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Propranolol treatment of infantile hemangioma: clinical and radiologic evaluations

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Abstract

Background: There is no way to predict the size that proliferative infantile hemangiomas (IHs) can reach and to expect the occurrence of complications. Moreover, there are no well-known characteristics that can affect the rate of involution of IHs and to predict its completion. Accordingly, intervention is frequently indicated. Different modalities have been reported for treatment of IHs. The possible mechanisms of action of propranolol on IHs are complex.

Methods: Fifty infants presented with 80 IHs treated by oral propranolol at a dose of 2 mg/kg body weight per day. Treatment outcomes were clinically and radiologically evaluated.

Results: The first noticeable effects on propranolol treatment were the changes in color and softening of IHs, followed by regression of their sizes. The clinically elicited color changes of superficial IHs and superficial components of compound IHs have been objectively proven by statistically significant color clearance ($P \leq .001$) and resisting index ($P \leq .01$) (~50% increase) as a good indicator of lower vascular activity within IHs. Moreover, the softening of lesions followed by the clinically elicited regression of sizes of deep IHs and deep components of compound IHs has been objectively proven by statistically significant changes at lesions' thickness ($P \leq .01$) (~50% regression) and resisting index ($P \leq .01$) (~50% increase).

Conclusions: Collectively, high efficacy and tolerance of propranolol treatment have been elicited. However, propranolol treatment of IHs is still an issue suitable for more studies to confirm the safety and efficacy of the drug and to investigate whether there are some hemangiomas that are, perhaps, nonresponsive to propranolol treatment.

Infantile hemangioma (IH) is the most common benign tumor of infancy. It affects 5% to 10% of all infants and up to 30% of premature infants with a clear female predominance [1]. Although IH is not believed to be familial, approximately 10% of the affected infants have positive family history [2]. This finding has been elicited by the controversial results regarding the influence of hereditary factors in the etiology of IH [1,3].

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The natural history of IH is unique. Most IHs usually appear during the first few weeks of life, despite of approximately 30% of lesions do present since birth [4]. It proliferates during the first year of life and then involutes during childhood period. Clinically, these 2 features distinguish IH from vascular malformations that neither proliferate nor involute [5-7]. By the end of the first year of life, an overlap from proliferation to involution is gradually elicited, when IH is gradually changing from the predominantly cellular into the predominantly vascular nature [5]. This change continues with progressive deposition of perivascular fibrofatty tissue, abundant mast cells, and less active endothelial cell proliferation.

Several hypotheses, including the possible somatic mutation in vascular endothelial growth regulatory pathways, have been put forth concerning the process of hemangiogenesis [8,9]. Blood vessels are formed by 1 of 2 processes, namely, vasculogenesis and angiogenesis [10]. The regulating mechanisms for angiogenesis are not fully understood yet; however, several regulators have been postulated including the role of the vascular endothelial growth factors (VEGFs) and basic fibroblast growth factor (bFGF) [9]. Recently, mesenchymal stem cells were recognized as a novel cellular constituent in IH that may contribute to the process of adipogenesis during involution of IH [11].

Cutaneous IH has been nowadays described according to its depth as superficial, deep, and compound [12]. Superficial IH originates from papillary dermis and presents as bright red macular or papular mass. Deep IH originates from reticular dermis or subcutaneous tissues and appears as bluish or relatively colorless mass. Collectively, compound IH is a combination of both superficial and deep components.

Approximately 40% of IH involutes spontaneously. Accordingly, current belief supposing that most IH should be left untreated along a policy of "benign neglect" was considered and is still firmly encountered in practice. However, the unpredictable outcome and the possible serious complications after proliferation and proposed involution, in addition to the consequences of cosmetic disfigurement associated with the psychologic trauma first in parents and later in the affected children, all alleviate for prompt treatment of IH [6]. Standard treatment options for IH include corticosteroids, laser surgery, cryosurgery, interferon, and vincristine [13-15]. Each of these treatment options has its restrictions and/or side effects [16].

