Propranolol for infantile hemangiomas: a preliminary report on efficacy and safety in very low birth weight infants

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SUMMARY: Erbay A, Sarıalioğlu F, Malbora B, Yıldırım SV, Varan B, Tarcan A, Gülcan H, Demir Ş, Derbent M, Uslu N, Abbasoğlu A. Propranolol for infantile hemangiomas: a preliminary report on efficacy and safety in very low birth weight infants. Turk J Pediatr 2010; 52: 450-456.

Despite the relatively recent introduction of propranolol in the treatment of infantile hemangiomas, there can be little doubt of its efficacy. With regard to safety issues, there are no prior data for very low weight infants. In this study, we used propranolol in preterm and very low weight infants. We used clinical criteria to assess the response to the therapy. We noted all side effects expected from ß-adrenergic blocking drugs, and followed the patients' weight gain during propranolol treatment. Objective, clinical evidence of hemangioma regression was seen after two months in all patients. None of the patients required treatment discontinuation due to adverse side effects. During the propranolol treatment, weight gain was normal in all patients. To the best of our knowledge, this is the first report on the use of propranolol in preterm and very low weight infants, and also the first report from Turkey on the use of propranolol in infantile hemangiomas.

Key words: infantile hemangioma, angiogenesis, ß-2 adrenergic receptors, propranolol.

Infantile hemangiomas (IHs) are benign vascular tumors frequently seen in infancy. The life cycle of the vast majority of IHs can be summarized as appearance, rapid development, slow development, rest, and regression[1,2]. Because of this benign and self-limited course, therapeutic abstention is the rule.

Nearly 10% of IHs cause life-threatening complications in the proliferation stage[2,3]. Another problem is cosmetic injuries, especially for those located on the face, though they are not life-threatening. Facial hemangioma is a source of psychological stress for the child and other family members[1,4].

Oral or intralesional corticosteroids were the most common treatment methods for hemangiomas with established treatment indication[5,6]. Interferon, vincristine, laser, radiosurgery, and conventional surgery are other methods used in the treatment of the condition[6-8]. Their use is considerably limited by different levels of efficacy and increasing side effects with decreasing age. Even corticosteroids, accepted as the most benign and commonly used treatment, may negatively affect mental functions in premature and newborn babies[9].

Propranolol has been used in medicine for 40 years; however, its effect on hemangiomas was coincidentally discovered in 2008[10]. In addition to reports of sporadic cases in a relatively short time, the report by Sans et al.[11] on this issue was such an important development that it became a classic in medicine, established as a seminal study[11-14].

In the present study, propranolol was first used in a patient who had infantile hepatic hemangioma (IHH) associated with

a serious abdominal compartment syndrome that was resistant to treatment using high-dose methylprednisolone, prednisolone and interferon-α. Subsequently, propranolol was used in prematurely born infants, whose corrected ages were between –5 weeks and -3 weeks, and who showed rapidly growing and alarming hemangioma indication. Thereafter, a research group was formed, composed of a pediatric oncologist, pediatrician, cardiologist, geneticist, neonatologist, and radiologist, and treatment was started in accordance with a protocol.

The main aim of this preliminary report was to determine the efficacy and safety of propranolol in very low weight infants.

Material and Methods

After reading an excellent and influential article by Sans et al.[11], it was decided to use propranolol for therapeutic purposes in all potentially life-threatening IHs. Firstly, we used propranolol in three cases with emergency therapeutic indications. Subsequently, a research protocol similar to that of Sans et al.[11] was prepared for a pilot trial in severe cases of IHs.

All patients with complicated IHs were included within the treatment, in accordance with the American Academy of Dermatology Guidelines/ Outcomes Committee[15]. Initial clinical evaluation was performed with photographs. Patients were referred to a pediatric cardiologist to rule out cardiovascular disease. Peripheral blood count, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) tests were performed in all patients. During propranolol treatment, growth was observed in patients using the standard charts according to age and gender[16,17]. Informed consent was obtained in all cases.

