Treatment of infantile hemangioma with topical imiquimod 5% cream

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Background: Infantile hemangioma is a congenital vascular malformation. Although almost all cases are self-limiting, treatment is sometimes necessary. According to previous studies, topical imiquimod induces resolution of lesions with an acceptable safety profile. The aim of the present study was to evaluate the effect of this topical treatment on Iranian infantile hemangioma patients.

Method: Patients under two years of age with infantile hemangioma who were not candidates for immediate systemic therapy with steroids were selected if the lesions were not ulcerated. Topical 5% imiquimod was applied on the lesions for 16 weeks. All the lesions were photographed before the commencement of the study and at the end of the treatment. Photographs were compared by two associate dermatology professors to evaluate the effect of treatment using a visual analogue scale.

Result: A total of 15 patients including five males (33.3%) and ten females (66.7%), with an age range of two to 18 months and a mean age of 9.1 (± 6.3) months, were enrolled in the study. The mean diameter of the lesions was 2.6 cm (± 1.8 cm). Nine patients (60%) had moderate response and five patients (33.3%) had good response while one patient had excellent response. Complications were mild local irritation and pruritus.

Conclusion: It seems that topical imiquimod could be a suitable option in the treatment of some infantile hemangioma lesions not candidate for systemic treatment and/or other local measures such as laser and intra lesional steroid or when other drugs are useless or harmful.

Keywords: imiquimod, infantile hemangioma, topical treatment

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INTRODUCTION

Infantile Hemangioma (IH) is the most common benign tumor of infancy [1, 2]. They are congenital or early infancy lesions and have a rapid postnatal growth followed by subsequent slow involution. Fibroblast growth factor (FGF) and other angiogenic growth factors such as vascular endothelial growth factor (VFGF), insulin-like growth factor 2 (IGF2) and monocyte attraction factor 1 have a known role in the growth of IH lesions [3-5]. Interferon-α regulates b-FGF and VEGF expression [6]. Several anti angiogenic factors may be used to halt proliferation of IH and induce resolution [5,7]. Management of most IHs is generally conservative except when IH can potentially cause life- or function-threatening complications, disfigurement, ulceration or scarring [1,8]. Imiquimod is an immune response modifier approved for the treatment of condyloma and some other dermatologic disorders [9]. Imiquimod acts via Toll Like Receptor 7 (TLR-7), and directly activates the innate immune response system [10]. Imiquimod has also been shown to have some intrinsic pro-

apoptotic activity, independent of its stimulation of the immune system [11]. Probably, all of the above contribute, to varying degrees, to the anti-angiogenic activity of imiquimod and provide a rational basis for its use in the treatment of IH [12-14]. The aim of the present study was to evaluate the effect of this topical preparation on infantile hemangioma in Iranian patients.

PATIENTS AND METHODS

We included patients younger than two years of age if they had IH. Patients were excluded if they had received any previous treatment, had ulcerated lesions or lesions with functional impairment that required to be treated urgently. All patients' legal care takers signed an informed consent form prior to participation in the study. Demographic data about patients were collected and documented in special questionnaires. All lesions were photographed with a Cannon 10 Megapixel camera with the same parameters, and all pictures were saved in separate folders. Following this step, topical imiquimod 5% cream was prescribed for all patients to apply once daily, on alternate days, on the lesion for a period of 16 weeks. Patients were visited every four weeks to evaluate response to treatment and its adverse effects and lesions were photographed. After 16 weeks, treatment stopped and serial photographs, including the first and the last photographs were saved on a removable media for further evaluation. All photographs were randomized and evaluated by two blinded academic associated dermatology professors, using a visual analogue scale (VAS) without knowledge about the time of taking the photographs (before or after treatment). Patients' responses were classified according to this scale:

- Score 1 or no response: less than 25% reduction in the size of the lesions
- Score 2 or poor response: between 25 to 50% reduction in the size of the lesions
- Score 3 or good response: between 50% to 75% reduction
- Score 4 or excellent response: more than 75% reduction in the size of the lesions

Patients were followed at least for 6 months, to evaluate course of lesions and call for other treatment modalities if indicated. All data collected throughout special questionnaires and statistical analysis performed using SPSS (ver. 16) and chi-square and t-test used when necessary.