In 2008, Léauté-Labrèze et al [17] described their serendipitous observation of the effect of propranolol on IH. Propranolol is a pure selective β-adrenergic antagonist, which competitively inhibits β1- and β2-adrenoceptors with the same affinity. On account of its lipophilic properties, propranolol also exhibits certain membrane-stabilizing characteristics. Since the accidental and innovative observation by Léauté-Labrèze et al [17], the use of propranolol for treatment of IH has become a subject of extensive investigations. Herein, current hypotheses of how propranolol interferes with endothelial cells, vascular tone, angiogenesis, and apoptosis along 3 different pharmacologic targets to induce early, intermediate, and long-term effects of propranolol on IH have been postulated [18].

Regardless of the lack of generally accepted exact mechanism(s) about how propranolol actually works on IH, the present study was conducted to clinical and radiologic evaluation of the outcome of propranolol as an introduction for a new era of IH treatment.

1. Patients and methods

Fifty infants presented with 80 IHs of different types, at different body regions, were included in the present study. Every patient was subjected to a thorough history taking and physical examination. Parents were thoroughly given a complete discussion about how IH grows in phases, possible treatment modalities, and side effects. After written informed consent was obtained from the parents, propranolol treatment was started. The objective of treatment was to inhibit further growth of the lesions and/or even to induce regression in their size. Treatment was continued until the objective goals were obtained or no further improvement could be achieved.

Propranolol was given at a dose of 2 mg/kg body weight per day in 3 divided doses. Blood pressure and heart rate were monitored shortly after starting propranolol treatment. In the absence of side effects, treatment was continued at home, and infants were reevaluated after a week, 2 weeks, and then every month. Clinical evaluation including photodocumentation was carried out before starting treatment as well as at each monthly follow-up visit. Monitoring of treatment compliance and tolerance (heart rate and blood pressure) as well as measuring of body weight for dosage adjustment was done at each monthly evaluation. Whenever it was possible, ultrasound examination was performed to measure the maximal thickness of the lesion and the resisting index (RI) before starting treatment, after 2 months of treatment duration, and at the end of treatment as well as up to 6 months after cessation of propranolol treatment. Ophthalmologic examination for assessment of infants with eyelid involvement was done as needed.

Inclusion criteria for propranolol treatment of IHs in the present study included those lesions of huge size, multiple lesions ($\geq$2), and complicated lesions including lesions with cosmetic/functional risks as well as lesions that exhibited rapid proliferation. Infants with cardiovascular disorders contraindicating propranolol use, family history with regard to atopy, or recent/repeated outbreak of wheezing and low–birth weight newborns especially with decreased energy intake were excluded from the present study.

1.1. Clinical evaluation of IHs

Regression in the size of deep IHs and deep component of compound IHs was clinically assessed by an independent

physician. It was evaluated according to 0%-to-100% scale. An excellent response denotes 76% to 100% regression. A good response denotes 51% to 75% regression. A fair response denotes 26% to 50% regression. Finally, a poor response denotes 25% or less regression. Continued growth, posttreatment complications, and/or relapse of growth were also reported [19,20]. Finally, all infants were followed up for up to 6 months after cessation of propranolol treatment.

Color changes of superficial IHs and superficial component of compound IHs were digitally analyzed using Adobe Photoshop 6.0 ME Software (Adobe System Incorporation, USA). The following equation was used to objectively evaluate the color clearance after treatment to minimize the possible artifacts during photodocumentation.

$$\text{Color Clearance}(\%) = \{(A - B) \div (A) \times 100\} - \{(C - D) \div (C) \times 100\}$$

A and B represent the numerical color values of identical areas of IHs at pretreatment and posttreatment photographs, respectively, whereas C and D represent the numerical color values of an identical area of normal skin at pretreatment and posttreatment photographs, respectively. The former fraction of the presented equation will serve to calculate the color clearance (percentages) of identical areas of IHs at pretreatment and posttreatment photographs, whereas the later fraction of the presented equation will help to calculate the color clearance (percentages) of an identical area of normal skin at pretreatment and posttreatment photographs. Accordingly, the color clearance (percentages) of identical area of normal skin at pretreatment and posttreatment photographs will be added to or subtracted from the color clearance (percentages) of identical areas of IHs at pretreatment and posttreatment photographs to bypass technical artifact.

