Medicine®

OBSERVATIONAL STUDY

OPEN

Clinical Characteristics and Treatment Options of Infantile Vascular Anomalies

Bin Yang, MD, Li Li, MD, Li-xin Zhang, MD, Yu-juan Sun, MD, and Lin Ma, MD, PhD

Abstract: To analyze the clinical characteristics and treatment outcomes of vascular anomalies, and determine which therapy is safe and effective.

The data of vascular anomalies pediatric patients who arrived at Beijing children's Hospital from January 2001 to December 2014 were analyzed retrospectively, including the influence of gender, age, clinical manifestation, diagnosis, treatment options, and outcomes. As to infantile hemangiomas, the outcomes of different treatments and their adverse reactions were compared. As to spider angioma and cutaneous capillary malformation, the treatment effect of 595 nm pulsed dye laser (PDL) is analyzed.

A total number of 6459 cases of vascular anomalies were reclassified according to the 2014 ISSVA classification system. Among them, the gender ratio is 1:1.69, head-and-neck involved is 53.3%, the onset age within the first month is 72.4%, the age of initial encounter that younger than 6 months is 60.1%. The most common anomalies were infantile hemangiomas (42.6%), congenital hemangiomas (14.1%), and capillary malformations (29.9%). In treating infantile hemangiomas, laser shows the lowest adverse reactions rate significantly. Propranolol shows a higher improvement rate than laser, glucocorticoids, glucocorticoids plus laser, and shows no significant difference with propranolol plus laser both in improvement rate and adverse reactions rate. The total improvement rate of 595 nm PDL is 89.8% in treating spider angioma and 46.7% in treating cutaneous capillary malformation. The improvement rate and excellent rate of laser in treating cutaneous capillary malformation are growing synchronously by increasing the treatment times, and shows no significant difference among different parts of lesion that located in a body.

Vascular anomalies possess a female predominance, and are mostly occurred in faces. Definite diagnosis is very important before treatment. In treating infantile hemangioma, propranolol is recommended as the first-line agent, and systemic use glucocorticoids should be considered when associated with serious complications. The 595 nm PDL is effective in managing superficial vascular malformations in childhood, and could attempt to increase the treatment times to improve the outcomes.

(*Medicine* 94(40):e1717)

Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, ISSVA = International Society for the Study of Vascular Anomalies, MRI = magnetic resonance imaging, Nd:YAG = neodymium-doped yttrium aluminum garnet, NICH = noninvoluting congenital hemangiomas, PDL = pulsed dye laser, PICH = partially involuting congenital hemangiomas, RICH = rapidly involuting congenital hemangiomas.

INTRODUCTION

Congenital lesions of abnormal vascular development are fairly common soft-tissue disorder in pediatric clinics. Traditionally, those anomalies were all considered as tumors until 1982, when a new classification system was created.[1] According to the classification system, vascular anomalies were divided into tumors and malformations based on their histology, biological behavior, and clinical presentation. This classification was soon adopted by the International Society for the Study of Vascular Anomalies (ISSVA).[2] The main distinction between vascular tumors and vascular malformations is that vascular tumors grew with cellular hyperplasia, but vascular malformations only represented a localized defect in vascular morphogenesis. At the 2014 ISSVA workshop in Melbourne, vascular anomalies were still divided into tumors and malformations as before. Furthermore, the new version was expanded, provided much greater details, and incorporated clinical associations.[3] Vascular tumors are subdivided into benign, locally aggressive or borderline, and malignant entities. The classic representatives of vascular tumors are infantile hemangiomas, which are further subdivided into patterns and different types. Noninvoluting (NICH) and partially involuting (PICH) were included in the congenital hemangioma. Pyogenic granulomas and other rare vascular tumors are also included in this category. Vascular malformations are subdivided into 4 main categories (simple, combined, of major named vessels, associated with other anomalies), based on the vessel types that are involved and the morphology of the affected area of the vascular system.[4] The lesions of vascular malformations usually present at birth, continue to expand over time, and sometimes, accompanied with other anomalies, such as soft tissue overgrowth, mucosal or ocular anomalies, etc.[5] The most common seen vascular malformations manifested as cutaneous capillary malformation (also known as port-wine stain) or telangiectasia. New data including causal genetic findings linked to the etiology of some identified vascular anomalies and syndromes were updated.

