retrospectively analyzed a group of children with IH to identify the therapeutic response and tolerability of a new type medicine, topical nano-propranolol hydrogel. The objective of this study was to assess the efficacy and safety of nano-propranolol hydrogel in the treatment of IH.

Methods

Subjects

This study included patients with IH between January 2013 and February 2014, diagnosed according to the criteria established by the International Society for the Study of Vascular Anomalies (ISSVA).[15] A total of 50 outpatients with superficial IH at the Department of Oral & Maxillofacial Surgery in the Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, China, were enrolled. Those with deep IH were excluded and encouraged to take other treatment (oral propranolol). All patients received a physical examination and clinical data were recorded, including sex, age, size and location of the lesion, disease duration, previous history, current therapies, etc. The study was approved by the Ethics Committee of the hospital. Informed consent was obtained from the patients' guardians prior to the study.

Materials

Nano-propranolol hydrogel was produced by the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, which contained 0.5% propranolol. Formulation: (1) 40 g glycerol, 16 g polyethylene glycol (Molecular Weight: 400 Da, PEG 400), 5 g sodium benzoate, and 20 g nanoparticles of colloidal silicon dioxide dispersed in 200 ml water, and then 5 g propranolol was added into the above suspension and made the propranolol sufficient for adsorption to nanoparticles of colloidal silicon dioxide; (2) 32 g polyvinyl alcohol (PVA, Molecular Weight: 100,000 Da) and 32 g PVA (Molecular Weight: 40,000 Da) dissolved in 650 ml water; (3) the suspension of 1) was added the solution of 2) and well dispersed.

The treatment regimen involved the application of nano-propranolol hydrogel to the lesions 3 times per day for 2 weeks to 11 months. The hydrogel was evenly rubbed onto the surface for 2 ml/cm^2 each time. As a routine, cardiac examination (electrocardiographic and ultrasound echocolor Doppler examination) was performed before treatment. Blood pressure (BP) and heart rate (HR) were measured and recorded. Patients were examined 2 h after treatment and every 1 month during the treatment to monitor the skin response or other side effects of nano-propranolol hydrogel. Drug administration was discontinued when 90% of the lesion disappeared or the treatment duration was over 1 year. Post-treatment evaluations were performed every 3 months. The response was assessed by comparing the status at the start of treatment and at the last appointment. The lesions were photographed at baseline, during treatment, and at each follow-up.

Clinical definition

Hemangioma size was recorded using "hemispheric" measurement.[16] A soft tape measure was draped over the lesion, and the longest diameter and a measurement perpendicular to it were recorded, giving a measurement in cm^2. The response was classified as follows: clinical resolution—complete clearance of the lesion, scored 4; excellent—75% to 99% improvement, scored 3; moderate—50% to 74% improvement, scored 2; minimal—25% to 49% improvement, scored 1; failure—<25% improvement, scored 0.[17] The overall efficacy was calculated from the sum of cases that were scored above 2. Local skin responses were as follows: none—scored 0; mild—scored 1 (+, erythematous reaction); moderate—scored 2 (++, erosion or light crusting); severe—scored 3 (+++, ulceration, thick crusting or scarring).

Results

Clinical data

A total of 50 cases were analyzed, 68% (34/50) of which were female and 32% (16/50) male, constituting a female/male ratio of