1.2. Objective evaluation of IHs

A high-resolution gray scale and Doppler sonography were done to determine the appearance and vascular characteristics of proliferative IHs. Hitachi and GE scanners with a 10-MHz linear array transducer and color Doppler imaging have been used. Gray-scale images of IH were obtained in transverse and longitudinal planes. Lesions with well-defined margins were measured in 3 dimensions, namely, length, width, and thickness. Echogenicity was assessed as hypoechoic or hyperechoic. Internal architecture was classified as homogeneous and heterogeneous. Peak arterial Doppler shifts and RI as good indicators of vascular activity within the IHs were ascertained by using pulsed Doppler sonography.

1.3. Statistical analysis

Results are presented in numbers, percentages, mean values ± SD, and ranges. Data were statistically analyzed using the Student t test, and statistical significance was set at $P \leq .05$.

2. Results

Patients' demographic data and lesions' data are collectively summarized in Tables 1 and 2, respectively. Forty-four infants (88%) with an age of 5.31 ± 3.59 months (range, 1-12 months) have been included in the present study for early treatment of 73 IHs (91.25%). Early treatment was indicated for rapidly proliferating lesions and huge-sized lesions as well as complicated lesions including those lesions with cosmetic and/or functional risks. On the other hand, 6 infants (12%) with an age of 15.75 ± 4.27 months (range, 13-22 months) have been included in the present study for late treatment of 7 IHs (8.75%). Late treatment was indicated for noninvoluting and/or slowly involuting lesions to accelerate the natural course of the lesions as well as to limit the incidence of local cosmetic disfigurement. Seven infants (14%) had previously received corticosteroid treatments with no response. Corticosteroid treatments were already discontinued before the infants were enrolled in the present study. None of the enrolled infants has been a candidate for interferone or vincristine treatment.

Superficial IHs have elicited dramatic color changes primarily from intense red to purple color, followed by a progressive lightening of lesions' color (Fig. 1). These clinically based color changes on propranolol treatment could be objectively proven by the statistically significant color clearance ($P \leq .001$) as well as by the statistically significant change at the RI ($P \leq .01$) on sonographic examination (~50% increase) as a good indicator of lower vascular activity within IHs. In addition to color changes,

Table 1 Patients' data at initial presentations

Patients' data	n	%
Total no.	50	100
Sex		
Male	10	20
Female	40	80
Male/female ratio	1/4	
Consanguinity		
Positive	12	24
Negative	38	76
Family history:		
Positive	3	6
Negative	47	94
Presentation		
Single lesion	36	72
Multiple lesions	14	28
Onset		
Since birth	28	56
Later after birth	22	44
Previous treatment	7	14
Age at initial presentation (mo)	6.4 ± 4.88 (range, 1.5-22)	

Table 2 Infantile hemangiomas' data at initial presentations

IHs' data	n	%
Total no.	80	100
Types of IHs		
Superficial	6	7.50
Deep	7	8.75
Compound/mixed	67	83.75
Sites (locations) of IHs		
Head	53	66.25
Scalp	6	7.50
Face	12	15.00
Periorificial	35	43.75
Periorbital and eyelids	9	11.25
Lips and tongue	7	8.75
Nose	10	12.50
Ear	1	1.25
Parotid region	8	10.00
Trunk	10	12.50
Limbs	10	12.50
Upper limbs	5	6.25
Lower limb	5	6.25
Anogenital	2	2.50
Extending/deeply seated IHs	5	6.25
Intraorbital, extraoccular, extraconal	2	2.50
Subgalial	1	1.25
Superior saggital sinus (sinus pericranii)	1	1.25
Subcapsular, intrahepatic	1	1.25
Presenting complaints		
Cosmetic disfigurement	75	93.75
Ulceration	2	2.50
Visual obstruction	2	2.50
Feeding problems	3	3.75
Nasal obstruction	1	1.25

