β-Blocker versus triamacinolone acetate in the treatment of infantile periocular hemangioma

Mona Abdel Kader, Ayman Mohamed Fawzy

Masnoura Ophthalmic Center, Mansoura University, Masnoura, Egypt

Correspondence to Mona Abdelkader, Assistant Prof., Masnoura Ophthalmic Center, Mansoura University, Masnoura, 35516, Egypt; Fax: 2202064;
e-mail: monaabdelkader78@yahoo.com

Received 7 March 2017
Accepted 7 March 2017

The Egyptian Journal of Cataract and Refractive Surgery 2016, 22:42–49

Purpose
The aim of this study was to evaluate the effectiveness of systemic and intralesional β-blockers in the treatment of periocular infantile capillary hemangiomas and to compare the effect of intralesional triamcinolone acetonoid injection and β-blockers.
Patients and methods
Totally, 60 patients with infantile periocular hemangioma were included in the study and were divided into three groups. Group 1 included 20 patients treated with systemic β-blocker. Group 2 included another 20 patients treated with intralesional triamcinolone acetate. Group 3 included 20 patients treated with intralesional β-blocker.
Results
In group 1, 55% of patients showed excellent response, 30% of patients showed good response, 10% of patients showed fair response, and 5% of patients showed poor response. In group 2, 50% of patients showed excellent response, 35% of patients showed good response, 15% of patients showed fair response, and no patients showed poor response. In group 3, 40% of patients showed excellent response, 25% of patients showed good response, 25% of patients showed fair response, and 10% of patients showed poor response.
Conclusion
Systemic propranolol is a good alternative for treating periorbital infantile hemangiomas. Systemic propranolol is superior to intralesional steroid because systemic propranolol has fewer side effects. Propranolol provides a more safe and effective modality of treatment of periocular infantile capillary hemangioma with a lower incidence of systemic side effects.

Keywords:
β-blocker, infantile periocular hemangioma, triamcinolone acetate

Egypt J Cataract Refract 22:42–49

1687-6997

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors in the world, affecting 5–10% of infants and up to 30% of premature babies. IH are more dominant in White, female, and premature infants [1].

Most of the IHs occur on the face, head, and neck [2]. Although benign, the involvement of the eyelids may endanger vision or cause cosmetic defect [3].

Prematurity and weight less than 1500 g are predisposing factors. IHs have a triphasic pattern: rapid proliferative phase followed by a plateau period and then a slow involutive phase [4].

In majority of IHs, treatment is not important, but strict follow-up is recommended. However, in some IHs, treatment is needed [3].

Bleeding, ulceration, and subsequent infection can occur in some cases. Early treatment minimizes complications [5].

Propranolol is a nonselective B1 and B2 antagonist developed in 1950s and it was found to be effective in IHs treatment [6].

The mechanism of action of propranolol is unknown. It may increase apoptosis and regulate vascular endothelium growth factor [7,8].

The aim of the study was to assess the value of β-blocker and triamcinolone acetate in the treatment of infantile hemangioma and to compare between the effects of both lines.

Patients and methods

This study was carried out in Mansoura Ophthalmic Center from July 2014 to July 2016 after obtaining approval of Mansoura Ophthalmic Ethics Committee.

Informed written consent was obtained from the parents of the participants in the study after explaining the management and answering all their queries.

Inclusion criteria were as follows: hemangiomas causing obstruction of the visual axis or inducing astigmatism, strabismus, amblyopia, or anisometropia, cosmetically annoying hemangiomas, painful IHs, IHs ulcerated or at risk of being ulcerated, rapidly progressive hemangiomas, or recurrently bleeding hemangiomas.

The exclusion criteria for propranolol groups (groups 1 and 3) were as follows: severe bradycardia, hypersensitivity to propranolol, and cardiologic pass rejection. There were no exclusion criteria for group 2.

In total, 60 randomly selected patients with IHs who need treatment were included and were randomly divided into three groups.

