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Topical imiquimod treatment of cutaneous vascular disorders in pediatric patients: clinical evaluation on the efficacy and safety*

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Abstract: Objective: To evaluate the clinical effect of topical imiquimod treatment on cutaneous vascular disorders in pediatric patients. Methods: A retrospective investigation was conducted in 25 pediatric patients with cutaneous vascular disorders, including 19 infantile hemangiomas (IHs) (12 superficial/7 mixed type), 5 nevus flammeus (NF), and 1 pyogenic granuloma (PG). Imiquimod 5% cream was applied every other day for 4 to 16 weeks (average 9.6 weeks). Results: Of the 19 IHs treated, an overall efficacy of 52.6% was achieved, with a clinical resolution rate of 15.8%, excellent rate of 26.3%, and moderate rate of 10.5%. The superficial type responded the best at 66.7%, while the mixed type showed only 28.6% effectiveness, which was predominantly from their superficial parts. No obvious response was noted in the 5 patients with NF. Side effects were observed in 78.9% of the patients, mostly mild to moderate local irritations and occasionally severe reactions such as thick crusting and ulceration. Systemic side events were observed in 4 IH patients including fever and digestive tract reactions. No recurrence was observed during the follow-up examination. Conclusions: Topical imiquimod could be an alternative option for the treatment of uncomplicated superficial IHs with satisfactory tolerability.

Key words: Infantile hemangioma (IH), Nevus flammeus (NF), Imiquimod, Treatment
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1 Introduction

Cutaneous vascular disorders, especially infantile hemangioma (IH), are commonly seen in pediatric patients, and are often quite challenging to manage. Early intervention may limit some sequelaes such as ulcerations and tissue necrosis during the fast proliferating phase, or residual skin changes after spontaneous involution (Welsh *et al.*, 2004). Several American and European reports have suggested the efficacy and safety of the topical application of imiquimod in the treatment of IHs (Martinez *et al.*, 2002; Welsh *et al.*, 2004; Hazen *et al.*, 2005; Ho *et al.*, 2007; Barry *et al.*, 2008; McCuaig *et al.*, 2009). In this report, 25 Chinese pediatric patients with various cutaneous vascular disorders were treated with topical imiquimod and evaluated for the therapeutic response and tolerability. Sometimes, the selection of indications was motivated by parental anxiety over the risk of incomplete involution of the hemangiomas or the complications of other invasive treatments, and served as an approach of psychological therapy (Bruckner and Frieden, 2006; Musumeci *et al.*, 2008).

2 Subjects and methods

2.1 Subjects

A total of 25 outpatients who came for various cutaneous vascular diseases (mostly superficial or mixed IHs) at the Department of Dermatology in the Second Affiliated Hospital, School of Medicine,

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Zhejiang University, China, between 2007 and 2008 were enrolled. Deep or complicated IHs were excluded and encouraged to take other treatments. All participants 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. Informed consent was obtained from the parents.

2.2 Methods

The treatment regimen involved the application of imiquimod 5% cream applied to the lesions every other day (about 3–4 times weekly) for 4–16 weeks. Patients were examined every 2–4 weeks during the treatment to monitor their skin response. When severe local reactions developed, topical antibiotics were applied to the site until the reactions disappeared. Treatment was terminated for severe reactions. The application frequency was increased to 5 times a week in 6 patients because of the lack of skin response after 3–4 weeks of treatment. Post-treatment assessments were performed every 3 months. Most lesions were photographed at baseline, during treatment, and at follow-up visits.

2.3 Clinical definition

Response to treatment was defined as follows: clinical resolution—complete clearance of the lesion, scored 4; excellent effect—75% to 99% improvement, scored 3; moderate effect—50% to 74% improvement, scored 2; minimal effect—25% to 49% improvement, scored 1; failure—<25% improvement, scored 0 (Welsh *et al*., 2004; Guo *et al*., 2009). The overall efficacy was calculated from the sum of cases that were scored above 2. Local skin responses were scored as: 0=none, 1=+/mild (erythematous reaction), 2=++/moderate (erosion or light crusting), 3=+++/severe (ulceration, thick crusting or scarring).

