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Demographic and clinical features of infants with hemangioma admitted to Afzalipour Hospital, Kerman

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Background and Aim: Infantile hemangioma is the most common type of vascular tumor in childhood. Risk factors for hemangioma include female gender, low birth weight, prematurity, higher maternal age, and multiple gestations. In this study, for the first time in Kerman, we describe and compare demographic features of infants with hemangiomatous lesions treated with two different systemic beta-blockers (atenolol or propranolol), examining their efficacy and adverse effects.

Methods: Forty-one infants with hemangiomatous lesions admitted to the pediatric dermatology ward of Afzalipour Hospital from 2011 to 2017 were enrolled in this study. Demographic features of infants and their mothers and clinical features and complications of hemangiomatous lesions were recorded. Also, we compared the efficacy and adverse effects of treatment protocols with two beta-blockers (atenolol and propranolol).

Results: Most infants were female (70.7%), and 9.7% were premature. The majority of the lesions were superficial (53.7%) and located in the head and neck area (82.9%). Multiple hemangiomas were recorded in 4.8% of the cases. The most common complication was ulceration (29.3%). Two out of 18 patients treated with propranolol had a complete response rate. Adverse effects were observed more frequently with propranolol (26.8%) than with atenolol (14.6%).

Conclusion: In our study, female gender and low birth weight were significantly more common in infantile hemangioma patients than in the normal population. Also, mothers of children with hemangioma had a significantly greater number of miscarriages than the average population. Propranolol and atenolol had no significant difference in efficacy and adverse effects.

Keywords: hemangioma, demographic, propranolol, atenolol

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INTRODUCTION

Infantile hemangioma is the most common vascular tumor in childhood, with an incidence rate of 3–10%. Hemangioma is seen more frequently in girls and non-Hispanics with white skin. Lesions usually do not exist at birth but gradually develop during the

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first month of life. The first manifestations may include telangiectasia, a pale-colored or ecchymotic patch that develops to a red or violaceous plaque (superficial type), deep blue-colored tumors (deep type), or a combination of these types (mixed type). Due to the similarity between immunohistochemistry characteristics and growth patterns of hemangiomas and placentas, the theory of hemangiomatous lesions originating from the placenta has been proposed [1-3].

Hemangiomas grow in three stages. In stage 1, the lesion grows rapidly within six months to two years, depending on the type of hemangioma (superficial or deep). In this stage, the lesion becomes thicker and darker. In stage 2 (plateau), the growth rate is proportional to the infant's body growth. In stage 3 (involution), which varies between 5 to 7 years, the color of the lesion gradually changes from red and violaceous to gray, and the lesion becomes soft in consistency. Finally, in 20-40% of cases, fibro-fatty tissue, telangiectasia, and dyspigmentation persist [1-3].

In previous studies, risk factors such as female gender, low birth weight, prematurity, higher maternal age, multiple gestations, and chorionic villus sampling have been reported to induce hemangioma. Other risk factors for complications include the size, site, and type of hemangioma [3-5].

Most hemangiomatous lesions do not need any kind of treatment and only active follow-up is sufficient, but nearly 10-30% of the lesions require treatment to prevent complications. Different treatment modalities have been used to treat infantile hemangioma, including topical, intralesional, and systemic corticosteroids, imiquimod, interferon alfa, vincristine, surgery, beta-blockers, and pulsed dye laser. Previously, systemic corticosteroids were used as first-line therapy, with possible side effects including Cushing's syndrome, hypoglycemia, hypertension, growth retardation, predisposition to infection, gastrointestinal upset, and mood alterations like irritability [6-8]. Nowadays, beta-blockers such as propranolol and atenolol are the first line of treatment for infantile hemangioma. The mechanism of action of beta-blockers is through microvascular vasoconstriction, inhibition of the production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiotensin II, matrix metalloproteinase, and induction of apoptosis [9-12]. Propranolol is a nonselective beta-blocker with side effects like hypoglycemia, bronchospasm, hypotension, seizure, sleep disturbance, gastrointestinal upset, and mood alteration. Atenolol is a selective β_1 blocker that is hydrophilic, so it cannot cross the brain-blood barrier. Thus, side effects such as hypoglycemia, bronchial spasm, and seizure rarely occur with this agent [13-17].