softening of lesions on palpation, followed by the noticeable regression of their sizes, could be elicited on propranolol treatment of deep IHs (Fig. 2). These clinically based changes in lesions' sizes could be objectively proven by the statistically significant changes at lesions' thickness ($P \leq .01$) (~50% regression) as well as by the statistically significant change at RI ($P \leq .01$) on sonographic examination (~50% increase). Collectively, the clinically elicited color changes and sizes' regression proved by the statistically significant changes at lesions' thickness ($P \leq .01$) as well as at the RI ($P \leq .01$) on sonographic examination could be noticeable on propranolol treatment of both the superficial and deep components of compound IHs (Fig. 3). Such appropriate results could be indeed noticed accompanied by satisfactory cosmetic and functional outcomes with early spontaneous ocular opening and healed painful ulcerations.

On cessation of propranolol treatment and follow-up period, IHs had become nearly flat. However, few expected, self-limited adverse effects were noted, where propranolol treatment was found to be needed to be administered again at 8 and 10 months of age. Table 3 summarizes the response and side effects of IHs on propranolol treatment. Fig. 4A and B demonstrates sonographic assessment of the thickness and RI of an IH before and 6 months after cessation of propranolol treatment, respectively.

Collectively, propranolol treatment at a dose of 2 mg/kg body weight per day in 3 divided doses was elicited to be uniformly rapid, well-tolerated, and effective modality for treatment for IHs resulting into a considerable shortening of the natural course of IHs. These findings were collectively associated with uniform parents' satisfaction.

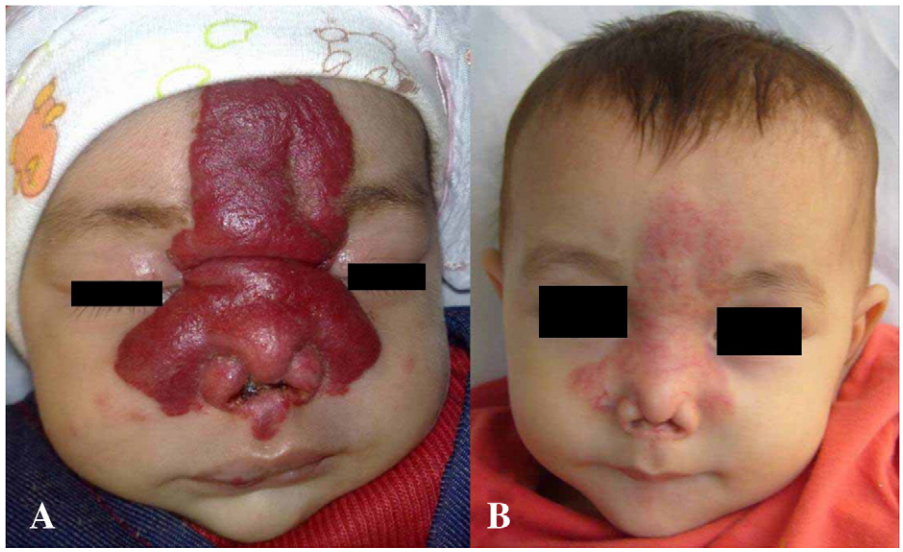

Fig. 1 Frontal view for a patient presented with a superficial infantile hemangioma. Before treatment (A) and after treatment and 6-month period of follow-up (B).