3 Results

3.1 Clinical data

The 25 subjects consisted of 19 IHs (5 males and 14 females, 12 superficial type and 7 mixed type), 5 nevus flammeus (NF), and 1 pyogenic granuloma (PG) (Table 1). All IHs were uncomplicated lesions in the proliferative stage and had not been treated by other methods except one participant who had previously received 5 injections of sclerotherapy. The majority of the 19 IH patients enrolled were under the age of 1 year (mean 6.5 months) to minimize the possible influence from the spontaneous regression of IHs. The duration of treatment ranged from 4 to 16 weeks with an average of 9.6 weeks.

3.2 Clinical outcomes

3.2.1 Efficacy

Of the 19 IHs treated, an overall efficacy of 52.6% (10/19) was achieved, with a clinical resolution rate of 15.8% (3/19), excellent rate of 26.3% (5/19), and moderate rate of 10.5% (2/19). The best response came from superficial type (66.7%, 8/12), while mixed type showed only 28.6% (2/7) effectiveness, which was predominantly from their superficial parts. A PG lesion of a 16-month-old boy was almost cured after 4 weeks of imiquimod application. However, no obvious response to the treatment was noted in the 5 patients with NF.

3.2.2 Side effects

Side effects were observed in 78.9% (15/19) of IHs and 33.3% (2/6) of non-IHs, including application site itching, erythema/edema, peeling, erosion, crusting, ulceration, and scarring. Most of the local irritations were evaluated as mild to moderate and resulted in no treatment interruption. These inflammatory skin reactions were mostly treated by topical antibiotics and were unlikely to result in scarring. Severe local reactions such as thick crusting and ulceration were reported (1 each), and resulted in scarring and texture change of the skin. Systemic side events were observed in 4 IH patients, including 2 fever, 1 nausea, and 1 diarrhea.

3.3 Special cases

3.3.1 Resolution time

The earliest resolution happened 1 month after the termination of a 4-week treatment in a 3-month-old girl (patient No. 10) with rapid proliferating IH (Fig. 1). At the last follow-up visit, the patient was in excellent health with no evidence of recurrence of the hemangioma. No neurological changes and other adverse events were noted during the 16-month period.

Table 1 Summary of clinical data and outcomes

Patient No.	Diagnosis/ type[1]	Sex	Age (month)	Location	Size (cm)	Dose (week)	Duration (week)	Final result[2]	Skin response[3]	Systemic response	Follow-up (month)
1	IH/S	M	5	Nose	0.5	3	8	4	1	−	12
2	IH/M	F	5	Forehead	1.5	3	4	2	1	−	1
3	IH/M	M	6	Lower limb	5.0	3	10	1	1	+ (fever)	2
4	IH/M	M	5	Upper limb	10.0	3	8	1	3	+ (nausea)	3.5
5	IH/S	F	4.5	Forehead	0.5	3	14	4	2	−	6
6	IH/M	F	7	Scalp	2.0	3	8	1	0	−	3
7	IH/S(2)	F	3	Upper limb Trunk	2.5×1.5 0.5	3	12	1	1	−	6
8	IH/S	M	8	Scalp	0.4	3	10	3	2	−	3
9	IH/S	F	11	Trunk	1.5×1.0	3	16	1	1	−	16
10	IH/S	F	3	Upper limb	1.5×1.0	3	4	3	2	−	16
11	IH/M	F	2	Trunk	4.0×2.0	3	16	2	2	+ (diarrhea)	9
12	IH/S	F	10	Upper limb	3.0×2.0	3	12	3	1	+ (fever)	12
13	IH/M	F	1.5	Face	3.0×5.0	3	4	1	3	−	3
14	IH/S	F	4.5	Lower limb	3.0	3	16	3	1	−	6
15	IH/M	F	6	Upper limb	1.0	5	10	1	0	−	3
16	IH/S	M	4	Lower limb	2.0	5	10	1	0	−	3
17	IH/S	F	4	Face	1.5	3	8	3	2	−	3
18	IH/S	F	21	Upper limb	1.0	3	8	1	0	−	4
19	IH/S	F	13	Trunk	1.0	3	4	4	2	−	3
20	PG	M	16	Face	0.5	3	4	3	2	−	2
21	NF	M	2	Foot, scalp	3.0	3	6	0	1	−	16
22	NF	F	36	Lower limb	15.0	5	7	0	0	−	2
23	NF	F	3	Upper limb	5.0×15.0	5	6	0	0	−	2
24	NF	M	25	Upper limb	4.0×7.0	5	10	0	0	−	3
25	NF	M	24	Nose	2.5×1.0	5	6	0	0	−	2

