Oral versus topical propranolol for management of superficial infantile hemangiomas: a comparative study

Safy M. Abdel Wahab, Hisham A. Almetaher, Hesham Fayad and Essam A. Elhalaby

Background/purpose **Oral propranolol has been used successfully for the treatment of infantile hemangiomas (IHs). However, its safety is questioned. Topical therapy with 1% propranolol ointment has been reported to be safe and effective. The objective of this study was to compare the effectiveness and safety of oral versus topical propranolol (1% ointment) as a nonselective β-blocker in the management of cutaneous IH.**

Patients and methods **Forty-eight patients with IH were randomly divided into two equal groups: group A ($n=24$) was treated with oral propranolol and group B ($n=24$) was treated with propranolol ointment 1%. The patients were followed up for 3 months after treatment was stopped.**

Results **There was a significant statistical difference between the two groups as regards the effectiveness of the drug ($P=0.041$). In the oral group, 50% ($n=12$) showed an excellent response, 33.33% ($n=8$) showed good response, and 16.67% ($n=4$) showed a fair response, whereas in the topical group 16.67% ($n=4$) showed an excellent response, 45.83% ($n=11$) showed good response, and 37.5% ($n=9$) showed a fair response. There was no significant adverse event in any group during the follow-up period.**

Conclusion **Oral propranolol is an effective, safe, and fast-acting drug for treating IH and can be monitored on an outpatient basis. Topical propranolol is an easily prepared drug and seems to be an alternative therapeutic option for superficial cutaneous hemangioma. However, the optimal dosing and duration of treatment are still to be defined.** ***Ann Pediatr Surg*** **13:1–7 © 2017 Annals of Pediatric Surgery.**

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Department of Surgery, Pediatric Surgery Unit, Faculty of Medicine, Tanta University, Tanta, Egypt

Correspondence to Hisham A. Almetaher, MD, Department of Surgery, Pediatric Surgery Unit, Faculty of Medicine, Tanta University, Tanta 31111, Egypt
Tel: +20 122 826 6136; fax: +20 403 344322;
e-mail: hishamalmohamady@yahoo.com

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Introduction

Infantile hemangiomas (IHs) are the most common, benign vascular tumors of infancy, present in 4–5% of the population [1]. Except for 10% of IH cases where intervention is required, treatment is not necessary [2,3]. However, strict follow-up is usually advised [4].

Standard treatment modalities for IH include corticosteroids, cryosurgery, interferon, and vincristine and laser surgery [5,6]. Each of these treatment options has its limitations and drawbacks [7].

The efficacy of propranolol, a nonselective β-blocker, in the treatment of IH has been demonstrated since 2008 [8]. Several studies have demonstrated the high potential of propranolol in the treatment of IH. However different opinions regarding its side effects, which include hypotension, hypoglycemia, bradycardia, sleep disturbances, and gastrointestinal disturbances, exit [9–11]. Numerous reports have indicated the efficacy and safety of topical βblocker for the treatment of IH and have concluded that it can be a replacement or an adjunct to systemic propranolol [12,13].

The aim of this study was to compare the effectiveness and safety of oral versus topical propranolol (1% ointment) in the management of cutaneous IH.

Patients and methods

After obtaining approval from the ethical committee at Tanta Faculty of Medicine, this prospective randomized comparative study was conducted in the Pediatric Surgery Unit, General Surgery Department, Tanta University Hospitals, during the period from January 2013 to January 2016, and included 48 patients who presented with superficial IH. Patients were prospectively recruited and randomly allocated into two groups using a simple coin toss method. Group A ($n=24$) was treated with oral propranolol and group B ($n=24$) was treated with propranolol ointment 1%.

Exclusion criteria included patients with a history of allergy or hypersensitivity to β-blockers, second-degree or third-degree atrioventricular block, heart failure, asthma or bronchial obstruction, a history of previous treatment, or having deep hemangiomas. However, patients with functional impairment, local discomfort, or esthetic disfigurement were included in the study. Written informed consent was provided by parents of all infants. Privacy of the participants and confidentiality of data were maintained.