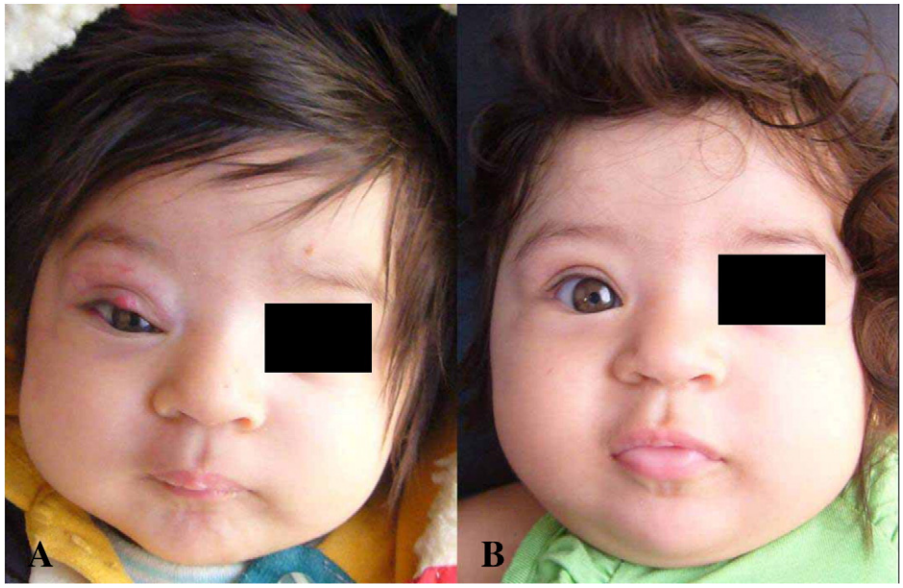

Fig. 2 Frontal view for a patient presented with a deep infantile hemangioma. Before treatment (A) and after treatment and 6-month period of follow-up (B).

3. Discussion

Unfortunately, there is no way to predict the size that proliferative IHs can reach as well as to expect the occurrence of complications. These mishaps depend upon the degree and duration of proliferation. Moreover, there are no well-known characteristics that can affect the rate of involution of IHs and to predict its completion [21]. That is why intervention is frequently indicated [10,15]. However, current belief dictates that most IHs should be left untreated, and accordingly, the policy of "benign neglect" was considered and is still firmly encountered in practice [7]. However, the unpredictable outcome after proliferation and proposed involution of IHs, in addition to the associated psychologic trauma, all alleviate for reevaluation of the benign neglect policy of follow-up. The optimum modality for treatment of IHs depends upon its stage, whether proliferating or involuting, and its type, whether superficial, deep, or compound, as well as for treatment of residual deformity. Accordingly, intervention should be tailored for each IHs, individually.

Infantile hemangiomas composed of a complex mixture of cell types, including mostly endothelial cells associated

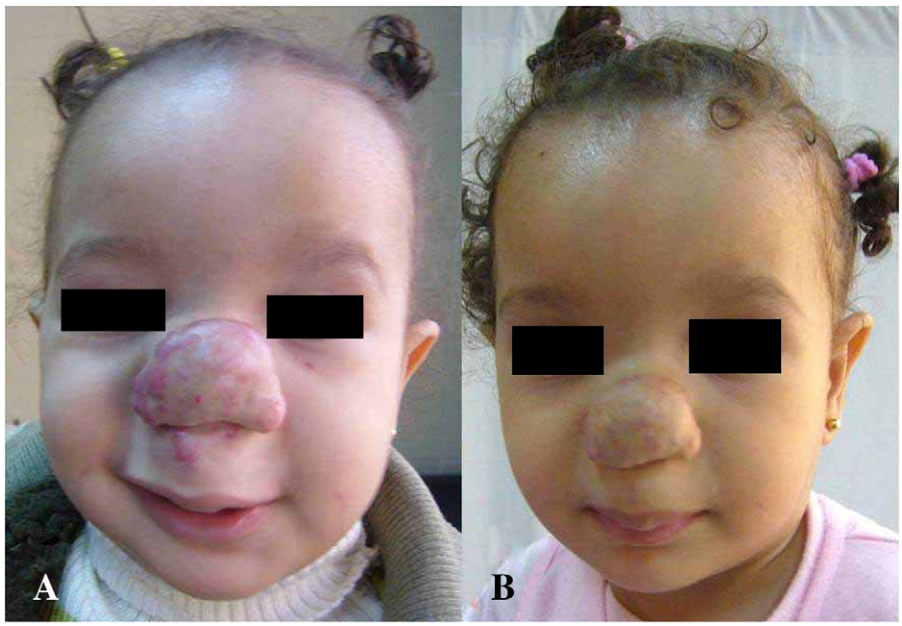

Fig. 3 Frontal view for a patient presented with a compound IH. Before treatment (A) and after treatment and 6-month period of follow-up (B).