Propranolol was initiated in hospital for patients less than three months of age. Other patients were followed up for a minimum of 8 hours (h) in the outpatient clinic. Because of the absence of other preparations in Turkey, 40 mg Dideral tablets (Sanofi-Aventis) were used in the therapy. Dideral tablets were dissolved in 20 ml distilled water. The prepared solution was stored in a refrigerator for 24 h. The solution was shaken before each use. The initial dose was 1 mg/kg/day (p.o.) for patients under 3,000 g. If this dose was well tolerated, it was increased to 2 mg/kg/day. For babies under 3,000 g, propranolol was administered in three divided doses; in other patients, the drug would be given in two doses. Heart rate and blood pressure were monitored hourly during the first 8 h of treatment. Continued monitoring was used for babies under 3,000 g. In the absence of side effects, treatment was continued at home and the child was re-evaluated after 10 days of treatment and then every month. Telephone consultation was held every week with the parents of all patients and side effects were questioned. A clinical and photographic examination was performed at every follow-up visit. Side effects were also noted in the monitoring of treatment compliance and tolerance. Body weight was measured for dose adjustments. All parents were informed about the negative interaction of drugs with propranolol, especially salbutamol therapy.

The following criteria were used in the evaluation of early regression of hemangiomas: (a) decreasing sensitivity and becoming much softer to the touch; (b) less expansion on child's cry; and (c) color change in superficial hemangioma from bright red to dark or purplish red to gray (Figs. 1, 2). The following criteria were used in the evaluation of complete regression: (a) skin change to completely normal; and (b) telangiectasias in skin, superficial dilated veins, hypopigmentation and/or redundant skin with fibro-fatty residua (Fig. 1D)[1,2]. Patients were photographed at each follow-up in order to provide objective evaluation. Superficial ultrasonographic findings were used in the evaluation of deep hemangiomas.

Results

Clinical data of 16 children who received propranolol are summarized in Table I. Thirteen children were girls and nine were born preterm. Due to the high percentage of very small premature babies within the present study, corrected ages were used to evaluate the patients. The corrected ages of the patients ranged between -5 and 109 weeks (median: 15.5 weeks). For the first

7 patients, the treatment indications included life-threatening complications, functional risks or local complications. The others treatments were given to accelerate the natural course of IHs. In previous treatment, only one patient had received high-dose methylprednisolone followed by prednisolone interferon and vincristine.

All patients were followed for a minimum of two months. All cutaneous hemangiomas progressively improved, both in color and thickness (Figs. 1, 2). The patient with IHH showed an excellent response to treatment. Because of the rarity of the disease and the resistance to high-dose methylprednisolone and interferon-alpha therapy, this case was previously described briefly in a letter (Case 2)[18].

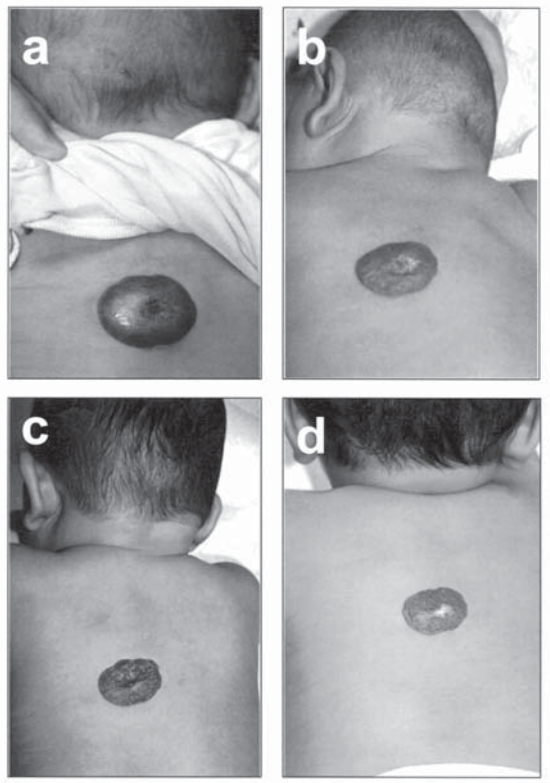

Fig. 1. Patient 6 with a painful ulcer, hemorrhagic hemangioma. (a) At 6 months of age before propranolol treatment. (b) At 3 weeks of the propranolol treatment, the lesion was less tender to touch and softer. Note the change in color. (c) After 2 months, obvious regression changes were observed and propranolol was ended. One month later, the lesion showed mild re-coloration and mild re-growth. Propranolol was restarted. (d) At 11 months of age, note the regressive changes - very soft in palpation and evident grayish hue.