In this study, for the first time in Kerman, we describe clinical features of hemangiomatous lesions in infants admitted to Afzalipour Hospital and evaluate and compare the efficacy and adverse effects of systemic treatment with two different beta-blockers.

METHODS

This is a retrospective, cross-sectional study of infants with hemangioma admitted to the Afzalipour Hospital of Kerman University of Medical Sciences from 2011 to 2017. Forty-one infants admitted to the pediatric dermatology ward were enrolled. Birth data of the normal population in Kerman were collected from Iranian Maternal and Neonatal Network (IMAN Net).

Hemangiomas were diagnosed based on clinical manifestations and history, with the diagnosis confirmed by a pediatric dermatologist. Laboratory data including complete blood count, electrolytes, and blood glucose were tested before treatment. Electrocardiography, echocardiography, and consultation with a pediatric cardiologist were done before starting treatment. Thyroid function test, abdominal sonography, brain computed tomography scan, and consultation with a pediatric neurologist were done in selected cases. Blood glucose, blood pressure, and pulse rate were checked 2 hours after commencing treatment or increasing the dose.

Indications of treatment were complicated hemangioma (ulceration, infection, or bleeding), life-threatening lesions (with a potential risk of cardiac insufficiency and liver failure), functional impairment (obstruction of the visual axis, auditory canal or airway), and risk of disfigurement and scar formation (large or rapidly growing lesions, or lesions of lip, nasal tip, and auricular areas) [2,18-23].

Demographic features of infants (age at the appearance of the lesion, gender, birth weight, gestational age, family history of hemangioma) and mothers (age at delivery, number of children, multiple gestations), type of delivery (Cesarean, vaginal), history of abortion, complications during pregnancy (eclampsia, gestational diabetes, etc.), and

drug history or interventions during pregnancy were recorded. We also documented the clinical features of the hemangiomas including the type of the lesion (superficial, deep, mixed), the site and number of the lesions, the stage of growth (proliferative or plateau) and patient's age at the beginning of treatment, the pattern of distribution (localized, segmental, multiple, visceral), hemangioma complications (ulceration, bleeding, infection, threatening disturbances of vision, airway or auditory obstruction) and associated anomalies. Then, the type of treatment (atenolol or propranolol), starting dosage, maximum treatment dosage and duration of the treatment, efficacy, and adverse effects were evaluated.

Statistical analysis

Data were analyzed by SPSS software (version 16; IBM, Armonk, NY, USA. For descriptive data, mean ± standard deviation, frequency, and relative frequency were obtained. The chi-squared test and independent t-test were applied to evaluate differences between groups as appropriate.

Ethical consideration

This study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.REC.1396.1249).

RESULTS

Demographic features of infants

Forty-one infants (70.7% girls, 29.3% boys) were enrolled in this study. The mean weight of infants at birth was 2830 g (range 850–3800 g). Nearly 90% of infants were mature, and 9.7% were premature. Most of the infants were the product of vaginal delivery (55.8%) and the first child of the family (31%). Three cases (7.3%) resulted from multiple gestations (Table 1).

Demographic features of the mothers

The mean age of the mothers at the delivery time was 28.58 (range 18-41) years. A quarter of the mothers reported a history of miscarriage. The mean number of children was 2.27 (range 1–8). Twelve (29.2%) mothers had a history of disease during the related pregnancy. Three were affected by hypothyroidism and treated with levothyroxine. Six were affected by gestational diabetes; two were treated with insulin, while four were controlled with dietary modifications. Two mothers had urinary tract infections treated with amoxicillin. None of the mothers had a history of intrauterine interventions such as amniocentesis and chorionic villous sampling. Also, none of the mothers had hypertension or eclampsia during pregnancy (Table 2).