Each patient in this work was subjected to full history taking. Local examination of the lesion to detect site, size, shape, color, consistency and functional defects was carried out. The maximal thickness of the lesions was

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measured with ultrasound. Full clinical examination by a pediatric cardiologist for cardiologic pass, including baseline clinical observations (pulse, blood pressure, respiratory rate, and basal ECG) and digital photographs, was carried out. If this evaluation was normal and ultrasound confirmed no subcutaneous components, the patients were included in the protocol. Random blood sugar was measured routinely in all patients while other basic biochemistry tests were selectively requested when patients were symptomatic or some diseases were suspected.

Treatment protocol

Group A: treated with oral propranolol (24 patients)

Incremental doses of oral propranolol starting at 1 mg/kg was given every 2 h (oral tablets dissolved in distilled water) until a target dose of 3 mg/kg in three divided doses was achieved on discharge. Between each dose, heart rate and blood pressure were recorded.

Group B: treated with topical propranolol (24 patients)

The hospital pharmacy prepared the propranolol ointment in the form of propranolol–hydrochloride at 1% concentration in a hydrophilic ointment form (oral propranolol crushed pills/petroleum jelly = 10 mg/1 g). The ointment was rubbed three times daily onto the clean dry IH area. The amount of cream applied was based on the surface area of the lesion. Patients were monitored once for blood pressure, heart rate, and blood glucose level after initiation of the treatment.

Follow-up and clinical assessment of efficacy

Patients were asked to attend the outpatient department at 48 h, 1 week, and then every 2 weeks throughout the duration of treatment and finally at 4-week intervals until 1 month after the treatment had stopped (the follow-up period, during which any rebound growth was documented). During each visit the patients underwent formal photographic, cardiological, and clinical evaluation. Changes in lesion size, color, and softening to palpation were recorded at each visit. Body weight was measured and the dose was adjusted accordingly in the oral propranolol group.

Treatment was discontinued if complete resolution occurred, if the lesion ceased to grow for a period of 2 months during treatment, or if any undesirable drawbacks from propranolol developed. Once the treatment was stopped, a final grading for the response was given. Response to treatment was assessed clinically from changes in the size of the tumor (regression or cessation of growth), thickness of the lesion (shrinkage or flattening of the lesion), and lightening of the surface color. Two independent observers evaluated and documented the effectiveness of the treatment from photographs of the patients before and after the therapy. The response was classified as follows:

Excellent

Complete resolution of IH: Treatment was considered complete when (a) normal skin color and consistency was observed and (b) the lesion had ceased to grow for 1 month after stopping treatment. Patients with residual lesions (telangiectasias and redundant tissue) were also considered to have complete resolution.

Good

Partial resolution of IH: There was (a) reduction in size, (b) change in color (slight hyperpigmentation/hypopigmentation) or consistency without achieving complete resolution, and (c) no regrowth for 1 month after stopping treatment.

Fair (no response)

No resolution of IH: There was (a) no change at all or there was thick lesional skin after treatment when compared with baseline photographs or (b) continued growth while in treatment, or scar formation.

Statistical methods

Data were statistically analyzed on intention-to-treat basis. Numerical variables are expressed as means and SDs. Categorical variables are expressed as frequencies and percentages. The independent *t*-test was used to compare quantitative data. The χ^2-test was used to examine the relationship between categorical variables. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 23; SPSS IMB, Armonk, New York, USA).

Results

The demographic and clinical characteristics of the patients and hemangioma lesions are shown in Tables 1 and 2.

In the oral group, the onset of response was change in color from red to light purple and then to blue, with softening of the lesion on examination. This response was achieved within 1–4 weeks (mean = 0.575, SD = 0.238) after starting the therapy. In the topical group, the onset of initial response was achieved within 4–12 weeks (mean = 1.83, SD = 0.702). There was significant statistical difference between the two groups ($P = 0.0001$) (Table 3). Superficial hemangiomas had a greater response than mixed hemangiomas in both groups, although there was no statistical difference.