RESULTS

A total of 15 patients including five males (33.3%) and ten females (66.7%), with an age range of two to 18 months and a mean age of 9.1 (± 6.3) months, were enrolled in the study. Except for one patient who had two lesions, all had only one lesion. Eleven patients had head and neck lesions, three had trunk IH and one patient had IH on his hand. The mean diameter of IH lesions was 2.6 cm (± 1.8cm). Nine patients (60%) had moderate response (between 25-50% reduction in lesion size) and five patients (33.3%) had good response (between 50-75% reduction in lesion size) while one patient had excellent response. Figures 1 to 3 show three of our patients before and after treatment. There was no significant association with age, sex and lesion diameter. After 6 months of follow up, we did not find any signs of recurrence; in fact, three patients who continued topical imiquimod after the end of the study were satisfied with its effects. Almost all patients had signs of local irritation including mild pruritus, erythema, scaling and sometimes edema and crust formation extending one to two centimeters beyond the lesion, and were treated with topical weak steroids and temporary treatment holding for two to three days.

DISCUSSION

The present study showed that imiquimod is an effective alternative to treatment of IHs that are not candidates for emergency treatment. Topical imiquimod can reduce the size of the lesion and surface erythema. Our findings are in agreement with previous reports of IH improvement with imiquimod [15,16]. Systemic corticosteroids can reduce proliferation and size of IH lesions, but have many side effects, including weight gain, immune-suppression, metabolic disturbances and many other complications of the high dose needed to induce IH resolution [17]. Steroid injection into IH lesions can produce rapid resolution of lesions, but may have catastrophic adverse effects such as blindness and induced cutaneous atrophy in some