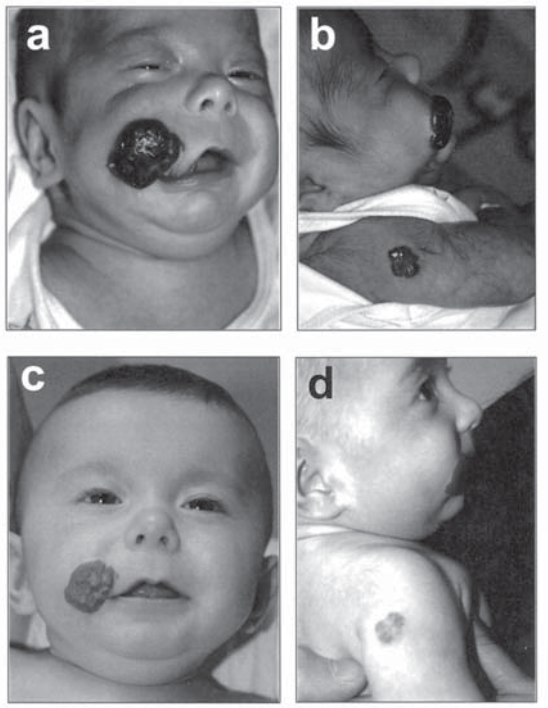

Fig. 2. Patient 3 (27-week preterm female baby) with feeding problem. (a, b) Rapidly growing hemangioma localized in cheek, corner of mouth, right buccal mucosa, and right shoulder. Her corrected age was -3 weeks before propranolol treatment. Size of the mucosal lesion approximately 60% of cheek one (not seen). (c, d) After 5.5 months of propranolol treatment, note change in color, mottled appearance and reduced size of lesion. Complete regression of the shoulder hemangioma and 75-80% regression of the mucosal lesion (not seen).

Propranolol Treatment in Premature Babies and Weight Gain During Therapy

The weight gains of patients during propranolol therapy are given in Figure 3. Nine of the 16 patients were preterm infants. As seen in Table I, they had very low birth weights. Three premature babies were small for their gestational age (SGA). One of them (Case 4) showed catch-up growth at the beginning of propranolol treatment. The other two patients (Cases 8, 14) were still under 3 percentile for body weight at the beginning of the therapy. These patients demonstrated a growth parallel to the 3 percentile line. No child showed a fall in growth below the line in their percentile.

Side Effects

Blood pressure and pulse rate were decreased in two patients, who were monitored for 24 h,

Table I. Clinical Characteristics of 16 Patients*

Patient No.	Corrected age at initiation of propranolol (weeks)/ sex/birth weight (g)	Location of infantile hemangioma	Other characteristics	Indication for treatment	Propranolol dosage mg/kg/day	Weight at initiation of propranolol (gram)	Duration of therapy (months)	Therapeutic response at two Months and outcome
1	7 / female / 1,500	Lip, neck, thorax	30 weeks prematurity, IVF, maternal hypertension, triplet pregnancy	Cosmetic risk	3	4,740	2.5	Early regression. Ongoing therapy.
2	43 / male / 3,250	Diffuse infantile hepatic hemangioma	NF-1, resistant to HDMP and IFN-α therapy	Severe abdominal compartment syndrome	2	8,250	6.5	Complete regression. Therapy stopped.
3	-3 / female / 1,050	Buccal mucosa, lip-cheek, shoulder	27 weeks prematurity	Functional risk, feeding problem, rapidly growing tumor	2,5	2,750	6.5	Early regression (70-80% regression in buccal lesion, full regression in shoulder lesion, 50-60% regression in cheek hemangioma). Ongoing therapy.
4	9 / female / 1,370	Labium majus, thigh	34 weeks prematurity, placental hemangioma, three prior fetal losses	Risk of infection	2	4,710	6.2	Early regression. Ongoing therapy.
5	-5 / female / 800	Buccal mucosa	27 weeks prematurity, triplet pregnancy, IUGR, preeclampsia	Rapidly growing tumor, potential feeding problem	2	1,600	1.5	Nearly 50% regression at 1.5 months. Propranolol stopped due to very low weight of baby. The patient was followed for 4 months after therapy. No regrowth.
6	16 / male / 1,500	Back	30 weeks prematurity, twin pregnancy	Painful ulceration, hemorrhage	2	7,890	6.1	Propranolol stopped at 3 months due to rapid regression. Minor re-coloration and regrowth occurred after 1 month. Propranolol restarted, and the lesion showed regression again.
7	109 / female / 890	Face, neck, thorax	28 weeks prematurity, maternal hypertension, oligohydramnios. IUGR	Cosmetic risk	2	10,500	6.0	Early regression. Treatment was discontinued after 10 days due to salbutamol therapy for bronchitis. Ongoing therapy.
8	15 / female / 880	Thigh	31 weeks prematurity, IUGR, maternal hypertension	Local complication	2	4,500	2.0	Complete regression at 2 months. Therapy stopped. No regrowth.
9	8 / male / 3,400	Forehead	None	Cosmetic risk	2	4,930	5.4	Complete regression in scalp lesion, early regression in forehead hemangioma. Ongoing therapy.
10	109 / female / 3,200	Lip, tongue	None	Functional risk, feeding problem	3	12,500	5.0	Early regression. Ongoing therapy.
11	59 / female / 3,000	Face	None	Cosmetic risk	3	14,000	4.5	Early regression. Ongoing therapy.
12	16 / female / 2,800	Back, foot	None	Functional risk, walking	3	5,250	1.5	Complete regression at 1.5 months. Therapy stopped. No regrowth.
13	35 / female / 3,250	Scalp, forehead, back	Twin pregnancy	Cosmetic risk	3	9,000	4.0	Early regression. Ongoing therapy.
14	-2 / female / 850	Hand	32 weeks prematurity, twin pregnancy, IUGR, polyhydramnios	High risk of local complication	2	2,900	2.5	Early regression. Ongoing therapy.
15	2 / female / 1,100	Hemangiomatosis, Vaginal mucosa	28 weeks prematurity	Rapidly growing tumors, infection	2	4,250	2.0	No new lesion, early regression. Ongoing therapy
16	16 / female / 3,600	Face	None	Cosmetic risk	3	7,000	2.0	Early regression, ongoing therapy