Most vascular tumors and malformations can be diagnosed clinically based on the lesion appearance. As to complicated cases, biopsy pathology and imaging examination such as magnetic resonance imaging (MRI) and ultrasound can be helpful to differentiate and confirmed the diagnosed. Though most cases are benign process and some of them have a spontaneous involution over their lifecycle, vascular anomalies can cause many functional complications. So, infants with

Editor: Sergio Gonzalez Bombardiere.
Received: July 2, 2015; revised: September 8, 2015; accepted: September 10, 2015.
From Department of Dermatology, Beijing Children's Hospital, Capital Medical University, Beijing, China (BY, LL, L-xZ, Y-jS, LM)
Correspondence: Lin Ma, Department of Dermatology, Beijing Children's Hospital, Capital Medical University, No. 56, Nan Lishi Road, Xicheng District, Beijing 100045, China (e-mail: bch_maleen@aliyun.com, rougerose@163.com)
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001717

vascular anomalies usually grow up with morbidity, cosmetic disfigurement or psychological disorder, such as social impairment, communication deficits, and social disability. Therefore, parents usually search for therapeutic methods anxiously. In serious cases, vascular anomalies may cause difficulty in feeding, ulceration, vision loss, airway compromise, disabled, or even death. Various therapeutic approaches had been described, proposed and applied to treat vascular anomalies,[6] including wait-and-see principle, laser therapy,[7] drug therapy (glucocorticoid, interferon, vincristine, imiquimod),[8] sclerotherapy (corticosteroid, bleomycin), radiotherapy, plastic surgery,[9] constraint treatment, etc., or a combination of these modalities. The 595 nm pulsed dye laser (PDL) was once commonly considered as the primary choice for vascular anomalies in pediatric patients,[10] and had performed for a long period.[11] In 2008, a serendipitous discovery was reported that propranolol can inhibit the growth of severe hemangiomas.[12] Since then, application of propranolol in treating infantile hemangiomas has rapidly spread across the world, and has greatly improved the cosmetic outcomes of hemangiomas.[13] However, an ideal option for all vascular anomalies was not exist.

The aim of this study was to analyze and compare retrospectively the clinical characteristics and treatment options of vascular anomalies, and determine which therapy is safe and effective.

METHODS

Patients and Clinical Characteristics

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our hospital. Because of the retrospective nature of the study, patients consent for inclusion in this study was waived.

Children with vascular anomalies who arrived at Beijing children's Hospital from January 2001 to December 2014 were reclassified according to the 2014 new ISSVA classification. The clinical data of those pediatric patients were analyzed retrospectively, including their clinical characteristics, laboratory examinations, diagnoses, treatments, etc., in order to investigate the influence of gender, age, presence, and treatment options. As a general pediatric dermatology clinical, we do not treat acquired immunodeficiency syndrome (AIDS), so children infected with human immunodeficiency virus (HIV) and manifested as Kaposi sarcomas were not included in this study.

Treatment Protocols

For infantile hemangiomas, doses of glucocorticoids (prednisone) were 1 to 3 mg/(kg day), and doses of propranolol were 1 to 2 mg/(kg day), which is gradually increased or decreased according to the change of baby weights and outcomes of follow-up. For full-term infants, the optimum time of start to prescribe propranolol is after the first month. Preterm and low birth weight infants should start a little later, at least after baby weight reached 2500 g. The full course of oral propranolol should cover the whole rapid growth stage, last at least 6 months, until the lesion shrank or showed good cosmetic result.

The treatment parameter of PDL (Vbeam, Candela, USA) was set as follows: wavelength 595 nm, pulse width 0.45 to 40 milliseconds, fluence density 7 to 40 J/cm^2, spot size 7 mm, frequency 1.5 Hz. Parameters were adjusted based on age, conditions of lesion (color, size, thickness, texture, volume), outcomes of the previous treatment, demands of parents, and other influencing factors. The commonly used parameters are: pulse width 3 to 20 milliseconds, fluence density 9 to 13 J/cm^2. The optimum time of start treatment is after the first month, no matter preterm or not. The treatment-free interval was at least 4 weeks, and within this time frame, moisturizer, and sunscreen cream should be used all through.

Treatment Outcomes

Patients were divided into separate groups according to their treatment methods. As to infantile hemangiomas, the outcomes of each patient were evaluated based on improvement of volume, color, and texture, judged by the following scale[14]: poor (proliferated, or no further growth, or intolerable adverse effects, or 0 to 25% reduction in volume); fair (26–50% reduction in volume); good (51–75% reduction in volume); and excellent (76–100% reduction in volume). Reduction more than 51% in volume (good and excellent) is considered improved, and the improvement rates were calculated and compared. Besides, the thickness of hemangioma was rechecked by color Doppler ultrasound, and these changes were also considered and included in the evaluation system. As to cutaneous capillary malformation, similar evaluation system was implemented, and the outcomes of each patient were evaluated based on improvement of erythema faded rates, judged by the following scale: poor (continued expanded, or no further expanded, or intolerable adverse effects, or 0–25% fading in size); fair (26–50% fading in size); good (51–75% fading in size); and excellent (76–100% fading in size). Reduction more than 51% in size (good and excellent) is considered improved, and the improvement rates were calculated and compared. The satisfaction and approval of parents was also an essential factor to be considered. The evaluation of efficacy was performed by 2 unrelated dermatologists who did not involve in the treatment process. Adverse reactions of each different therapy methods were also recorded and compared.