Group 1 (the systemic propranolol group)

Propranolol was administered orally at a dose of 2 mg/kg daily divided in two doses. The first dose was given at full dose and not gradually increased. Cardiac history was taken from the patients to exclude any cardiac abnormality. Before beginning of treatment, all patients were sent to the pediatric cardiologist for examination. If this evaluation was normal, patients were included in the group. During treatment, the dose was adjusted according to the increase in infant body weight. If any propranolol complication appeared during treatment, the dose was readjusted or even completely stopped. All parents were informed about the possibility of bronchial obstructive diseases and hypoglycemia with prolonged fasting due to the inherent risks of propranolol. If lesions rebounded after stoppage of propranolol, treatment was started again with the same scheme until the desired response was obtained and then weaned. Propranolol was weaned gradually at the end of the treatment to 1 mg/kg daily for 1 month and then completely stopped.

Group 2 (the intralesional steroid group)

Quantity of 40 mg/ml triamcinolone was injected intralesionally and repeated every month according to the patient's response. Volume of 0.2 ml was injected per cm of lesion diameter with a maximum of 1 ml. Intralesional injection was performed under general inhalation anesthesia with monitoring of respiration and cardiac conditions during and after injection. During injection, a dilated fundus examination was carried out. Patients were discharged few hours after injection.

Group 3 (the intralesional propranolol group)

Quantity of 1 mg/ml propranolol was injected intralesionally and repeated every month according to the patient's response. Volume of 0.2 ml was injected per cm of lesion diameter with a maximum volume of 1 ml. Injections were performed under general inhalation anesthesia with monitoring of heart and chest conditions during and after injection. Patients were observed for 12 h, during which blood pressure and heart rate were measured every hour.

Evaluation of effectiveness

Patients were observed every week in the first month, every 2 weeks for second month, and every 4 weeks after that. The size of the hemangioma was followed up with clinical examination and measured with photography and was graded according to the final outcome with respect to size, color, and parent satisfaction as follows:

(1) Excellent response: complete disappearance of the IHs. Residual lesions (telangiectasia and redundant tissue) are allowed and also considered complete resolution.
(2) Good response: 50% or more reduction in the size of hemangiomas but not reaching excellent response.
(3) Fair response: less than 50% decrease in the size of hemangiomas.
(4) Poor response: no response or worsening of hemangiomas.

Results

Totally, 60 patients with IH who needed treatment were included.

In total, 44 (73.3%) patients were female and 16 (26.6%) were male.

The mean age of the patients at the beginning of treatment was 7.12 months ranging from 1 to 24 months.

The patients were randomly categorized into three groups.

Group 1 (the systemic propranolol group)

This group included 20 patients, of whom 15 patients were female and five patients were male (Table 1).

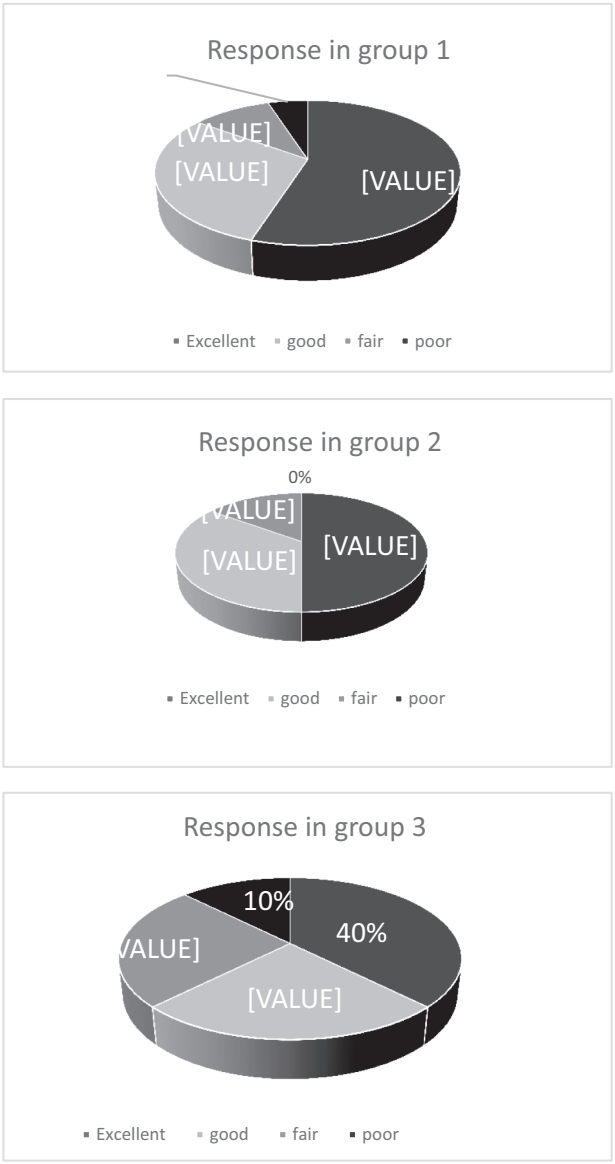
The mean duration of treatment in this group was 8 months (range: 3–14 months) (Table 2).