[1] Diagnosis: IH=infantile hemangioma, NF=nevus flammeus, PG=pyogenic granuloma; type: S=superficial, M=mixed. [2] Final result: 4=clinical resolution—complete clearance of the lesion; 3=excellent effect—75% to 99% improvement; 2=moderate effect—50% to 74% improvement; 1=minimal effect—25% to 49% improvement; 0=failure—<25% improvement. [3] Local skin response: 0=none, 1=+/mild (erythematous reaction), 2=++/moderate (erosion or light crusting), 3=+++/severe (ulceration, thick crusting or scarring)

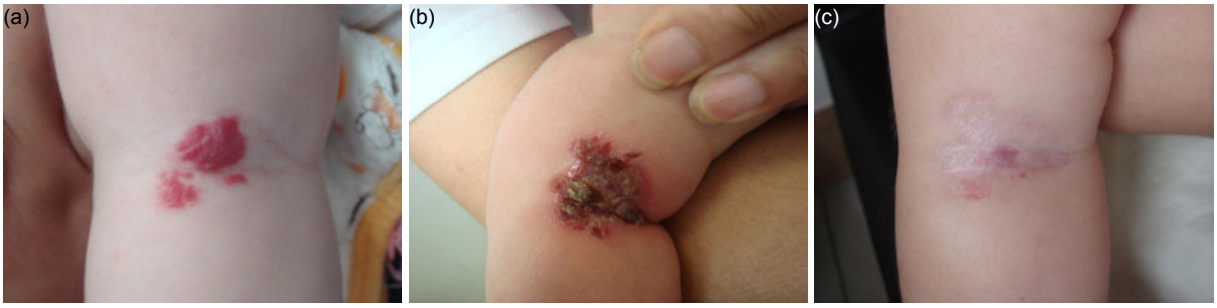

Fig. 1 The earliest resolution after 4-week treatment in a 3-month-old girl with rapid proliferating IH

(a) A 1.5 cm×1.0 cm hemangioma on the right elbow, which was visible at birth and grew rapidly. (b) A moderate inflammatory response with erythema, erosion, and crusting developed at the application site four weeks after the starting point, leading to the termination of imiquimod treatment. (c) Almost complete regression of the lesion without obvious scarring one month after termination of the treatment

3.3.2 Severe local reactions

A 5-month-old boy (patient No. 4, Fig. 2a) with a 10 cm diameter mixed-type hemangioma on his upper limb developed severe ulceration at the middle of the lesion after 8 weeks of imiquimod application. The treatment was discontinued subsequently with a 3.5-month follow-up which showed little improvement of the lesion.

Thick crusting was noted on the lesion (3 cm× 5 cm sized mixed-type hemangioma on the face) of another 1.5-month-old girl (patient No. 13, Fig. 2b) after 4 weeks of imiquimod application. The treatment was stopped and the patient was followed up for 3 months with minimal improvement observed. Irregular scarring and skin texture change were noted.

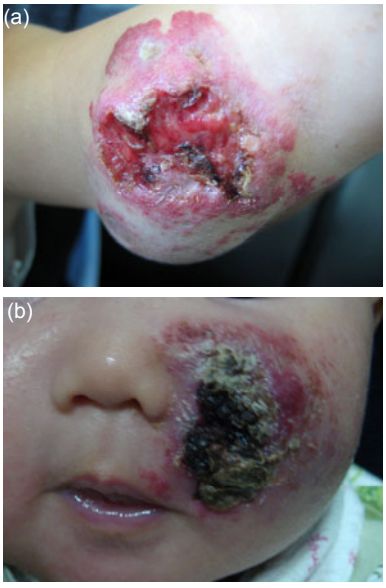

Fig. 2 Severe local reactions in two patients with mixed- type IH after imiquimod application
(a) Severe ulceration in a boy with big mixed-type IH after 8-week treatment. (b) Thick crusting on the lesion of a girl with mixed-type IH after 4-week treatment

3.3.3 Systemic side effects

A 10-month-old girl (patient No. 12) developed fever (up to 38.5 °C for 2 d, with no evidence of other etiologies upon PE) after two applications of imiquimod cream, but continued treatment for 16 weeks. Marked reduction in the color and thickness of the lesion was achieved 11 weeks after initiation. Seven months after the end of the treatment, the lesion improved significantly with only minimal residual change. There were no neurological changes or other adverse effects noted. Transient fever was also observed in patient No. 3.