Table 1. Demographic features of infants with hemangioma

Variable	Frequency (%)
Sex	
Female	29 (70.7)
Male	12 (29.3)
Birth weight (grams)	
< 1500	2 (4.8)
1500–2499	7 (16.7)
≥ 2500	26 (61.9)
Gestational age	
> 37 weeks	33 (82.5)
32–37 weeks	3 (7.3)
< 32 weeks	1 (2.4)
Family history of hemangioma	
Yes	1 (2.4)
No	39 (95.2)
Residence location	
City	24 (58.5)
Rural	17 (41.5)

Clinical features of the hemangiomatous lesions

Most lesions were superficial (53.7%) and focal (72.1%). The mean number of lesions per patient was 1.9, and the mean size was 1.88 cm^2. Nearly 40% of infants had more than one lesion, and two infants (4.8%) had multiple hemangiomatous lesions (more than five lesions). The most common site of involvement was the head and neck (82.9%), mostly in the periorbital area (36.6%). The most and the least frequent adverse effects of hemangioma were ulceration (29.3%) and poor feeding, as well as hypothyroidism (each 2.4%), respectively (Table 3). Associated anomalies were seen in 26.9% of the cases, including cardiac defects [atrial septal defect (ASD, 42%), mitral regurgitation (21.4%), tricuspid regurgitation (21.4%), patent ductus arteriosus (PDA, 7.1%), and left ventricular hypertrophy (7.1%)], Dandy-Walker syndrome (4.9%), PHACES (posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies) syndrome (4.9%). One patient had left ventricular hypertrophy secondary to mitral regurgitation.

Table 2. Demographic features of mothers in delivery

Variable	Frequency (%)
Maternal age at delivery (years)	
< 20	2 (4.8)
20–29	19 (45.2)
30–40	9 (21.4)
> 40	1 (2.4)
Number of children	
1	12 (28.6)
2	14 (33.3)
3	4 (9.5)
4	3 (7.1)
5	2 (4.8)
8	1 (2.4)
Disease during pregnancy	
Hypothyroidism	3 (7.3)
Gestational diabetes	6 (14)
Urinary infection	2 (4.8)
Fibromyalgia	1 (2.4)
Drug usage during the pregnancy	
Yes	6 (14.6)
No	35 (85.4)
Previous history of miscarriage	
Yes	11 (25.6)
No	32 (78)
Type of the delivery	
Cesarean section	15 (36.5)
Vaginal	19 (46.3)
Type of pregnancy	
Multiple	3 (7.3)
Single	38 (92.7)

Table 3. Clinical features of hemangioma lesions and adverse effects

Variable	Frequency (%)
Age of infant at presentation	
At birth time	26 (63.4)
< 30 days	11 (26.8)
30–90 days	4 (9.7)
Location of the lesions	
Head & neck	34 (82.9)
Trunk	7 (17.1)
Upper limb	5 (12.2)
Lower limb	1 (2.4)
Genitalia	5 (12.2)
Pattern of distribution	
Localized	31 (72.1)
Segmental	7 (16.3)
Visceral	1 (2.3)
Multiple	4 (9.3)
Type of hemangioma	
Superficial	22 (53.7)
Deep	0 (0)
Mixed	19 (46.3)
Adverse effects	
Infection	5 (12.2)
Stridor & short breath	2 (4.9)
Ptosis and threat to vision	3 (7.3)
Ulceration	12 (29.3)
Bleeding	10 (24.4)
Poor feeding	1 (2.4)
Hypothyroidism	1 (2.4)
Obstruction of lacrimal duct	1 (2.4)
Associated anomalies	
Cardiac defects	7 (17.1)
PHACES syndrome	2 (4.9)
Dandy-Walker malformation	2 (4.9)
Stage of growth at the beginning of study	
Proliferative	36 (87.8)
Plateau	5 (12.2)
The number of lesions	
1	25 (61)
2	8 (19.5)
3	3 (7.3)
4	1 (2.4)
5	2 (4.9)
6	2 (4.9)