The final response of the patients in this group was as follows: 11 patients showed excellent response, six patients showed good response, two patients showed

Table 1 Demographic features among groups

Groups	Number	Age	Sex	
			Female	Male
Group 1	20 patients (20 eyes)	1–12 months (7.8±6 month)	15	5
Group 2	20 patients (20 eyes)	1–23 months (8.7±5 months)	14	6
Group 3	20 patients (20 eyes)	5–24 months (7.9±8 months)	15	5

Figure 1



Responses to treatment among groups

fair response, and one patient showed poor response (Tables 3 and 4, Figs 1 and 2).

Only one patient developed symptomatic bradycardia after 1 month of treatment and the treatment was discontinued. None of the other cases needed readjustment of the dose of the medication. After discontinuation of treatment, the patients were followed up for at least 6 months for evaluation of the risk for recurrence (Fig. 3).

Table 2 Duration of treatment among groups

Groups	Total	Less than mean duration (8 months) [*n* (%)]	Greater than mean duration (8 months) [*n* (%)]
Group 1	20	12 (60)	8 (40)
Group 2	20	12 (60)	8 (40)
Group 3	20	10 (50)	10 (50)

Table 3 Response to treatment among groups

Groups	Total	Excellent [*n* (%)]	Good [*n* (%)]	Fair [*n* (%)]	Poor [*n* (%)]
Group 1	20	11 (55)	6 (30)	2 (10)	1 (5)
Group 2	20	10 (50)	7 (35)	3 (15)	0 (0.0)
Group 3	20	8 (40)	5 (25)	5 (25)	2 (10)

Table 4 Complication of treatment among groups

Groups	Total	Complicated [*n* (%)]	Noncomplicated [*n* (%)]
Group 1	20	1 (5)	19 (95)
Group 2	20	3 (15)	17 (85)
Group 3	20	10 (50)	10 (50)

Table 5 Recurrence of the lesion after discontinuation of treatment among groups

Groups	Total	Recurrence [*n* (%)]	Nonrecurrence [*n* (%)]
Group 1	20	2 (10)	18 (90)
Group 2	20	1 (5)	19 (95)

Only two cases showed regrowth of the lesion after 2 months of discontinuation of treatment. The treatment was restarted again for 2 months and then weaned again as stated in our protocol, and the primary response was regained (Table 5).

Group 2 (the intralesional steroid group)

This group included 20 patients, of whom 14 patients were female and six patients were male.

The mean duration of treatment was 5.25 months (range: 3–10 months).

The final response of the patients in this group was as follows: 10 patients showed excellent response, seven patients showed good response, three patients showed fair response, and no patients showed poor response.

Figure 2

Facial hemangioma of the right side of the upper eye lid and forehead showing excellent response

Four of the patients showed local side effects after the injection. Two cases showed skin atrophy and one case showed skin depigmentation.