Statistical Analysis

The Statistical Package for the Social Science (SPSS, Inc., Chicago, IL), version 21, was used for descriptive statistics. Crossovers were evaluated for significance using Pearson's Chi-square (χ^2) tests, or Fisher exact test if needed. Significance was set at P less than 0.05.

RESULTS

General Information

From January 2001 to December 2014, there were a total number of 6459 pediatric patients with vascular anomalies arrived at Beijing children's Hospital. The most common anomalies were infantile hemangioma (42.6%, 2752/6459), congenital hemangioma (14.1%, 910/6459), and capillary malformations (29.9%, 1933/6459), which included spider angioma (14.0%, 907/6459) and cutaneous capillary malformation (12.3%, 796/6459) (Table 1, Figure 1).

The gender ratio was 1:1.69 in total, 1:1.86 in tumors, 1:1.47 in malformations, shows vascular anomalies with a female predominance.

Clinical Characteristics

Among 6459 pediatric patients, 53.3% involved head-and-neck (3443 cases), followed by multiple lesions, upper limbs, lower limbs, and chest. In infantile hemangioma alone, 57.7% involved head-and-neck (Table 2). The lesions in Kasabach–

TABLE 1. General Information About All of the Vascular Anomalies Children

	Cases (n)				Gender		
					Male (n)	Female (n)	Ratio
Vascular tumors	3904				1365	2539	1:1.86
Benign		3881			1353	2528	1:1.87
Infantile hemangioma			2752		925	1827	1:1.82
Congenital hemangioma			910		323	587	1:1.51
Rapidly involuting (RICH)				863	289	574	1:1.99
Noninvoluting (NICH)				41	29	12	1:0.41
Partially involuting (PICH)				6	5	1	1:0.20
Kasabach–Merritt syndrome			68		37	31	1:0.84
Pyogenic granuloma			147		66	81	1:1.23
Others			4		2	2	–
Locally aggressive or borderline*		23			12	11	1:0.92
Kaposiform hemangioendothelioma			21		10	11	1:1.1
Dabska tumor			2		2	–	–
Malignant		0			–	–	–
Vascular malformations	2544				1028	1516	1:1.47
Simple		2213			856	1357	1:1.58
Capillary malformations (CM)			1933		706	1227	1:1.74
cutaneous capillary malformation				796	340	456	1:1.34
Telangiectasia				1071	362	709	1:1.96
Spider angioma (nevus araneus)				907	269	638	1:2.37
Generalized essential telangiectasia				15	4	11	1:2.75
Hereditary hemorrhagic telangiectasia				2	2	0	–
Others				147	87	60	1:0.69
Cutis marmorata telangiectasia congenital				9	4	5	1:1.25
Others				57	22	35	1:1.59
Lymphatic malformations (LM)			33		21	12	1:0.57
Venous malformations (VM)			226		121	105	1:0.87
Arteriovenous malformations (AVM)			15		6	9	1:1.50
Arteriovenous fistulas (AVF)			6		2	4	1:2.00
Combined		205			88	117	1:1.33
Capillary–venous malformation			114		48	66	1:1.38
Capillary–lymphatic malformation			27		12	15	1:1.25
Lymphatic–venous malformation			43		17	26	1:1.53
Other			21		11	10	1:0.91
Associated with other anomalies		126			84	42	1:0.50
Klippel–Trenaunay syndrome			82		64	18	1:0.28
Sturge–Weber syndrome			31		14	17	1:1.21
Other			13		6	7	1:1.17
Provisionally unclassified	11				9	2	1:0.22
Verrucous hemangioma		2			2	–	–
Angiokeratoma		8			6	2	1:0.33
Kaposiform lymphangiomatosis		1			1	–	–
Total	6459				2402	4057	1:1.69

* Children infected with HIV and manifested as Kaposi sarcomas were not included.

Merritt syndrome were mainly located in lower limbs, shared 45.6% (31/68, in Table 2, 38 limbs included 7 upper limbs).

The onset age within the first month is 72.4% in total cases (4678/6459). The rate of born with anomalies is 100% (910/910) in congenital hemangioma, 77.9% (53/68) in Kasabach–Merritt syndrome, 88.0% (1702/1933) in capillary malformations, 51.5% (17/33) in lymphatic malformations, 62.4% (141/226) in venous malformations.

The age of initial encounter that younger than 6 months is 60.1% in total cases (3884/6459), 64.6% in infantile hemangioma (1778/2752), 97.9% in congenital hemangioma (891/910), 98.5% in Kasabach–Merritt syndrome (67/68), but broadly dispersed in vascular malformations.