After the initial response, the improvement was described as gradual regression of the size with grayish-white color in the central part and flattening of the lesions. The oral group received treatment for a mean 5.50 ± 1.68 months, whereas the topical group received treatment for a mean 6.88 ± 1.13 months to achieve the final response (Table 2). There was significant statistical difference between the two groups as regards the response to the drug ($P = 0.041$). In the oral group, 50% ($n = 12$) showed an excellent response (Fig. 1), 33.33% ($n = 8$) showed good response (Fig. 2), and 16.67% ($n = 4$) showed a fair response, whereas in the topical group 16.67% ($n = 4$) showed an excellent response (Fig. 3), 45.83% ($n = 11$) showed good response (Fig. 4), and 37.5% ($n = 9$) showed a fair

Table 1 Patients demographics

Demographics	Oral propranolol	Topical propranolol	*t*-test	*P*-value
Age				
Mean ± SD	5.45 ± 2.57	5.29 ± 2.71	0.191	0.849
Age less than 6 months				
Mean ± SD	3.42 ± 1.19	3.15 ± 1.21		
n (%)	13 (54.17)	11 (45.83)	0.572	0.573
Age larger than 6 months				
Mean ± SD	7.81 ± 1.40	7.82 ± 1.47		
n (%)	13 (54.17)	11 (45.83)	0.001	1.00
Sex [*n* (%)]				
Male	9 (37.5)	10 (41.67)	Pearson $\chi^2 = 0.087$	0.768
Female	15 (62.5)	14 (58.33)		

Table 2 Relationship between variables and degree of improvement after treatment in each group

Variable	Oral propranolol [*n* (%)]	Topical propranolol [*n* (%)]	Pearson χ^2	*P*-value
Site			0.202	0.904
Head neck	14 (58.33)	14 (58.33)		
Trunk	5 (20.83	6 (25)		
Extremities	5 (20.83)	4 (16.67)		
Size (cm)			1.026	0.599
0.5–2	12 (50)	15 (62.5)		
2–10	8 (33.33)	5 (20.83)		
>10	4 (16.67)	4 (16.67)		
Distribution			0.223	0.637
Single	22 (91.67)	21 (87.5)		
Multiple	2 (8.33)	3 (12.5)		
Type			1.500	0.221
Superficial	6 (25)	10 (41.67)		
Mixed	18 (75)	14 (58.33)		
Duration of treatment				
Mean ± SD (months)	5.50 ± 1.68	6.88 ± 1.33	*t*-test = 2.024	0.058
Range	3–7	6–9		

Table 3 Onset of response in each group

Onset of response	Mean ± SD	SEM	*t*-test	*P*-value
Oral propranolol	0.579 ± 0.230	0.047	8.317	0.0001**
Topical propranolol	1.83 ± 0.702	0.143		

response. Table 4 summarizes the proportions of excellent, good, and nonresponse among the patients.

Adverse events

Four infants in the oral group developed mild side effects to treatment in the form of loss of appetite and diarrhea. One case reported having had a fainting episode, although there were no variations in blood pressure or blood glucose level with continuation of the treatment. No patients had symptoms/signs suggestive of hypoglycemia requiring prompt study, laboratory workup, or withdrawal of the drugs.

Rebound growth

Regrowth of the IH when the medication was stopped against medical advice was noted in six patients (12.5%): four patients in the oral group and two patients in the topical group. This rebound growth occurred in the form of a sudden increase in size and worsening of color. In all of them the drugs were reintroduced and the previous response rate was achieved.