* g: Gram. IVF: In-vitro fertilization. NF-1: Neurofibromatosis type-1. HDMP: High-dose methylprednisolone. IFN-α: Interferon-α. IUGR: Intrauterine growth retardation.

in the first 6 h of the treatment. They were within normal physiological limits and neither patient exhibited bradycardia or hypotension. When these infants were stimulated, these values returned to normal levels. No decrease was observed in blood pressure and pulse rate among patients who were manually monitored every hour. Salbutamol was started in one patient during a period of bronchiolitis; therefore, the propranolol treatment was ceased for seven days. One patient had excessive sweating within the first 4 h following the use of the drug. None of the patients in our series experienced hypoglycemia, wheezing, diarrhea, agitation, or cold hands. No serious adverse effects were observed thus far that would lead us to stop propranolol therapy.

Discussion

Treatment indication in four patients was rapidly growing hemangiomas. No progression was observed after the propranolol treatment in any of the cases. There was evident regression in hemangiomas in all cases within two months of follow-up. Because the majority of the patients were followed in the outpatient clinic, the effect of early change in color of hemangiomas was not taken into consideration.

As the responses were found satisfactory, treatment was stopped in three patients after 1.5, 1.5 and 2.0 months of follow-up. One month later, a slight progression was observed in one of these patients. Consequently, the treatment was restarted and the patient showed response again. There was no re-growth in the other patients.

Preliminary findings demonstrated that response was obtained in all patients; however, response was slower than mentioned in the literature[11-14]. There could be two reasons for this. First, propranolol was marketed as 40 mg tablets in Turkey. As mentioned above, the treatment solution was prepared from 40 mg tablets of the drug. The decreased solubility of the drug might have resulted in its low bio-availability. Second, the majority of the cases reported in the literature consisted of alarming hemangiomas, and patients received corticosteroids before the propranolol treatment and continued to take them with the propranolol for some time. Therefore, it should be considered that corticosteroids could potentiate the response to propranolol.

In the present study, three patients received propranolol after one year of age. Although the response was slower than in the patients in the proliferative phase, regression was observed in all three patients in two months of follow-up. This finding was considered to be important, as it demonstrated that propranolol could be effective for cases other than progressive hemangiomas. The number of cases in the study was limited. For this reason, it is planned to increase the number of patients in this group to enable a better analysis.

There has been no report of death or serious morbidity related to propranolol, which has been used clinically in infants and small children for more than 40 years[20]. As propranolol is a β-adrenergic receptor blocker, several well-known side effects such as bradycardia, hypotension or bronchospasm may be seen. Within the first hour of treatment, reduced blood pressure and pulse rate were observed in two patients, who were then monitored for 24 h; these were normal effects of the drug. These normal pharmacological effects were not observed in other patients, and may have been caused by the measuring method. In the cases where blood pressure and pulse rate were measured manually, the infants' stress during measurement could mask the expected pharmacological effect. In future studies, it is proposed to continuously monitor blood pressure and pulse rate for 24 h before and after the propranolol application. Measurements made without waking the infants could better demonstrate the effect of propranolol on blood pressure and pulse rate.

