**Materials and Methods**

**Patient Selection**

This is a retrospective study of 11 cases of IHs treated with the Tixel device (NOVOXEL Ltd., Israel) prior to application of topical propranolol 4% in pluronic lecithin organogel (PLO) gel or Timolol 0.5% eye drops solution between January 2018 and March 2019. The diagnosis of IH was based on the criteria set by the International Society for the Study of Vascular Anomalies (1996). If additional treatment was used, the patients were excluded from the study. Written consent was received from the legal guardians of the patients after they were informed about the nature of the procedure and possible side effects.

**Beta-Blockers Selection**

Since specifically optimized topical preparation of bBs does not exist, timolol eye drops solution and compounded topical propranolol preparations are both used for the treatment of IHs [11, 12, 14]. The patients in our study were treated with either timolol 0.5% eye drops solution or propranolol 4% in PLO gel supplied by a compounding pharmacy. The compounded propranolol in PLO gel is used in the treatment of IHs as well as pyogenic granuloma for several years, with good effect and only minor topical AEs [14–16]. PLO is an emulsion liposomal gel enriched with several chemical penetrating enhancing agents in which propranolol hydrochloride is totally dissolved thus being available for stratum corneum (SC) penetration. The liposome as an amphiphilic vehicle, probably can deliver better the hydrophobic propranolol through the hydrophilic viable epidermis and dermis, and this could be the reason for the efficacy of this formulation in the topical treatment of IHs [17, 18].

**Tixel-Associated Drug Delivery**

One of the important factors influencing the efficacy of topical drugs is their ability to penetrate the different skin layers, primarily the SC [13]. The Tixel technology is a medical device registered in several countries worldwide. The hand piece of the device is equipped with precise motion system which enables accurate preset skin contact duration. The moving active surface (tip), consists of an array of 81 titanium square-based pyramids 1.25 mm tall with a flat rectangular apex (of approximately 0.01 mm2) heated to 400°C. The blunt apex of the pyramid allows effective heat transfer and prevents mechanical puncturing of the skin. The protrusion (the distance in which the heated tip is moving aimed to acquire better thermal matching between the tissue and the tip) and the pulse duration (the period that the tip is in contact with the skin) determine the thermal energy which is delivered to the skin. At low energy settings, most of the thermal effect is concentrated in the SC, with minimal thermal effect on the viable epidermis and dermis [13, 19]. When the tip moves forward onto the SC, strains occur inside the dehydrated layer generating cracks which allow drug permeation through these new micro-channels, and maybe also to some extent through all the dehydrated tissue. The dimensions of the micro-channels are proportional to the shape of the pyramids’ apexes. The dehydrated SC creates a relatively high-water concentration gradient inside the micro-channel, between the drug on the surface of the skin and the viable epidermis beneath it. Since the water content in the extracellular matrix is approximately 70%, it is expected that the dry tissue will be filled with water relatively fast, until the water concentration in the entire tissue will be equalized. This new delivery system dictates the following demands: (1) The vehicle of the topical medication applied on the pre-treated skin should be hydrophilic with low viscosity to allow a fluent flow along the micro-channel. Hydrophobic or viscous vehicles might block the channel and fail the drug delivery. Solutions and non-viscous gels are appropriate vehicles for this system. (2) The drug application should be performed immediately and up to 6 h after creating the micro-channels in the SC to take the advantage of open channel with high-water concentration gradient. (3) It is logical that more hydrophilic drugs will benefit from the Tixel technology manipulation of the SC, as this layer is the major obstacle for the skin's penetration of hydrophilic molecules. Therefore, the more hydrophilic bBs like timolol and atenolol [20] are better candidates for testing the efficacy and safety of this drug delivery system in the topical treatment of his. (4) Occlusion of the hydrophilic preparation on the Tixel manipulated skin can increase the contact time with the skin surface area and increase the flow of the preparation into the micro-channels.

**Treatment Protocol**

Tixel (Novoxel, Israel) treatment, as well as follow-up evaluation, once every 2–4 weeks until cessation of the treatment were performed on every IH with the following parameters: exposure time of 6 ms, and protrusion of 400 µm. The Tixel application duration, obviously depending on the size of the IHs, usually lasted few seconds. Either propranolol 4% in PLO gel or timolol 0.5% eye drops solution were applied over the entire IH immediately and 4 times 1 h apart, after the Tixel drug delivery application. In order to achieve better results, in 3 cases the parents were instructed to apply topical propranolol 4% in PLO gel over the IHs twice daily without occlusion for the first month of treatment, as usually recommended in the topical treatment of IHs. In case of a large IH, awareness to AEs and special consideration were emphasized. In the event of any systemic, generalized, or local AEs, the treatment would be discontinued.

**Clinical Evaluation Score**

Prior to treatment initiation, at each treatment visit and 3 months after treatment cessation, the IHs were evaluated and photographed. Epidemiologic (sex, age at the beginning of treatment), clinical (location, size, color, number, type of IH), and treatment data (total duration, response, side effects) were recorded. The response to treatment was evaluated using a previously reported scoring system [15]. Four parameters were used for grading the IHs: size regression, lightening of the surface color, flattening, and deep component reduction. The response to treatment of each category was scored from 0 to 3. All evaluated scores were summed and then divided by the number of evaluated parameters thus obtaining a final lesion score, with values between 0 and 3. A value of up to 1 was considered to represent poor or no response, values between 1.1 and 2 were considered as partial response, and values of more than 2.1 were considered as a good response (Table 1). Statistical analysis was performed using SPSS software (version 21.0; IBM Corporation, Armonk, NY, USA).