Type of treatment, adverse effects, and response rate

The mean age of the infants at the time of treatment was 4.9 ± 3 .37 months (range 1-17 months). Nineteen infants were treated with propranolol, and 18 were treated with atenolol. The guardians of 4 patients (9.8%) did not allow treatment. Altogether, 25 infants with hemangiomatous lesions were treated for at least six months. Starting dose for propranolol and atenolol was 0.5 mg/kg/day. The maximum treatment dose for atenolol and propranolol was 2 and 3 mg/kg/day, respectively. The mean duration of treatment was 9.48 months (range 1–20 months), and the mean age of infants at the end of treatment was 16.8 months (range 10–24 months).

Treatment side effects were observed in 41.4% of patients, with none being serious. The most and the least common side effects were non-symptomatic hyperkalemia (13.51%) and cold extremities (2.7%), respectively. We observed more side effects in infants treated with propranolol (26.8%) than atenolol (14.6%). Treatment response was defined as the reduction in the size of the lesions and was categorized into six groups: no response (no change in lesion size), mild response (< 25% reduction in size), moderate (25-49% reduction in size), good (50-75% reduction in size), excellent (> 75% reduction in size), and complete response (100% reduction

in size). Fifteen (60%) percent of the patients had an excellent response, and two patients (8%) had a complete response to treatment with propranolol. A response rate of more than 50% reduction in the size of the lesions was observed in 21 (84%) patients. Six patients had infected lesions that were treated with topical or systemic antibiotics (Table 4).

Iranian maternal and neonatal data

Sex, birth weight, gestational age, abortion rate, and maternal age were collected from Iranian Maternal and Neonatal Network (IMaN Net). The mean age of mothers was 27.7, and a Cesarean section was done in 44% of them. Abortion was recorded in 15.8% of pregnancies. Low birth and very low birth weights were observed in 8.5% and 1.6% of neonates, respectively. The female-to-male ratio of neonates was 0.93. Preterm and very preterm labor were reported in 6.4% and 1.6% of the neonates, respectively.

Table 4. Type of treatment and treatment response rate

Variable	Propranolol n (%)	Atenolol n (%)	*P*-value
Treatment response			
1–24%	1 (7.6)	0 (0)	0.17
25–49%	2 (15.3)	1 (8.3)	
50–74%	3 (23)	3 (25)	
75–99%	5 (38.4)	8 (66.6)	
100%	2 (15.3)	0 (0)	
Adverse effects			
Cough	2 (18.18)	1 (16.66)	0.07
Hypoglycemia	2 (18.18)	0 (0)	
Cold extremity	0 (0)	1 (16.66)	
Diarrhea	1 (9.09)	3 (50)	
Hyperkalemia	5 (45.45)	0 (0)	
Hypotension	1 (9.09)	1 (16.66)	

DISCUSSION

This study described the demographic features of infants with hemangioma treated with systemic therapy in Kerman. In this study, the female-to-male ratio was 2.4 to 1, in compatibility with other studies (2-5 to 1), and was significantly higher than the general female-to-male ratio in the Kerman population (0.93) ($P = 0.04$) [1-5,11,18,23] (Table 5).

Hemangiomatous lesions can be associated with anomalies like PHACES syndrome [1,2]. Our study revealed associated anomalies such as PHACES syndrome, Dandy-Walker syndrome, and cardiac anomalies in 26.9% of infants with a female-to-male ratio of 10 to 1, which is nearly compatible with other studies (7 to 1) [1-4]. In the present study, we had two cases of PHACES syndrome, both having Dandy-Walker malformation. Based on previous studies, this malformation is the most commonly reported structural brain anomaly (43-81%) in PHACES syndrome [21].