It should be noted that 9 of 16 patients were preterm infants. The corrected median age of preterm infants was 7 weeks. It is significant that 8 of 16 patients (50%) were less than 5 kg and 3 patients were less than 3 kg in weight. The corrected age and weight of the smallest infant were -5 weeks and 1,600 g, respectively. It was demonstrated in the study that the drug could be used in such small infants without leading to any complications.

Another important aspect of the study was the finding that somatic growth of preterm born and very low weight infants was found to be normal during propranolol treatment (Fig. 3). *In-vitro* fertilization increases the rates of multi-pregnancy and, therefore, the rate

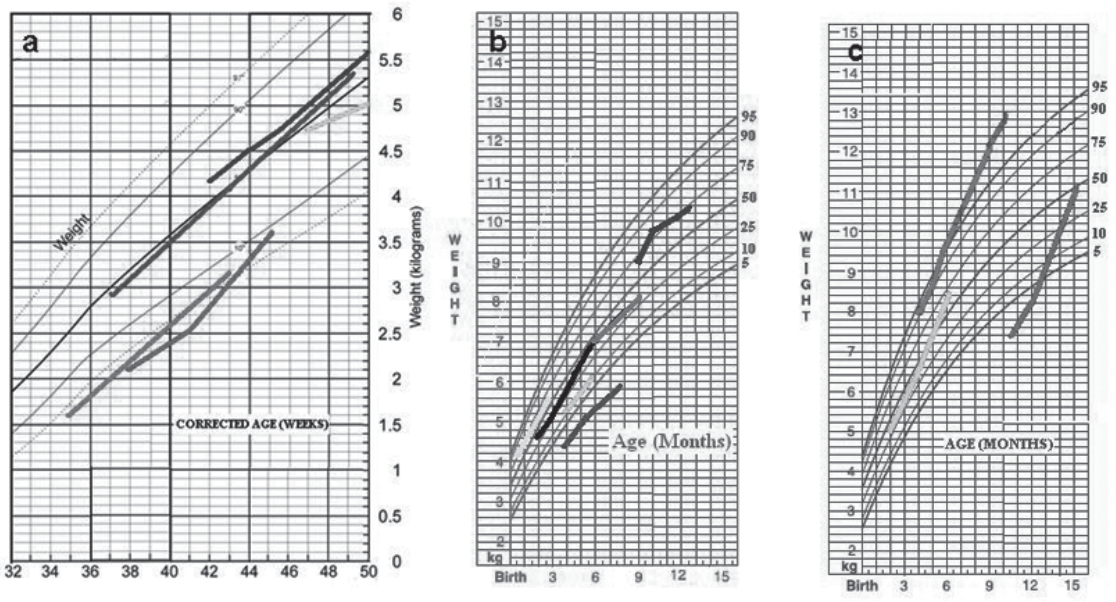

Fig. 3. Weight gain charts of patients during propranolol treatment. (a) term or preterm girls whose corrected ages were more than 50 weeks at the beginning of propranolol treatment; (b) term or preterm boys whose corrected ages were more than 50 weeks at the beginning of propranolol treatment; and (c) preterm infants whose corrected ages were less than 50 weeks. Graphs were prepared by marking the weight of patients during propranolol treatment over the original charts taken from references numbered 16 and 17.

of premature delivery. On the other hand, it is known that hemangioma is more frequent in premature infants [1,2]. Due to the serious side effects[9], the use of steroids in treatment is problematic in these infants. Propranolol has been used in cardiovascular indications in young children for many years. However, its effects on growth parameters in very young infants were not previously reported.

Despite the relatively recent introduction of propranolol in the treatment of dermal IHs, there can be little doubt of its efficacy[11-14]. In addition, as happened in one case in the present study, successful results have been obtained in the treatment of diseases like diffuse IHH, which have a different biology from that of dermal hemangiomas[18,21]. The high efficacy of propranolol without causing serious side effects extended the treatment indications of hemangiomas.