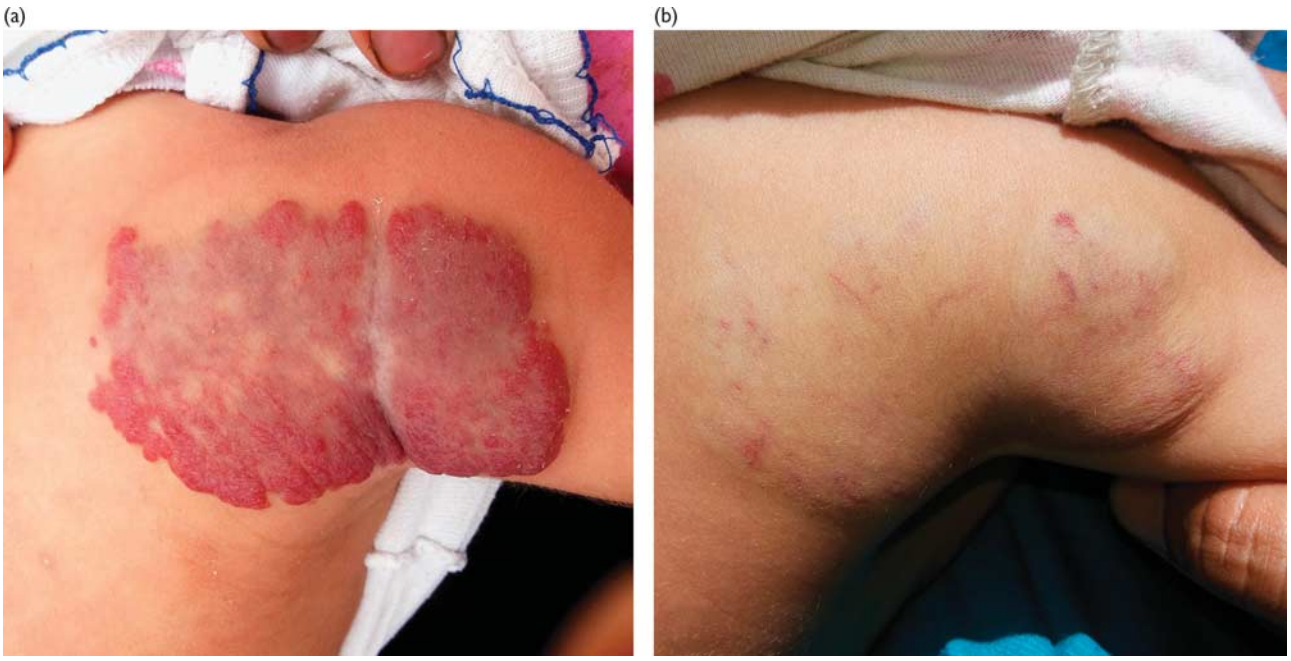
Discussion

Early treatment of IH, especially those showing rapid functional impairment, cosmetic deformities, or unpredictable growth, has been gaining more interest in the last few years, and because several modalities of treatment exist, including topical, oral, intralesional and laser therapies, it may not always be advisable to wait for spontaneous regression. The choice of the safest and most effective treatment remains difficult because of shortage of comparative studies. This study was conducted to compare the effectiveness and safety of oral propranolol versus topical propranolol 1% ointment in the management of cutaneous IH.

The characteristics of our patients were similar to those generally described for infants with hemangiomas [14] and are consistent with the patient profiles in other case series [15]. There was no statistical difference as regards the demographics of the patient in both groups.