Treatment Options

Before 2008, glucocorticoids and laser therapy was the most common management used for treating vascular anomalies. Interferon, vincristine, imoquimod, sclerotherapy, radiotherapy, plastic surgery, constraint treatment were also performed in some cases according to specific conditions. Since 2008, patients treated by propranolol increased year by year. Some cautious parents, concerned about side effects deeply, full

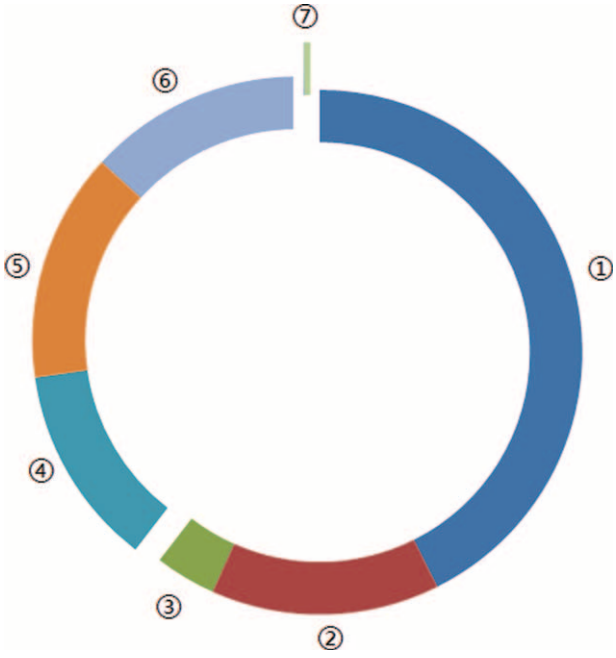

FIGURE 1. Components of vascular anomalies in 6459 patients. Vascular tumors 60.4%. Vascular malformations 39.4%. (1) Infantile hemangiomas 42.6%. (2) Congenital hemangiomas 14.1%. (3) Other vascular tumors 3.7%. (4) Cutaneous capillary malformations 12.3%. (5) Spider angiomas 14.0%. (6) Other vascular malformations 13.0%. (7) Provisionally unclassified vascular anomalies 0.2%.

of worries about continuous administrating, chose wait-and-see principle. Some parents suspected the effect of propranolol, and still prefer to traditional glucocorticoids and laser therapy. So, among 2752 infantile hemangiomas patients, 20.9% treated with glucocorticoids (including intralesional injection and systemic use), 34.2% with laser, 11.3% with glucocorticoids plus laser, 16.8% with propranolol (including topical application), 2.4% with propranolol plus laser, 7.6% with other treatments, and 6.8% untreated (Table 3).

For congenital hemangiomas, especially those rapidly involuting congenital hemangiomas (RICH), wait-and-see principle was the first option. For noninvoluting congenital hemangiomas (NICH) and partially involuting congenital hemangiomas (PICH), laser and plastic surgery was usually performed. So among 910 congenital hemangiomas patients, 59.8% (544/910) was just followed up and waited, 35.4% (322/910) was treated with laser, 4.2% (38/910) with plastic surgery, and 0.7% (6/910) with other treatments.

On account of thrombocytopenia, 85.3% of Kasabach–Merritt syndrome (58/68) turned to glucocorticoids systemic use. For pyogenic granuloma, 42.1% (62/147) chose laser, and 37.1% (55/147) chose surgery.

As for vascular malformations, laser is effective in helping to fade the superficial erythema. So, in spider angioma (nevus araneus), the most common vascular malformations seen in outpatient, 82.0% (744/907) turn to laser treatment, and in cutaneous capillary malformation, the rate is 78.3% (623/796). As to other vascular malformations, treatment methods included sclerotherapy (corticosteroid, bleomycin), radiotherapy, plastic surgery, constraint treatment, etc., or a combination of these modalities (Table 4).

TABLE 2. Characteristics About Children With Vascular Tumors

	Cases (n)	Location (n, %)				Size (n, %)			Ages of Initial Encounter (n, %)			
		Head-and-Neck	Trunk	Limbs	Multiple	$\leq 10\,cm^2$	$10–30\,cm^2$	$>30\,cm^2$	≤1 Month	1–6 Months	6–12 Months	>12 Months
Infantile hemangioma	2752	1588 (57.7%)	582 (21.1%)	305 (11.1%)	277 (10.1%)	1928 (70.4%)	586 (21.3%)	238 (8.3%)	390 (14.2%)	1388 (50.4%)	642 (23.3%)	332 (12.1%)
Congenital hemangioma	910	348 (38.2%)	202 (22.2%)	255 (28.0%)	105 (11.5%)	380 (41.8%)	438 (48.1%)	92 (10.1%)	726 (79.8%)	165 (18.1%)	19 (2.1%)	–
Kasabach–Merritt syndrome	68	6 (8.8%)	16 (23.5%)	38 (55.9%)	8 (11.8%)	0 (0%)	16 (23.5%)	52 (76.5%)	45 (66.2%)	22 (32.4%)	1 (1.5%)	–