In our study, the most common associated anomaly was cardiac problems (17.1%), nearly half (42.5%) of which were ASD. Blei *et al.* reported echocardiographic results of infants with hemangioma who were candidates for treatment with propranolol. They found cardiac structural abnormalities in 21% of patients. Moreover, ASD was the most common cardiac abnormality found in their study (78%), similar to our results [22]. Rates of reported anomalies were higher in our study compared to most other studies. Our survey was carried out only on admitted patients in our center, a referral pediatric dermatology center in southeast Iran; therefore, our survey included more complicated cases. However, most other studies were on either inpatient or outpatient cases; thus, they had

Table 5. Comparison between our results and other studies

Variables	Present study	Bayat [18]	Haggstrom [23]	Munden [5]	Li [11]
Site of the study	Kerman, Iran	USA	USA	USA	China
Number of patients	41	80	1058	29	1832
F/M ratio	2.4:1	1.85:1	2.4:1	1.2:1	1.77:1
Most common site of involvement	Head & neck (82.9%)	Head &neck (58%)	-	Trunk (53%)	Head & neck (69.1)
Preterm	9.7	-	26.1%	25.8	8.7
LBW	21.5	-	18.5	22.3	9.1
Multiple gestation	7.3	14	10.6	10.3	17.2
Positive family history	4.8	-	12.3	-	36.8
Mean age of mother	28.58	-	29.9	-	-
Most common complication of hemangioma	Ulceration (29.3%)	Ulceration (24%)	Ulceration (16%)	-	Ulceration (19.7)

less complicated cases with fewer reported anomalies. Furthermore, cardiac evaluation with echocardiography was performed only in patients suspected of having PHACES syndrome, which explains lower rates of cardiac abnormalities in other studies [5,11,18,22].

In our study, 21.5 % of the cases had a birth weight of less than 2500 g, 22.2% of whom weighed below 1500 g. This means that nearly 1 out of 4 infants with infantile hemangioma had a low birth weight—a significantly greater rate than the general population ($P = 0.006$). In the general population in Kerman, 8.5% of infants have low birth weight (1500–2499 g), and 1.6% have very LBW (< 1500g), in comparison with 16.7% and 4.8% in our study, respectively. Furthermore, in the present study, nearly 10% of the infants were premature (GA < 37 weeks), and 25% of them were very premature (GA < 32 weeks). In the normal population in Kerman, 6.4% of the infants are premature and 1.6% are very premature, which is insignificantly lower than our results ($P = 0.80$). In one prospective study in the USA on 1,058 infants with hemangioma, nearly 20% had GA less than 37 weeks, and 18.5% were born with low birth weight (less than 2500 g) compared with 10% and 21.5% in our study, respectively [4].

In the current study, most mothers were between 20-29 years old (mean age 28.5), and only one person was older than 40. The mean age of mothers in the general population is 27.7 years, representing statistical similarity ($P = 0.91$). More than 25% of mothers had a previous history of abortion, which is significantly more than the general population (15.8%) ($P = 0.0001$). Also, multiple gestations were observed in 7.3% of pregnancies, and a family history of hemangioma was observed in 2.4% of their first relatives. In the study done in the USA, mothers had a mean age of 29.9 years, and 10.6% of pregnancies were multiple gestations, representing similarities to our study. But in contrast to our study, a positive family history of hemangioma was reported at a higher ratio (12.3%) [4].

In the present study, all hemangiomatous lesions appeared in the first three months of birth, and most parents mentioned the appearance of the herald lesions of hemangioma (including telangiectasia, pale-colored or ecchymotic patch) at birth (63.4%). The most common type of hemangioma was superficial (53.7%), located more frequently in the head and neck areas (82.9%), and the distribution pattern of the lesions in the majority of the cases was localized (72.1%). Moreover, 61% of the infants had only 1 lesion, and multiple hemangiomatosis (more than five lesions) was seen in 4.8% of cases. In previous literature, it has been mentioned that approximately 50% of hemangiomas were located on the head and neck, and the superficial type comprised the most common type of hemangioma (50-60%). Also, most superficial hemangiomas were distributed as focal, which is compatible with our results [3-5]. In one study in China in 2017 on 1,832 cases with 3,012 hemangiomatous lesions, 40% of the patients had hemangioma lesions at birth, and the majority of the lesions (82%) were located on periorificial areas of the face (vs. 85.4% in our study) [3].