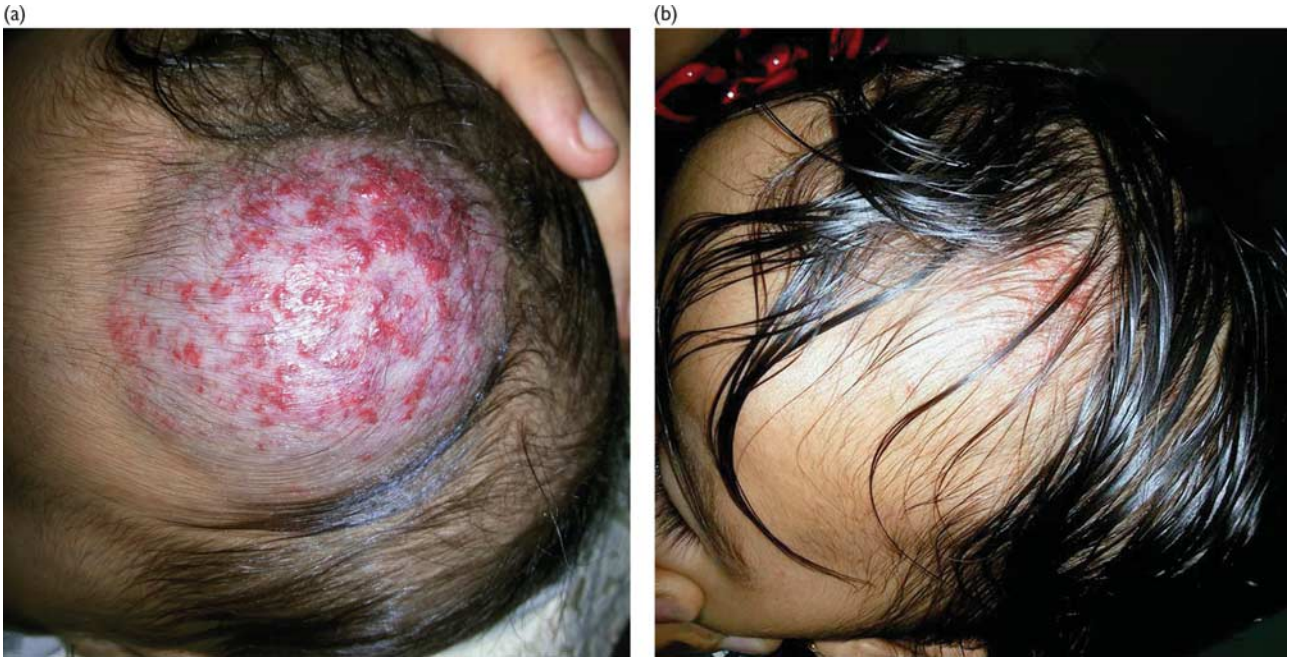
In the oral group, we started therapy with lower dosages of 1 mg/kg and gradually increased the amount to 3 mg/kg based on periodic evaluations [16]. We recommended three doses per day. Some authors, however, have

Fig. 1



(a) A 4-month-old girl with hemangioma on the shoulder. (b) The same patient (6 months) after receiving oral propranolol (1–3 mg/kg/day in three divided doses) showing (excellent) final response.