The possible systemic side effects of intralesional steroid were not investigated unless they were symptomatic.

After discontinuation of treatment, the patients were followed up for at least 6 months for evaluation of the risk for recurrence. In this study, only one case showed regrowth of the lesion after 1 month of discontinuation of treatment.

The treatment was restarted again using the same protocol for 3 months.

Group 3 (the intralesional propranolol group)

This group included 20 patients, of whom 15 patients were female and five patients were male (Table 1 and Figs 4 and 5).

The mean duration of treatment was 7.75 months (range: 4–13 months).

The final response of the patients in this group was as follows: eight patients showed excellent response, five patients showed good response, five patients showed fair response, and two patients showed poor response (Fig. 4).

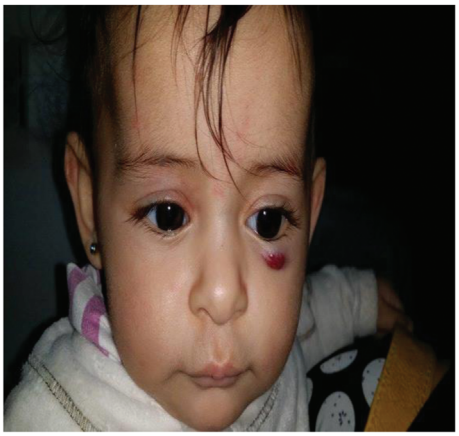
No patients developed local side effects during or after the injection. There were no significant changes in heart rate or blood pressure.

After discontinuation of treatment, the patients were followed up for at least 6 months for evaluation of the risk for recurrence.

According to our study, only two cases showed regrowth of the lesion after 1 month of discontinuation of treatment.

The treatment was restarted again with the same protocol for 3 months and the primary response was regained.

Figure 3



Before start of triamcinolone injection

After 5 injections

After 2 injection

Lower lid hemangioma with excellent response after intralesional triamcinolone

Discussion

IH occurs in about 10% of infants and is more common in female infants, premature infants, and White infants [1].

IH is characterized by proliferative phase first followed by the involuting phase, during which cellular elements are replaced by fibrofatty deposition [4].

However, functional and cosmetic sequelae may occur and need management [3].

This study was conducted to study the efficacy of propranolol in the treatment of periocular infantile capillary hemangioma and to compare between effects of propranolol and triamcinolone in the treatment.

The sex distribution in this study in the three groups was as follows: 73.3% female and 26.6% male; this is in agreement with other studies that reported that IH is more common in female infants [8,9].

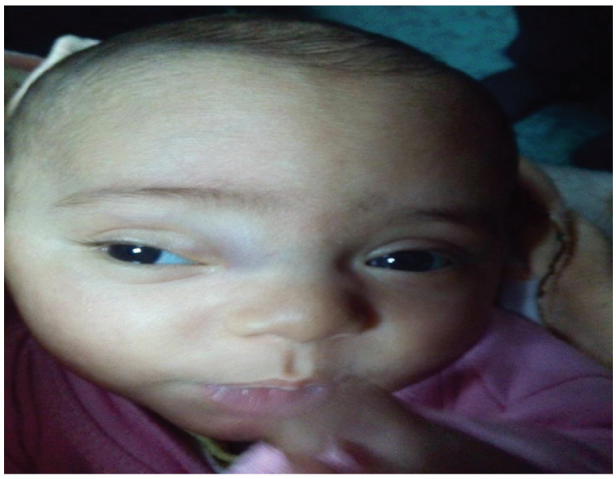
In this study, in group 1, propranolol was started in an outpatient regimen at a dose of 2 mg/kg twice daily orally. The full dose was given without a gradual increase in dose, which is different from the treatment regimen described by Holmes *et al.* (2010), in which propranolol was started at a dose of 0.5 mg/kg orally. Therefore, a second dose of 1 mg/kg was given after 4 h after monitoring of blood pressure and heart rate and measurement blood glucose. If observations remained stable, the patient was followed up for further two doses and discharged at the target dose of 3 mg/kg/day given in three divided doses [10].