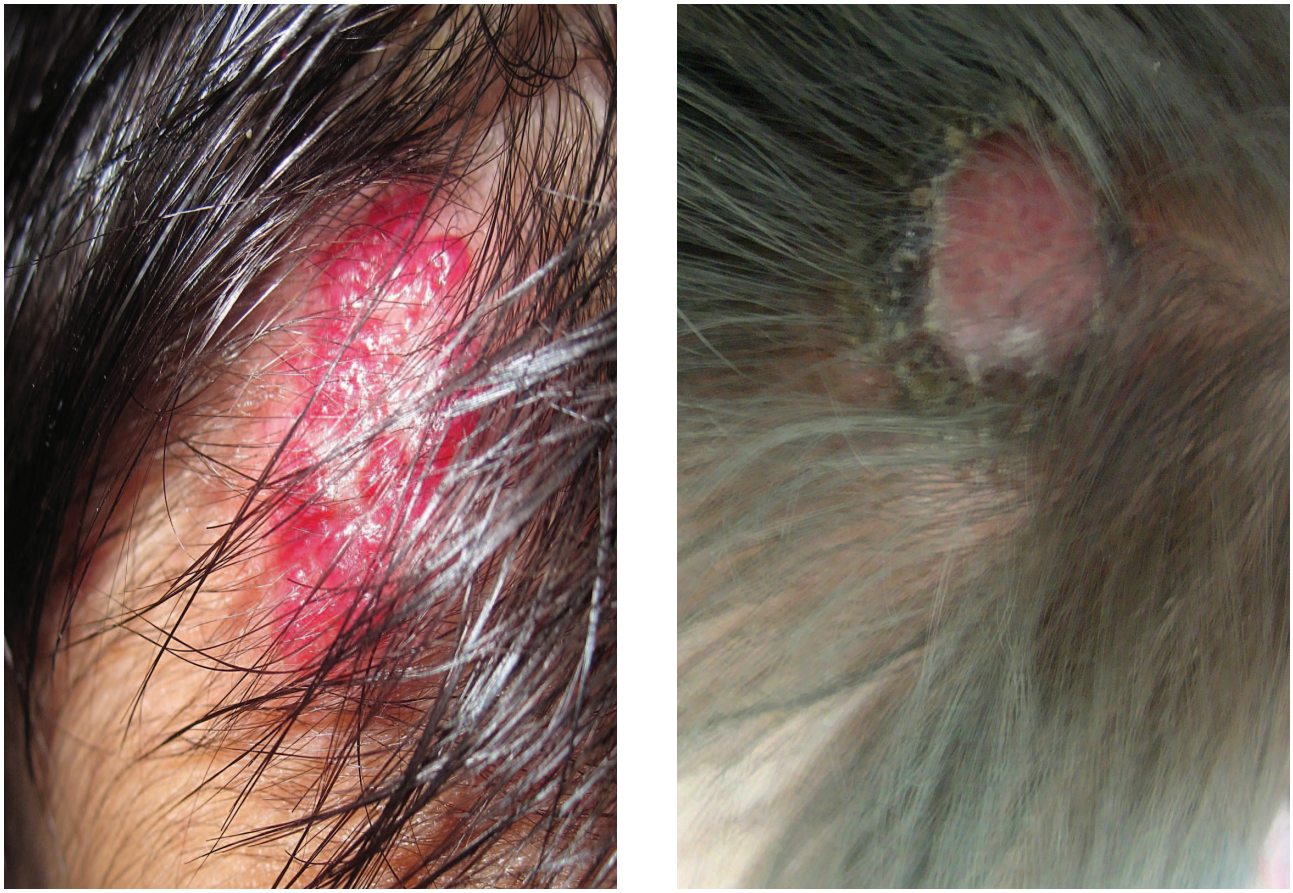

Figure 1. Scalp lesion before and after imiquimod application.