TABLE 3. Effects of Different Treatments on Infantile Hemangioma (Total: 2752)

	Cases (n)	Mean Duration of Treatment (Months)	Efficient Cases (n)	Ineffective Cases (n)	Improvement Rate (%)*	Adverse Reactions (n, %)	
Glucocorticoids (including intralesional injection and systemic use)	574	10	309	265	53.8	325	56.6%
Laser	942	6	609	333	64.6	28	3.0%
Glucocorticoids + laser	311	6	172	139	55.3	157	50.5%
Propranolol (including topical application)	462	8	416	46	90.0	55	11.9%
Propranolol + laser	67	6	64	3	95.5	9	13.4%
Other treatments	208	–	–	–	–	–	
Untreated or loss of follow-up	188	–	–	–	–	–	

* Improved more than 50% are considered as efficient. Improvement rate (%) = efficient cases (n)/cases of that row (n).

Treatment Outcomes

As to infantile hemangiomas, the effect of different treatments shows significant difference across the 5 groups ($P < 0.05$). Through multiple comparisons (significance was set at P' less than 0.005 here, $P' = P/10$), there is no significant difference between the propranolol group and the propranolol plus laser group ($P' = 0.148$), no significant difference between the glucocorticoids group and the glucocorticoids plus laser group ($P' = 0.675$). But there is significant differences between other multiple compared groups ($P' < 0.005$). Briefly, propranolol (90.0%) and propranolol plus laser (95.5%) shows no significant difference, and the 2 methods each shows better effect compared with laser (64.6%), laser plus glucocorticoids (55.3%), glucocorticoids alone (53.8%) (Table 3, Table 5).

Adverse reactions of glucocorticoid included central obesity, hirsutism, blood glucose risen, muscle wasting, infection, hypertension, etc. Adverse reactions of laser included erythema, postinflammatory hyperpigmentation, infection, cicatrix, acneiform eruption, etc. Adverse reactions of propranolol included diastolic blood pressure fallen, sleep disorder, mild diarrhea, hypoglycemia, cold extremities, bronchial hyperreactivity, elevated alanine transaminase/aspartate aminotransferase or creatine kinase isoenzyme, etc.[15,16] The adverse reactions of different treatments shows significant difference across the 5 groups ($P < 0.05$). Through multiple comparisons, there is no significant difference between the glucocorticoids group and the glucocorticoids plus laser group ($P' = 0.08$), no significant difference between the propranolol group and the propranolol plus laser group ($P' = 0.72$). But there is significant differences between other multiple compared groups ($P' < 0.005$). Briefly, laser (3.0%) shows significant the lowest adverse reactions than all the other 4 groups. Propranolol (11.9%) and propranolol plus laser (13.4%) show no significant difference, and each of them shows significant lower adverse reactions than the glucocorticoids group and laser plus glucocorticoids group. Glucocorticoids (56.6%) and laser plus glucocorticoids (50.5%) show no significant difference (Table 3, Table 5).

In treating spider angioma, the improvement rate of laser is 89.4% in a single time of treatment, and 91.0% in twice, 88.4% in 3 times of treatment (Table 6). By increasing of treatment times, the improvement rate shows no significant difference ($\chi^2 = 0.515$, $P = 0.773$). In treating cutaneous capillary malformation, according to the difference of treatment times, the curative effect of laser shows significant difference both in improvement rate ($\chi^2 = 162.4$, $P < 0.001$) and in excellent rate ($\chi^2 = 70.985$, $P < 0.001$), but the adverse reactions rate ($\chi^2 = 9.000$, $P = 0.109$) shows no significant difference

TABLE 4. The Treatment Options of Vascular Malformations (Total: 2544)

		Laser	Sclerotherapy	Plastic Surgery	Other Treatment	Untreated or Loss of Follow-Up
Spider angioma (nevus araneus)	907	744	–	–	–	163
Cutaneous capillary malformation	796	623	–	–	18	155
Other capillary malformations	230	56	11	15	33	115
Lymphatic malformations	33	–	–	19	–	14
Venous malformations	226	–	21	79	93	33
Arteriovenous malformations	15	–	2	7	5	1
Arteriovenous fistulas	6	–	–	4	–	2
Combined vascular malformations	205	44	31	53	22	55
Vascular malformations associated with other anomalies	126	36	25	16	44	5

TABLE 5. Comparison of Different Treatments on Infantile Hemangioma (Total: 2752)