The protocol of this study is also different from that of Qin *et al.* [11], who used 1–1.5 mg/kg of propranolol in 58 IHs. The patients were hospitalized for 7–10 days, continued medication at home, and revisited every 2 weeks [11].

The protocol of treatment in this study is consistent with that of Buckmiller *et al.* [5] and Zegpi-Trueba *et al.* [12],

Figure 4

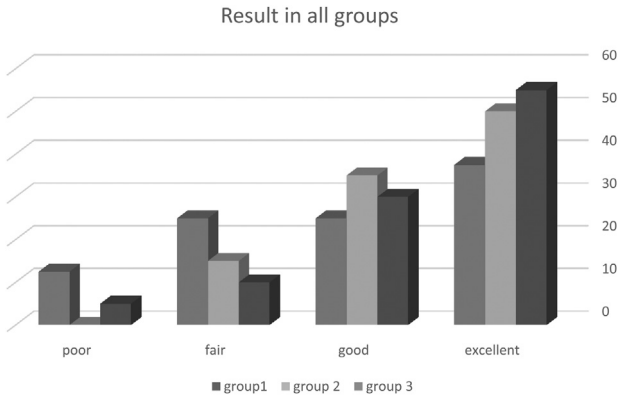
Before start of intra-lesional beta-blocker injection



After 4 months

Medial hemangioma with good response after intralesional β-blocker

Figure 5



Comparison of the results in all groups

in which there were no evaluations of vital signs unless they were symptomatic.

The mean age of patients in group one was 7.8 months, which is contradictory to that reported by Qin *et al.* [11] and Sans *et al.* [13], in which the mean age was 4 months (range: 1–12 months) and 4.2 months, respectively.

The mean duration of treatment in this group was 8 months (range: 3–14 months). Similarly, the mean duration of treatment in the study by Sans *et al.* [13] was 6.1 months.

In this study, the final response of the patients in group one was as follows: 11 (55%) patients showed excellent response, six (30%) patients showed good response, two (10%) patients showed fair response, and one (5%) patient showed poor response. Moreover, Holmes *et al.* [10] treated 31 consecutive patients with hemangioma and revealed rapid halt in hemangioma proliferation in 100% of cases and a significant reduction in 87% of cases. The difference in the final outcome is attributed to the differences in protocol of evaluation of effectiveness [10].

Similarly, Sans *et al.* [13] reported that the efficacy of propranolol in 32 patients was 100% according to the judgment of the doctor in most cases.

This differs from this study because they considered any response as a response, unlike the classification in our study.

The final outcome is consistent with that of Qin *et al.* [11], who used propranolol in 58 infants with IH, and the overall responses were as follows: one (1.7%) patient had scale I, 12 (20.7%) patients had scale II, 35 (60.4%) patients had scale III, and 10 (17.2%) patients had scale IV (excellent). However, in this study, excellent response was higher (55%).

The final outcome is also similar to that of Buckmiller *et al.* [5], who studied 32 patients managed with propranolol and reported that 50% of patients were excellent responders, 47% were partial responders, and 3% were nonresponders.

Recurrence of IH after stopping propranolol was seen in children more than 12–14 months of age, this corresponding to well-completed natural proliferation phase. This unexplained phenomenon raises the question whether treatment with propranolol delays the natural growth phase of IH. However, in this study, recurrences of IH were mild and the patients responded well to retreatment.

Buckmiller *et al.* [5] recommend the use of propranolol until the age of 12 months and not to be weaned before this age even in the presence of a complete response before this age.

Similarly, there were two cases that showed recurrence. They were below 1 year of age at the time of weaning from propranolol.