Sans et al.[11] reported that propranolol was also effective in hemangiomas after 18-24 months of age. Similar findings were determined in three cases in this study. In the coming periods, it could be used in children older than 9 years of age with hemangiomas with completed regression period. If the efficacy of propranolol in these cases is demonstrated, the next step will be anti-angiogenic therapy in cancer treatment. Experimental and *in-vitro* studies with animals on this subject show encouraging results[22-24]. Clinical studies have been started regarding the use of chemoprotective agents to prevent metastasis[25]. It is considered that propranolol has the potential to open a new era in clinical oncology.

REFERENCES

1. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003; 48: 477-493.
2. Frieden IJ, Haggstrom A, Drolet BA, et al. Infantile hemangiomas: current knowledge, future directions: proceedings of a research workshop of infantile hemangiomas. Pediatr Dermatol 2005; 22: 383-406.
3. Margileth AM, Museles M. Cutaneous hemangiomas in children: diagnosis and conservative management. JAMA 1965; 194: 523-526.
4. Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. Pediatrics 1998; 101: 446-452.
5. Akyüz C, Yarış N, Kutluk MT, Büyükpamukçu M. Management of cutaneous hemangiomas: a retrospective analysis of 1109 cases and comparison of conventional dose prednisolone with high-dose methylprednisolone therapy. Pediatr Hematol Oncol 2001; 18: 47-55.

6. Uysal KM, Olgun N, Erbay A, Sarialioglu F. High-dose oral methylprednisolone in childhood hemangiomas. Pediatr Hematol Oncol 2001; 18: 335-341.

7. Enjolras O, Breviere GM, Roger G, et al. Vincristine treatment for function and life-threatening infantile hemangiomas [in French]. Arch Pediatr 2004; 11: 99-107.

8. Rizzo C, Brigthman L, Chapas AM, et al. Outcomes of childhood hemangiomas treated with the pulsed-dye laser with dynamic cooling: a retrospective chart analysis. Dermatol Surg 2009; 35: 1947-1954.

9. Yeh TF, Lin YJ, Lin HC, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med 2004; 350: 1304-1313.

10. Léauté-Labrèze C, Dumas de la Roque ED, Hubiche T, Boralevi F, Thrombo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008; 358: 2649-2651.

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

12. Qin ZP, Liu XJ, Li KL, Zhou Q, Yang XJ, Zheng JW. Treatment of infantile hemangiomas with low-dose propranolol: evaluation of short-term efficacy and safety [in Chinese]. Zhonghua Yi Xue Za Zhi 2009; 89: 3130-3134.

13. Taban M, Goldberg RA. Propranolol for orbital hemangioma. Ophthalmology 2010; 117: 195.

14. Truong MT, Chang KW, Berk DR, Heerema-McKenney A, Bruckner AL. Propranolol for the treatment of a life threatening subglottic and mediastinal infantile hemangioma. J Pediatr 2010; 156: 335-338.

15. Frieden IJ, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy. J Am Acad Dermatol 1997; 37: 631-637.

16. Fenton D. A new growth chart for preterm babies: Babson and Benda's chart updated with recent date and new format. BMC Pediatr 2003; 3: 13-22.

17. Development by the National Center for Health Statistics in Collaboration with the National Center for Chronic Disease Prevention and Health Promotion 2000; http://www.cdc.gov/growthcharts

18. Sarialioglu F, Erbay A, Demir S. Response of infantile hepatic hemangioma to propranolol resistant to high dose methylprednisolone and interferon-α therapy. Pediatr Blood Cancer (accepted for publication).

19. Lowe JN, Sikka N. Are 1-2 tablets dangerous? Beta blocker exposure in toddlers. J Emerg Med 2004; 26: 309-314.

20. Marsciani A, Pericoli R, Alaggio R, Brisigotti M, Vergine G. Massive response of severe infantile hepatic hemangioma to propanolol. Pediatr Blood Cancer 2010; 54: 176.

21. Glasner A, Avraham R, Rosenne E, et al. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and cyclooxygenase-2 inhibitor. J Immunol 2010; 184: 2449-2457.

22. Hajighasemi F, Hajighasemi S. Effect of propranolol on angiogenic factors in human hematopoietic cell lines in vitro. Iran Biomed J 2009; 13: 157-162.

23. Guo K, Ma Q, Wang L, et al. Norepinephrine–induced invasion by pancreatic cancer cells is inhibited by propranolol. Oncol Rep 2009; 22: 825-830.

24. Zmora O. β-adrenergic blocker and a COX2 inhibitor for prevention of colorectal cancer recurrence. http://clinicaltrials.gov/et2/show/NCT00888797.