Hemangioma can lead to complications including ulceration, infection, bleeding, organ dysfunction (heart, liver, thyroid, urogenital), vision loss, and auditory and airway obstruction. In our study, the most common hemangioma complication was ulceration (29.3%), which is compatible with previous studies (24%) [18].

This is the first study in Iran and the third in the world that compares the efficacy of propranolol with atenolol in the treatment of hemangioma. In our study, complete response with propranolol was only seen in two cases (15.3%). The excellent response rate was 38.4% and 66.6% in the propranolol and atenolol groups, respectively, indicating statistical similarity. Adverse effects like hyperkalemia, diarrhea, cough, hypoglycemia, hypotension and cold extremities were reported during treatment in 44.7% of cases, but none were serious. The most common adverse effect was hyperkalemia (13.15%), observed only in the propranolol group. The least common adverse effect was cold extremities/acrocyanosis (2.63%), seen only in the atenolol group. Hypoglycemia was seen only in 5.26% (2 infants) treated with propranolol. Also, the predominant adverse effects in both propranolol and atenolol groups were hyperkalemia (5 out of 18 patients) and gastrointestinal symptoms (3 out of 19 patients). Although adverse effects were observed more frequently in the propranolol group (64.7%) than in the atenolol group (35.2%), this difference did not reach statistical significance ($P = 0.07$).

In one study in the USA on 80 infants with hemangioma (27 treated with atenolol and 53

treated with propranolol), there was no significant difference regarding the efficacy and adverse effects of treatment between these two groups, similar to our results. Adverse effects were seen in 10% of cases (13% in the propranolol group and 4% in the atenolol group) and included diarrhea (one patient in each group), acrocyanosis (1 out of 27 patients in the atenolol group) and respiratory symptoms (wheezing/reactive airway disease in 6 out of 53 patients in the propranolol group) [18]. In contrast with the USA study, in our study, diarrhea was seen more in the atenolol group (3 out of 19 patients) than in the propranolol group (1 out of 18 patients). Also, respiratory symptoms in our study presented as a cough and were more prevalent in the propranolol group than in the atenolol group. However, similar to the USA study, we found acrocyanosis only in 1 patient in the atenolol group.

In one study in Chile in 2014 on 23 infants with hemangioma, 53.8% and 60% of the patients had complete clearance with atenolol and propranolol, respectively. Also, in that study, 40% and 46.1% of the patients showed partial response (any reduction in size, color, or consistency of the lesion) [19]. In our study, partial response in atenolol and propranolol was 99.9% and 84.3%, respectively, which is higher than in the Chile study. However, the complete response rate in our study was lower than in the Chile study (15.3%). This can be because of the difference between the type and size of the lesions. In another study in 2015 on 635 infants treated with propranolol, 91.2% of infants experienced a reduction of more than 25% in the size of hemangioma (vs. 92% in our study), which is similar to our study [20]. Also, in their study, the rate of excellent, good, and fair responses was 37.8%, 27.8%, and 25.5% (vs. 38.4%, 23%, and 15.3% in our study), respectively.

CONCLUSION

In our study, female gender and low birth weight were significantly more common in infants with hemangioma than in the normal population. Also, mothers of children with hemangioma had a significantly greater number of miscarriages than the normal population. There was no significant difference between atenolol and propranolol regarding the efficacy and adverse effects when used to treat infantile hemangiomas.

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Authors' contributions

S.F., M. Kh. contributed to the study conception and design. Material preparation and data collection were performed by S.F, S.M, M. A, R.A., Z.H. and M.Kh. The acquisition, analysis and interpretation of data for the work were performed by S.F. M.Kh and M.A. The first draft of the manuscript was written by M.A. and M.Kh. All authors revised the final version of the manuscript.

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