Fig. 2

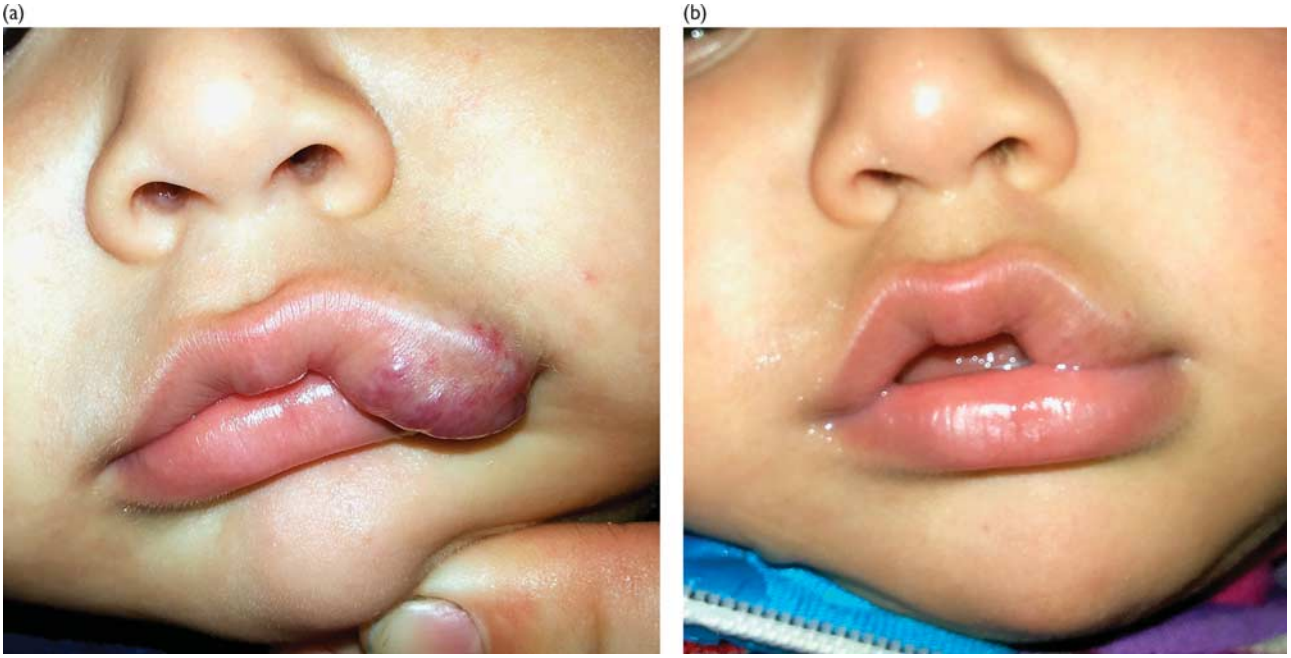


(a) A 4-month-old girl with hemangioma in the upper lip. (b) The same patient (3 months) after receiving oral propranolol (1–3 mg/kg/day in three divided doses) showing (good) final response.

prescribed regimens of 2 mg/kg/day; the dosage has even been doubled to 4 mg/kg/day on observation of no response [16,17]. In the topical group, the ointment was applied three times daily. This regimen was also recommended by Xu *et al.* [18] and Wang *et al.* [19] in their studies.

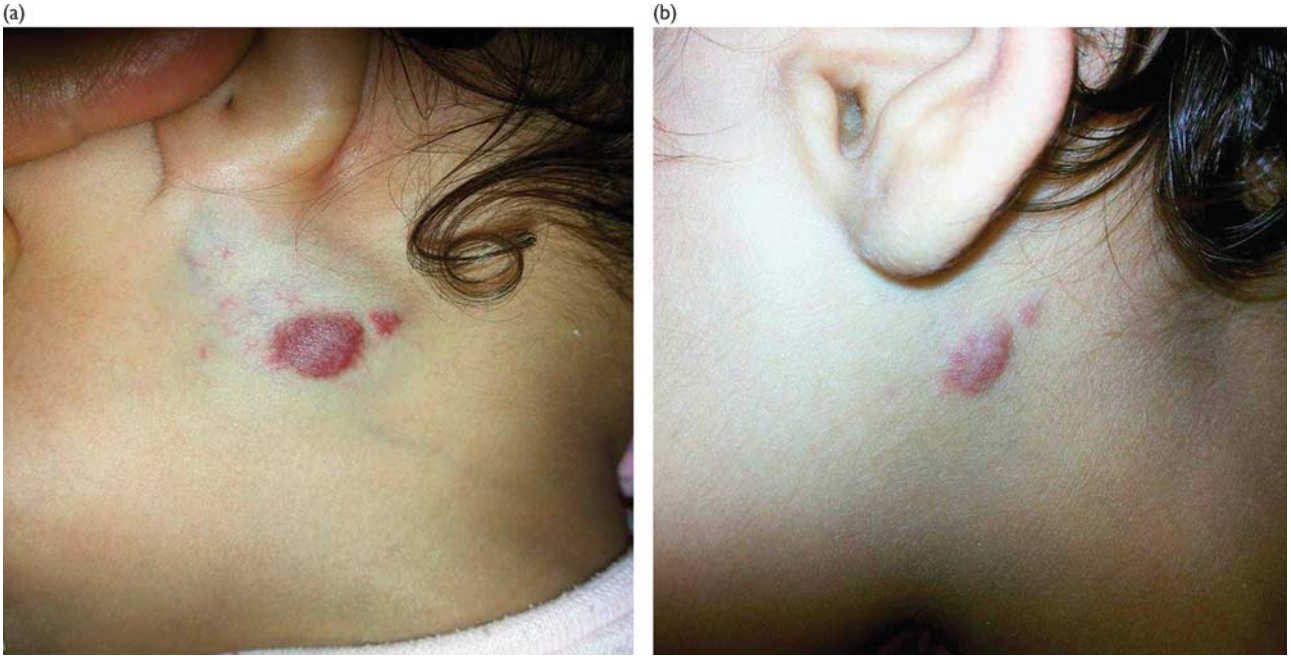
We would like to emphasize how quick the improvement was in a high percentage of cases in the oral group, in which parents observed significant color fading in the first week of treatment. In the topical group, color fading was seen in the first 1–2 months of treatment. Thus, the onset of response appeared more rapid with oral