Table 3 Response and side effects of IHs on propranolol treatment

Item	Finding
Age at start of treatment (mo)	6.5 ± 4.93 (range, 1.5-22)
Age at end of treatment (mo)	13.03 ± 5.69 (range, 7-30)
Duration of treatment (mo)	6.53 ± 0.75 (range, 5-8)
Regression of the size	
Excellent	60 (75%)
Good	15 (18.75%)
Fair	5 (6.25%)
Poor	–
No response	–
Color clearance	
Before treatment	153.2 ± 21.7 (171.5-103.7)
After treatment	41.6 ± 13.2 (57.3-18.9)
P	≤.001
Sonographic assessment	
Thickness (mm)	
Before treatment	9.22 ± 9.45 (range, 3-39)
After treatment	4.33 ± 6.91 (range, 0-25)
P	≤.01
RI	
Before treatment	0.58 ± 0.10 (range, 0.5-0.8)
After treatment	0.80 ± 0.05 (range, 0.7-0.9)
P	≤.01
Side effects	
Ulceration and scarring	1 (1.25%)
Residual and/or recoloration	5 (6.25%)
Epidermal atrophy	2 (2.50%)
Telangiectasia	6 (7.50%)
Residual fibrofatty tissue	10 (12.50%)
Regrowth	2 (2.50%)

Data are presented as numbers (percentages) and mean values ± SDs (ranges).

with pericytes, dendritic cells, and mast cells. Endothelial cells derived from proliferative IHs are clonal in origin, which suggests that IHs may arise from clonal expansion of an endothelial precursor cell [22]. Regulators for growth and involution of IH are still poorly understood. Different modalities have been reported for treatment of IHs. These include laser surgery, cryosurgery, and pharmacotherapy, namely, corticosteroids, vincristine, α-interferon, and cyclophosphamide. Each has its risk of serious side effects. However, the spectacular effect of propranolol treatment of hemangiomas described for the first time in 2008 by Léauté-Labrèze et al [17] has dramatically changed the therapeutic strategies used for treatment of hemangiomas to date. This was the motive for us to subjectively and objectively evaluate the efficacy and tolerance of this innovative new modality for treatment of a relatively larger series of IHs in the present study. The possible mechanisms of action of propranolol on IHs are complex. These include vasoconstriction, inhibition of angiogenesis, and induction of apoptosis [18].

Regarding vasoconstriction, propranolol as β-adrenoceptor antagonist inhibits vasodilation mediated by adrenaline leading to vasoconstriction [23]. In IHs, vasoconstriction of supplying capillaries on propranolol treatment induces a reduction of blood flow within the lesions [17]. This could explain the early and long-standing clinically evidenced color changes and softening of superficial IHs and superficial components of compound IHs on propranolol treatment in the present study that could be objectively proven by the changes at the color clearance and RI on sonographic examination.