The adverse effects of propranolol according to our protocol were not observed unless they are symptomatic, unlike other studies such as those of Buckmiller *et al.* [5], Laforgia *et al.* [14], and Sans *et al.* [13], which classify and monitor the effect of propranolol on body systems, even the mild changes. No hemodynamic changes happened during treatment with propranolol. Hypoglycemia may occur due to β-blocking therapy. There were no symptomatic hypoglycemia in our study as blood glucose levels were not routinely measured.

Disadvantages of propranolol treatment appear minor as compared with other modalities for the treatment of IH, such as systemic corticosteroids and interferon-α [5].

Mazzola [15] first reported the use of intralesional corticosteroid injection for the treatment of hemangiomas. Intralesional injections of steroids were introduced in an attempt to overcome the steroidal systemic effects; steroids are still the first-line of treatment for hemangioma.

According to our study in group 2, the age of our cases in this group varies from 1 to 23 months, unlike the study by Chantharatanapiboon [16], in which the age ranged from 1 month to 15 years.

According to the number of injections, the mean number of injections was 5.25 (range: 3–10 injections) in our study, and this is comparable to that reported by Chantharatanapiboon [16], in which the mean number of injections was 5.7 (range: 1–12 injections).

According to the protocol of treatment in group 2, our study determined the volume of material injected according to the size of the lesion (0.2 ml injected per cm of lesion diameter with a maximum of 1 ml), unlike the study by Chantharatanapiboon [16], in which the volume was determined according to the age of the patient (1–2 mg/kg of body weight with a maximum of 60 mg).

Waner and Suen [17] recommended the use of a combination of triamcinolone and β-methasone. The aim of combining the short-acting β-methasone with the long-acting triamcinolone was to ensure an immediate effect, which is in contradictory to our study in which we used only intralesional triamcinolone [17].

The final response of the patients in group 2 was as follows: 10 (50%) patients showed excellent response, seven (35%) patients showed good response, three (15%) patients showed fair response, and no patients showed poor response. This is consistent with the findings of Chantharatanapiboon [16], who reported an overall response rate of 90% (excellent at 70% and good at 20%).

In this study, four patients showed local side effects after the treatment. Two cases showed skin atrophy and one case showed skin depigmentation. This is contradictory to the study by Awadein and Fakhry [9], in which no cases in the steroid group showed local side effects. However, our finding is consistent with that of Callahan and Yoon [18].

Retinal artery occlusion of both eyes may occur after periocular intralesional steroid injections as the injected material may cause retinal artery occlusion [14]. In this study, there was no case with retinal occlusion.

Systemic effects of adrenal suppression and growth retardation have been reported by Chantharatanapiboon [16], but none of these complications was observed in our study.

According to our study, in group three the mean age in our study was 5.75 months in the propranolol group, which is consistent with the finding of Awadein and Fakhry [9].

The final response of the patients in this group was as follows: eight (40%) patients showed excellent response, five (25%) patients showed good response, five (25%) patients showed fair response, and two (10%) patients showed poor response. This is consistent with the findings of Awadein and Fakhry [9], in which five (42%) patients showed excellent response, three (25%) patients showed good response, and two (17%) patients showed fair response, and two (17%) patients were resistant to treatment.

Intralesional propranolol was not associated with significant side effects during or after injection.

Systemic effects of propranolol may possibly be reduced with intralesional injection but this is not proved because hemangiomas are very vascular and systemic absorption may occur. The injection was performed under general anesthesia with careful observation of the heart for immediate management if significant bradycardia or hypotension occurs. Atropine would be given in the event of such a complication. However, we did not encounter such complications during injection in our study.

Gunturi *et al*. [19] documented that β-blocker carries promise as a potential replacement for steroid as first-line therapy.

Xu *et al*. [20] found that β-blockers are superior to corticosteroids in volume shrinkage and in subsequent appearance of hemangioma.

Conclusion

Systemic propranolol and intralesional steroid provide an effective modality for the treatment of periocular infantile capillary hemangioma. Systemic propranolol has a lower incidence of local side effects and the final outcome is more cosmetic without the changes, which are common with intralesional steroid, such as skin necrosis, depigmentation, fat atrophy, and calcification.