3.4 Follow-up

After termination of the treatment, the patients were followed up for 1–16 months with an average of 6 months. No recurrence was observed during the follow-up examination.

4 Discussion

In this study, we retrospectively analyzed the clinical effect of topical imiquimod on the treatment of cutaneous vascular disorders, and found it efficacious and tolerable particularly for superficial IHs. In accordance with previous reports (Hazen *et al.*, 2005), regression occurred after approximately 6 weeks of treatment in most cases. Interestingly, imiquimod was effective in a PG lesion but ineffective for NF, reflecting the different nature of these diseases. The major factors responsible for the complete clearance of IH lesions have not yet been well defined.

Side effects were observed but mostly expectative local irritations. The application site reactions were widely accepted as a required sign of therapeutic response rather than of toxicity (Martinez *et al.*, 2002; Sidbury *et al.*, 2003; Welsh *et al.*, 2004; Hazen *et al.*, 2005; Barry *et al.*, 2008). In this study, most low-responders showed relative minimal inflammation, which appeals the theory that the lack of clinical efficacy correlates to an insufficient inflammatory reaction. According to our experience from this survey, the appropriate frequency and duration of treatment to induce this reaction varied from patient to patient. In our opinion, this individual difference of response to imiquimod may suggest a gene-based variation of some crucial elements such as toll-like receptors. In another study, however, two patients (out of 18) achieved complete clearance of their hemangiomas without exerting any inflammation (Ho *et al.*, 2007), indicating another latent pathway within the broad mechanism network of imiquimod. We have also described two patients who showed severe local reactions including deep ulceration and thick crusting, which have rarely been previously reported in the treatment of IH. The possibility of ulceration

caused by rapid progress of proliferating IH cannot be excluded in these cases. Systemic reactions were observed in some patients including fever, which is similar to other reports (van Seters *et al.*, 2008); however, digestive tract symptoms of nausea and diarrhea have not been reported before. Although fever is not a prevalent complication during the application of topical imiquimod, it is considered as a systemic response of the body to topical application of imiquimod (Barry *et al.*, 2008). In this study, no correlation between the probability of systemic symptoms and severity of local responses was observed.

The major advantages of topical imiquimod treatment are the convenient application, satisfactory tolerability, excellent cosmetic result, and low recurrence. Up to now, the optimal time of imiquimod treatment for IH remains unclear. The use of topical imiquimod might be combined with conventional or laser therapy to improve the prognosis.

Since the first report in 2002 that showed the potential of imiquimod in accelerating the regression of IH (Martinez *et al.*, 2002), continuous efforts have been made to investigate the role and potential toxicities of imiquimod in the treatment of cutaneous vascular disorders (Sidbury *et al.*, 2003; Welsh *et al.*, 2004; Hazen *et al.*, 2005; Sanchez-Carpintero *et al.*, 2006; Ho *et al.*, 2007; Barry *et al.*, 2008). A variety of mechanisms might be involved in imiquimod-induced regression of vascular tumors (Sanchez-Carpintero *et al.*, 2006), including an immune response (Sun *et al.*, 2007). Imiquimod can induce cytokine production such as interferon, interleukin (IL), and tumor necrosis factor. Interferon, especially interferon-γ, can decrease cellular production of several pro-angiogenic factors, inhibit vascular motility and invasion, and induce apoptosis of endothelial cells (Brouty-Boyé and Zetter, 1980; Sidky and Borden, 1987; Stanley, 2002; Sidbury *et al.*, 2003). IL-12 can inhibit endothelial proliferation and tube formation in vitro and angiogenesis in vivo through intracellular signaling and other undefined pathways (Wang C. *et al.*, 1999; Duda *et al.*, 2000; Li *et al.*, 2005). These anti-angiogenic and apoptotic effects are considered to contribute to the influence of imiquimod on hemangioma regression (Sidbury *et al.*, 2003; Hazen *et al.*, 2005). Recently we described two cases of lymphangioma circumscriptum successfully treated with topical imiquimod, and the similar anti-proliferative and apoptotic effects on lymphatic vessels were supposed to be the curative mechanism (Wang J.Y. *et al.*, 2012).

5 Conclusions

To summarize, this study demonstrates that topical imiquimod is minimally invasive and likewise effective in treating uncomplicated superficial IHs. However, it is not recommended for deep, complicated IHs. Our results may provide some insight into the mode of action of imiquimod on cutaneous vascular disorders and other potential therapeutic applications.

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