	Effective Rate				Adverse Reactions			
			Fisher Exact Test				Fisher Exact Test	
	χ^2	P'	Exact Sig. (2-Sided)	Exact Sig. (1-Sided)	χ^2	P'	Exact Sig. (2-Sided)	Exact Sig. (1-Sided)
G vs. L	17.47	<0.005	<0.005	<0.005	574.7	<0.005	<0.005	<0.005
G vs. Prol	159.8	<0.005	<0.005	<0.005	220.4	<0.005	<0.005	<0.005
G vs. G + L	0.176	0.675	0.724	0.364	3.06	0.080	0.090	0.047
G vs. Prol + L	42.86	<0.005	<0.005	<0.005	44.81	<0.005	<0.005	<0.005
Prol vs. L	101.4	<0.005	<0.005	<0.005	44.46	<0.005	<0.005	<0.005
Prol vs. G + L	123.2	<0.005	<0.005	<0.005	139.0	<0.005	<0.005	<0.005
Prol vs. Prol + L	2.09	0.148	0.180	0.105	0.13	0.720	0.690	0.423
L vs. G + L	8.69	0.003	0.004	0.002	419.4	<0.005	<0.005	<0.005
L vs. Prol + L	26.84	<0.005	<0.005	<0.005	19.38	<0.005	<0.005	<0.005
Prol + L vs. G + L	38.01	<0.005	<0.005	<0.005	30.72	<0.005	<0.005	<0.005

G = glucocorticoids (including intralesional injection and systemic use), G + L = glucocorticoids + laser, L = laser, P + L = propranolol + laser, Prol = propranolol (including topical application).

(Table 7, patients who received more than 6 times of PDL treatments were merge into 1 group as their numbers are few). Through linear regression analysis and Spearman rank correlation analysis, there is a positive correlation relationship between treatment times and improvement rate ($F = 70.253$, $P = 0.001$), and also a positive correlation relationship between treatment times and excellent rate ($F = 109.807$, $P < 0.001$) (Figure 2). As to the lesion that located in different parts, the effect of PDL shows no significant difference in improvement rate ($\chi^2 = 10.004$, $P = 0.075$) and in excellent rate ($\chi^2 = 8.607$, $P = 0.126$), and the adverse reactions rate ($\chi^2 = 1.862$, $P = 0.868$) shows no significant difference either (Table 8).

DISCUSSION

General Information

Among all the vascular anomalies children, infantile hemangiomas, capillary malformations, and congenital hemangiomas were the most common anomalies, and show a female predominance. The gender ratio of infantile hemangiomas (1:1.82), congenital hemangiomas (1:1.51), vascular malformations (1:1.47) are all different from previous data (which showed the gender ratio of infantile hemangiomas is 1:3–6, congenital hemangiomas and vascular malformations occur with equal frequency in males and females).[17,18]

Clinical Characteristics

The lesions occurred on head-and-neck in more than half pediatric patients, displayed an interesting anatomical predilections.[3,19] From another point of view, head-and-neck involved spoiled appearances, so parents tempted to intensive or even aggressive medical treatment, but other parts of body involved usually be underappreciated by parents, and lead to a lower visitation rates. The lesions in Kasabach–Merritt syndrome were mainly located in lower limbs, maybe associated with a poor distal extremity and peripheral circulation.

In hemangiomas, no matter infantile, congenital, or Kasabach–Merritt syndrome, the age of initial encounter is focused on less than 6 months. But in vascular malformations, the age of initial encounter is very scattered. This may be because hemangiomas grow rapidly (infantile hemangiomas) or manifest fully developed at birth (congenital hemangiomas), but most vascular malformations grow slowly and steadily, or even unchanged at the initial stage.

In capillary malformations, the onset age is usually within the first month (88%), but in lymphatic malformations and venous malformations, the onset age is often after the first month. The reason may be partly because the lesions of capillary malformations is reddish or dark red patches on the surface of skin, and easy to noticed by scrupulous parents. As for other malformations, the lesions usually the same color as

TABLE 6. Number of Treatment Times and the Effect of Pulsed Dye Laser in Treating Spider Angioma

Number of Treatments (Times)	Cases (n)	Efficient Cases (n)	Ineffective Cases (n)	Improvement Rate (%)*
1	490	438	52	89.4
2	211	192	19	91.0
≥3	43	38	5	88.4
Total	744	668	76	89.8

* Erythema faded more than 50% are considered as improvement. Improvement rate (%) = excellent cases (n) + good cases (n)/cases of that row (n).