Although β-blocker is safe with fewer systemic side effects, overall adverse events during propranolol treatment appear minor as compared with the serious side effects of previous modalities for the treatment of IH, such as systemic corticosteroids and interferon-α.

Intralesional propranolol according to our study provides a good alternative modality of treatment of hemangiomas, which has slightly lower effectiveness compared with systemic propranolol and intralesional steroid. However, further investigations on a large number of patients for more accurate evaluation and to investigate the possible local or systemic side effects.

Declaration of consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Storch CH, Hoeger PH. Propranolol for infantile haemangiomas – insights into the molecular mechanisms of action. Br J Dermatol 2010; 163: 269–274.

2 Haggstrom AN, Drolet BA, Baselga E. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics 2006; 118:882–887.

3 Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. Semin Cutan Med Surg 2010; 29:106–114.

4 Chang LC, Haggstrom AN, Drolet BA. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008; 122: 360–367.

5 Buckmiller LM, Munson P, Dyamenahalli U. Propranolol for infantile hemangiomas: early experience at a Tertiary Vascular Anomalies Center. Laryngoscope 2010; 120:676–681.

6 Shayan YR, Prendiville JS, Goldman RD. Use of propranolol in treating hemangiomas. Can Fam Physician 2011; 57:302–303.

7 7.Frieden IJ, Drolet BA. Propranolol for infantile hemangioma: promise, peril, pathogenesis. Pediatr Dermatol 2009; 26:642–644.

8 Hsu TC, Wang JD, Chen CH. Treatment with propranolol for infantile hemangioma in 13 Taiwanese newborns and young infants. Pediatr Neonatol 2012; 53:125–132.

9 Awadein A, Fakhry MA. Evaluation of intralesional propranolol for periocular capillary hemangioma. Clin Ophthalmol 2011; 5: 1135–1140.

10 Holmes WJM, Mishra A, Gorst C. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. J Plast Reconstr Aesthet Surg 2010; 64:1–7.

11 Qin ZP, Liu XJ, Li KL. Treatment of infantile hemangiomas with low dose propranolol: evaluation of short term efficacy and safety [Chinese]. Zhonghua Yi Xue Za Zhi 2009; 89:3130–3134.

12 Zegpi-Trueba MS, Abarzúa-Araya Á, Silva-Valenzuela S. Oral propranolol for treating infantile hemangiomas: a case series of 57 patients. Actas Dermosifiliogr 2012: 103:708–717.

13 Sans V, Dumas de la Roque E, Berge J. Propranolol for severe infantile hemangiomas: follow up-report. Pediatrics 2009; 124: 423–431.

14 Laforgia N, Milano A, De Leo E, Bonifazi E. Hemangioma and propranolol. Some remarks at the end of treatment. Differences from corticosteroids. Eur J Pediatr Dermatol 2009; 19:175–191.

15 Mazzola RF. Treatment of haemangiomas in children by intralesional injection of steroids. Chir Plast (Berl) 1978; 4:161–168.

16 Chantharatanapiboon W. Intralesional corticosteroid therapy in hemangiomas: clinical outcome in 160 cases. J Med Assoc Thai 2008; 91:90–96.

17 Waner M, Suen JY. Hemangiomas and vascular malformations of the head and neck. London: Wiley-Liss; 1999; 8:pp. 233–238.

18 Callahan AB, Yoon MK. Infantile hemangiomas: a review. Saudi J Ophthalmol 2012; 26:283–291.

19 19.Gunturi N, Ramgopal S, Balagopal S. Propranolol therapy for infantile hemangioma. Indian Pediatr 2013; 50:307–313.

20 Xu SQ, Jia RB, Zhang W, Zhu H. -blockers versus corticosteroids in treatment of infantile hemangioma: an evidence-based systematic review. World J Pediatr 2013; 9:221–229.