Regarding angiogenesis, during proliferation of IHs, endothelial cells exhibit an increased expression of proliferating

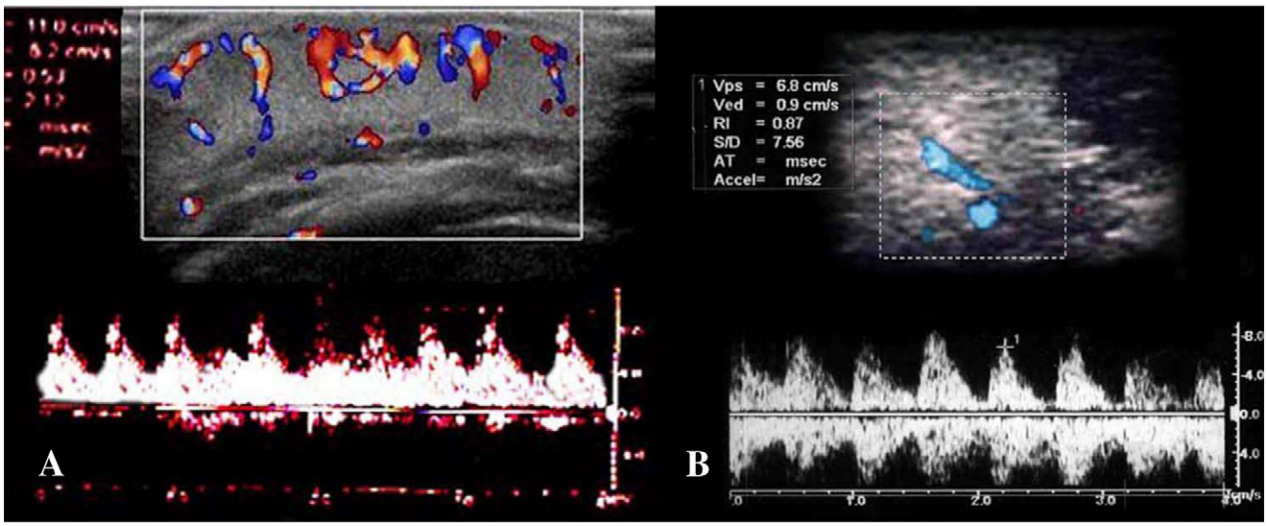

Fig. 4 Sonographic assessment of the thickness and RI of an IH. Before treatment (A) and after treatment and 6-month period of follow-up (B).

cell nuclear antigen, type IV collagenase, and proangiogenic factors, in particular, VEGF more than bFGF [24]. Conversely, expression of VEGF and bFGF is significantly reduced during involution phase as well as in completely involuted hemangiomas [25]. These findings are evidence that IHs result from a dysregulation of angiogenesis, characterized by an imbalance between proangiogenic and antiangiogenic factors [26]. Physiologically, hypoxemia leads to increased expression of VEGF [27]. Accordingly, perinatal hypoxemia has been identified as an important etiologic factor in IHs [28]. This effect was found to be mediated by the transcription factor hypoxia-inducible factor 1a. As a result, VEGF is secreted from the cell, diffuses into the surrounding tissue, and induces proliferation of adjacent endothelial cells, which, in turn, leads to secretion of proteases necessary for reorganization of matrix metalloproteinases, and the coordinated differentiation of vascular cells (endothelial cells, smooth muscle cells, pericytes) into functional vessels (angiogenesis). Conversely, propranolol as β-receptor blocker leads to a reduced expression of VEGF and, thus, to an inhibition of angiogenesis. Collectively, this antiangiogenic effect of propranolol could explain once more the early and long-standing clinically evidenced color changes of superficial IHs and superficial components of compound IHs on propranolol treatment in the present study that could be objectively proven by the changes at the color clearance and resisting index on sonographic examination.

Regarding apoptosis, it was reported that during proliferation, IHs express a low rate of apoptosis, whereas during involution of IHs, apoptosis increases [28]. Storch and Hoeger [18] hypothesized that β-adrenergic antagonists are capable of disengaging the inhibition of apoptosis caused by β-adrenergic agonists, resulting into an increased apoptosis rate. Accordingly, induction of apoptosis represents another possible mechanism of action of propranolol in the treatment of IHs in the present study. This could explain softening of lesions, followed by the noticeable regression of sizes of deep IHs and deep components of compound IHs that could be objectively proven by the changes of the thickness of lesions on sonographic examination in the present study.