Fig. 3



(a) A 3-month-old boy with hemangioma in the scalp. (b) The same patient (9 months) after receiving topical propranolol (1% ointment three times daily) showing (excellent) final response.

Fig. 4



(a) A 6-month-old girl with hemangioma below the left ear. (b) The same patient (6 months) after receiving topical propranolol (1% ointment three times daily) showing (good) final response.

propranolol compared with topical propranolol. This was confirmed statistically ($P = 0.0001$).

The optimal duration of propranolol treatment in IH remains unconfirmed [20]. Some prefer to maintain propranolol treatment after the first year of life when the proliferation phase is usually completed, whereas others prefer fixed treatment durations [21]. Some authors based treatment duration on IH resolution or progression. [17]. One of the randomized controlled trials described treating patients for up to 24 weeks, with further treatment at patient discretion [22]. In our study, the total duration of the treatment ranged between 3 and 7 months in the oral group and between 6 and 9 months in the topical group ($P = 0.058$).

Table 4 Final response in each group

Response type	Oral propranolol [*n* (%)]	Topical propranolol [*n* (%)]	Pearson χ^2	*P*-value
Excellent	12 (50)	4 (16.67)	6.397	0.041*
Good	8 (33.33)	11 (45.83)		
Fair	4 (16.67)	9 (37.50)		

The overall final response was better in the oral group and this was proved statistically ($P = 0.041$). These observations are consistent with several reports regarding its efficacy [7,20,23–27]. Because of this dramatic response, several authors considered oral propranolol as the drug of choice in the management of IH [28].

In our study, the response of the patients to the topical application of propranolol ointment 1% was 62.5% and these results were nearly similar to those of Zaher *et al.* [29]and much lower than that observed by others (93%, $n = 15$, in Bonifazi *et al.* [30]; 90%, $n = 25$, in Xu *et al.* [18]; and 85% in Kunzi-Rapp's study [24]). The different rates of response could be attributed to the duration of treatment, as it has been reported that the longer the duration of treatment, the greater the improvement in IH appearance [31]. Furthermore, the protocol of application, the different drug formulations, as well as compliance of patients are other factors that could be a reason for this variation.

This study confirmed the superiority of the oral route as regards efficacy, which may be attributed to the drug dosage and the serum concentration of the drug in this route [29]. However, McMahon *et al.* [32] studied the bioavailability of systemic propranolol and topical timolol gel, and assumed that each drop (0.05 ml) of topical timolol was equivalent to 2–8 mg of oral propranolol. We assume that these levels of systemic absorption of timolol may be much lower when applied to intact skin. Future research in topical preparations using advanced technologies could develop ways by which the drug can reach the tissues at optimal concentrations and be administered for longer durations.

Propranolol has a very good safety profile, and has been widely used in the pediatric population for a host of medical diseases in doses reaching up to 7 mg/kg/day [33]. The known adverse effects of propranolol include hypoglycemia, bronchospasm, mood disturbances, hypotension, and bradycardia [34]. In this study, there was no significant adverse event in any group during the follow-up period. We have proposed an easy protocol to follow in the hospital and at home and we treated our patients on an outpatient basis with a short follow-up. Before starting the regimen, we educated the parents on the possible drawbacks so that they could seek medical advice if necessary.

Conclusion

Oral propranolol is an effective, safe, and fast-acting drug for treating IH and can be monitored on an outpatient basis. However, it does not produce complete resolution in some cases. Topical propranolol 1% seems to be an alternative therapeutic option for superficial IH. However, the optimal dosage and duration of treatment are still to be defined.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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