TABLE 7. Number of Treatment Times and the Effect of Pulsed Dye Laser in Treating Cutaneous Capillary Malformation

Number of Treatments (Times)	Cases (n)	Excellent (n, %)	Good (n, %)		Fair (n, %)		Poor (n, %)		Improvement Rate (%)*		Adverse Reactions (n, %)	
1	88	0	–	2	2.3%	35	39.8%	51	58.0%	2.3%	3	3.4%
2	197	11	5.6%	53	26.9%	58	29.4%	75	38.1%	32.5%	2	1.0%
3	138	24	17.4%	52	37.7%	24	17.4%	38	27.5%	55.1%	0	–
4	65	14	21.5%	24	36.9%	11	16.9%	16	24.6%	58.5%	3	4.6%
5	94	26	27.7%	49	52.1%	16	17.0%	3	3.2%	79.8%	2	2.1%
≥6	41	18	43.9%	18	43.9%	3	7.3%	2	4.9%	87.8%	2	4.9%
Total	623	93	14.9%	198	31.8%	147	23.6%	185	29.7%	46.7%	12	1.9%

* Erythema faded more than 50% are considered as improvement. Improvement rate (%) = excellent cases (n) + good cases (n)/cases of that row (n).

skin, and occurred deep under the skin, caused an overlook in early stages by those thoughtless parents.

Treatment Options and Outcomes

Unless accompanied with serious complications, vascular anomalies are usually benign disorder and not life-threatening. The biggest influence of them is just cosmetic problems. Therefore, it is very essential to strike a balance during the process of treatment, and to prevent performing excessively radical treatments. In some cases, the psychology of parents should also be considered.

The treatment of vascular tumors or vascular malformations is differently nowadays. So, before treatment, the first principle that should be followed is to differentiate and

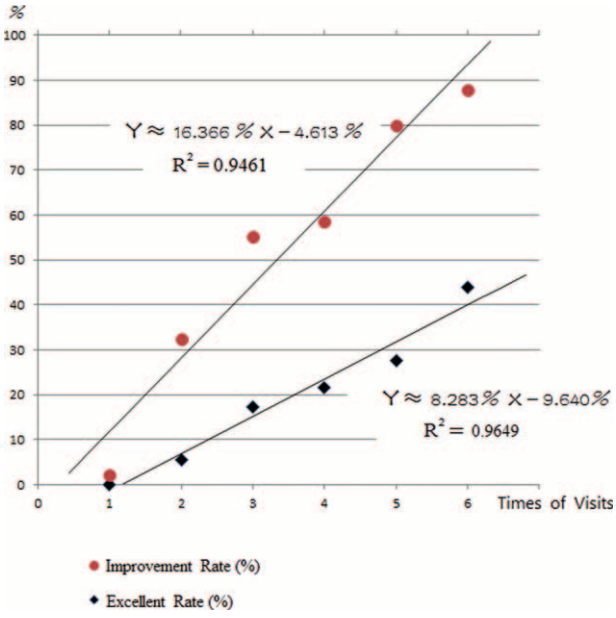

FIGURE 2. Effect of pulsed dye laser in treating cutaneous capillary malformation, with different treatment times. With the increase of treatment times, improvement rate and excellent rate are growing synchronously. Through linear regression analysis and Spearman rank correlation analysis, there is a positive correlation relationship between treatment times and improvement rate ($F = 70.253$, $P = 0.001$), and also a positive correlation relationship between treatment times and excellent rate ($F = 109.807$, $P < 0.001$).

diagnostic the lesion clearly and definitely, especially in those infants with complex anomalies or syndromes.[20]

In treating infantile hemangiomas, numerous treatment options are available, but deciding which modality to pursue is dependent on a detailed and accurate assessment of the disease process. Historically, laser is once widespread used to treat various vascular anomalies, as a main approach or as an adjunctive therapy. In our study, PDL is effective in treating infantile hemangiomas indeed,[21] and even, its improvement rate (64.6%) is high than cutaneous capillary malformation (46.7%). But compared with propranolol, PDL has a lower improvement rate and excellent rate.[22] Thus the role of PDL could not be overstated. The improvement rate of PDL combination with propranolol, when compared with propranolol, shows no significant difference. Meanwhile, the adverse reactions rate shows no significant difference either. So, in our experience, oral propranolol should the first-line therapy in treating infantile hemangiomas, and PDL could be recommended to use in superficial lesion of hemangiomas as an adjuvant therapy in order to promote involution.[23,24] Besides, topical application of β-adrenoceptor blocker (β-adrenoceptor antagonist) is also a preferred option for some superficial lesions,[25,26] but the effect of topically external use of β-adrenoceptor blocker (different drugs, different preparation, and different dosage regimen, such as ointment, gel, membrane, sustained-release reagent, etc.) compare to oral propranolol in treating infantile hemangiomas with different types (superficial, deep, mixed) are still needed to be further discussed. The expectation of intensive treatment was associated with serious complications (such as thrombocytopenia in Kasabach–Merritt syndrome) or lesions located in particular region (such as eyelid, orbit, nasal cavity, pharynx, larynx, perineum), which could cause destructive dysfunction or even life-threatening symptoms. In such circumstances, systemic glucocorticoids should be considered.