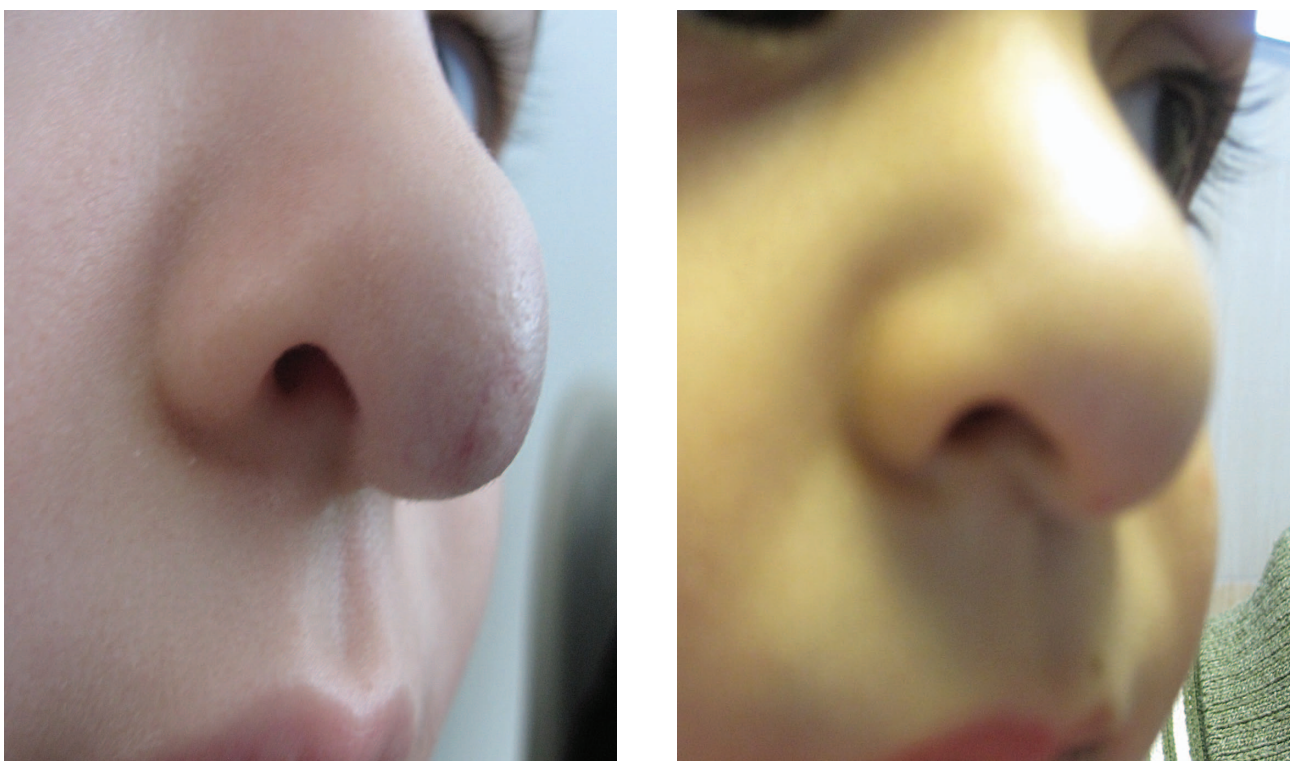

Figure 2. Excellent response after imiquimod local therapy.

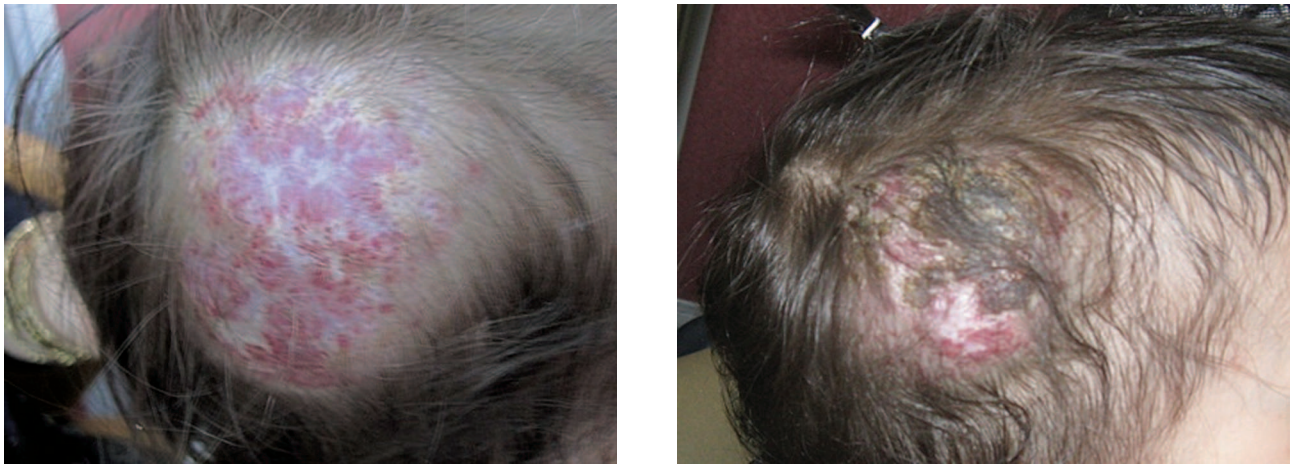

Figure 3. Reduction in size and color after topical imiquimod application.

situations [18-20]. Physical modalities of treatment including laser therapy with pulsed dye laser (PDL) and cryosurgery with liquid nitrogen [21-24] are other suggested treatment modalities with limitations such as non sufficient depth of effect, post treatment scarring, and recurrence after treatment. Hence, it is logical to try to find other treatment options. Imiquimod is a topical immune-modulator with potential benefits on IH lesions in previous studies [15,16,25]. Some studies have reported better response rates than our study [25] which may be due to a longer treatment period, more accurate adherence to treatment by the patients and some other unknown factors. We found no significant relationship between age, sex and size of the lesions and response to treatment. Some studies have presented conflicting data about the effect of these parameters on treatment response. After 6 months of follow up, we did not find any signs of recurrence; in fact, three patients who continued topical imiquimod after the end of the study were satisfied with its effects. As we mentioned earlier, there were a few side effects including mild local pruritus and irritation and we had no treatment cessation because of local irritating effects of the drug. We had some study limitations including the little sample size and indirect judgment on results by referees. We also had a limited time period to include cases in the study and not all IH patients agreed to participate. Our referees evaluated the response only via photographs and cases were not examined clinically. However, due to the good quality of the photographs taken under the same condition, we had little concern regarding this limitation.

In conclusion, it seems that topical imiquimod could be a suitable option in the treatment of some IH lesions not candidate for systemic treatment and/or other local measures such as laser and intra-lesional steroid or when other drugs are useless or harmful.

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