Collectively, high efficacy and tolerance of propranolol treatment of IHs have been elicited in the present study. The first noticeable effects on propranolol treatment were the changes in color with continuing brightening of the lesions as well as softening of the lesions, followed by regression of their sizes. The clinically based color changes on propranolol treatment of superficial IHs and superficial components of compound IHs have been objectively proven by the statistically significant color clearance ($P \leq .001$) and RI ($P \leq .01$) (~50% increase) as a good indicator of lower vascular activity within IHs. Moreover, the clinically based changes in lesions' sizes on propranolol treatment of deep IHs and deep components of compound IHs have been objectively proven by the statistically significant changes at lesions' thickness ($P \leq .01$) (~50% regression) and RI ($P \leq .01$) (~50% increase).

However, there is an important inquiry that still has to be established, namely, "when to stop propranolol treatment of hemangiomas?" The remarkable results of propranolol treatment of IHs were found not only upon growth stabilization of IHs that could be often achieved with corticosteroids but for the continued improvement until complete involution of lesions was achieved as well. Moreover, the RI was reported to be increased significantly to values similar to those elicited during late involutive phase of hemangiomas. Finally, propranolol treatment has reported the same efficacy with respect to color and thickness of IHs that were considered fully developed (late interventions) [16]. This observation was found to be a striking difference between propranolol and systemic corticosteroid treatments of hemangiomas. That is why the objective of treatment in the present study was to inhibit further growth of the lesions and/or to induce regression in their size. In cases of early propranolol treatments in the present study, a considerable shortening of the natural course of IHs could be achieved especially for those lesions at proliferative phase. This will harbor not only a reduced incidence of complications along with the natural history of IHs, but it will also establish a better outcome at the end of treatment. However, both relapses after cessation of propranolol treatment in the present study occurred before the ages of 8 and 10 months. This suggests that the optimal propranolol treatment must at least cover the entire proliferative phase of IHs and may last until the age of 12 months, especially for those IHs with subcutaneous components. On the other hand, for late propranolol treatments started after the end of proliferative phase of hemangiomas, we do think that propranolol treatment should be continued empirically until the maximal improvement has been achieved.

The mainstay problem with propranolol treatment of IHs is still the nonavailability of propranolol in a pharmaceutical formulary dose appropriate for newborns, infants, and children younger than 6 years currently in many countries including Egypt. For now, oral propranolol treatment for IHs has to be prepared from tablets dissolved to suitable smaller dosages, which may complicate dose adaptation and drug administration.

4. Conclusions

Infantile hemangiomas are composed of a complex mixture of cell types. Regulators for growth and involution of IHs are still poorly understood. Different modalities have been reported for treatment of IHs. The mechanisms of action of propranolol on IHs are complex and orchestrated. Propranolol has early, intermediate, and long-term effects on IHs that can be attributed to 3 pharmacologic targets. First, the early color clearance of IHs is attributable to vasoconstriction owing to decreased release of nitric oxide. Second, the intermediate effects are because of blocking of proangiogenic signals, namely, VEGF, bFGF, and matrix metalloproteinases resulting into growth arrest. Third, the

long-term effects are characterized by induction of apoptosis in proliferating endothelial cells resulting into tumor regression.

Within the limitations of the present study, oral propranolol treatment of IHs at a dose of 2 mg/kg body weight per day in 3 divided doses had rapid and effective therapeutic outcomes in all cases. The first noticeable effects were the changes in color and softening of IHs followed by regression of their sizes. The clinically based color changes have been objectively proven by the statistically significant color clearance and RI. On the other hand, the regression of the sizes has been objectively proven by the statistically significant changes at lesions' thickness and RI. Collectively, propranolol treatment of IHs has elicited high efficacy and tolerance with few expected adverse effects. However, propranolol treatment of IHs is still an issue suitable for more comparative, randomized studies with a greater number of patients to confirm the safety and efficacy of the drug on a larger population as well as to investigate whether there are some hemangiomas that are, perhaps, nonresponsive to propranolol treatment.

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