Vascular malformations are not unusual anomalies, shared nearly 40% in total cases. They are diverse variety disorders, and their clinical presentation is not only just vascular structural abnormalities, but also more frequently complicated with vascular function abnormalities, and sometimes associated with other anomalies. Treatment options are relatively few. As for spider angioma and cutaneous capillary malformation, the most common vascular malformations in pediatric clinic, laser is a less invasive approach, and could been used to handle the lesions.[27,28] For superficial lesions, 595 nm PDL is very sensitive and effective, and for deep lesions, 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is available for alternative. Unlike adult, the lesions of infants are much

TABLE 8. Effect of Pulsed Dye Laser in Treating Different Areas of Cutaneous Capillary Malformation

Locations		Cases (n)	Excellent (n, %)		Good (n, %)		Fair (n, %)		Poor (n, %)		Improvement Rate (%)*	Adverse Reactions (n, %)	
Glabella		104	8	7.7%	36	34.6%	17	16.3%	43	41.3%	32.7	2	1.9%
Scalp		35	3	8.6%	7	20.0%	8	22.9%	17	48.6%	28.6	0	–
Trigeminal nerve	V1	181	26	14.4%	70	38.7%	38	21.0%	47	26.0%	53.0	5	2.4%
	V2	184	35	19.0%	46	25.0%	57	31.0%	46	25.0%	42.9	3	1.6%
	V3	98	17	17.3%	31	31.6%	21	21.4%	29	30.0%	49.0	2	2.0%
Other parts		21	4	19.0%	8	38.1%	6	28.6%	3	14.3%	57.1	0	–
Total		623	93	14.9%	198	31.8%	147	23.6%	185	29.7%	46.7	12	1.9%

* Erythema faded more than 50% are considered as improvement. Improvement rate (%) = excellent cases (n) + good cases (n)/cases of that row (n).

shallower and smaller, so PDL is enough in handling most regular vascular malformations. Even so, the effect of laser with different wavelength (532, 577, 585, 595, 1064 nm, etc.) in treating various capillary malformations in children among different age groups are still needed to be further discussed.

The most common vascular malformation is spider angioma, a subclass of telangiectasia, which may be related to the infection of hepatitis B in some cases. So, child with spider angioma child are usually suggested to make an appointment with physicians and begin antiviral therapy if necessary. As to the superficial lesion, laser is effective in helping to fade the erythema and to make a cosmetic improvement.

As shown in our study, the improvement rate (46.7%) and excellent rate (14.9%) of PDL in treating cutaneous capillary malformation is relatively lower in infants than in older children or adults. The reason account for this discrepancy may be partly related to the treatment times. Nearly half of the infants (45.7%, 285 infants) received no more than twice treatments, shows a low improvement rate (23.2%), but with the increase of treatment times, improvement rate and excellent rate are growing synchronously (Figure 2). For those infants who received more than 5 times of treatment (21.7%, 135 infants), the improvement rate is 82.2%, which is much close to the datum of adult. So, if the PDL treatment remain acceptable and withstand in patients and their families, we suggest adopting a measures of increasing treatment times in order to improve outcomes. For some less efficacious hypertrophic or profundus cutaneous capillary malformation, long-pulsed 1064 nm ND:YAG laser[29] or topical application of rapamycin[30] can be try with cautious, but further research is needed to better understand the best treatment for these complicated presentations.

As to other vascular malformations, selective operation could be performed to correct complex deformities.[31] For lymphatic malformations, oral sildenafil may be a new approach.[32,33] Propranolol is not appropriate for venous malformations, arteriovenous malformations, and arteriovenous fistula, as it only achieved a light improvement initially in single cases. Further therapeutics, such as vincristin, marmistat, are still underway, as them either undertaking a significant risk with questionable success or only applied in older children before. In summary, it can be stated that small and unifocal malformations usually can be treated curatively, but combined, associated with other anomalies, diffuse, multifocal malformations are a major therapeutic challenge, and often bear the high risk of recurrence and progression.[20]

CONCLUSIONS

Infantile hemangiomas, capillary malformations, and congenital hemangiomas were the most common vascular anomalies, which possess a female predominance, and are more inclined to occur in head and neck areas. Before treatment, the first principle that should be followed is to diagnostic clear, especially in those infants with complex anomalies, mixed tumor, tumor accompanied malformations, or multisystem syndromes. Pathological examination can be helpful to differentiate and confirmed the diagnosed in those complicated cases. Propranolol is recommended as the first-line agent in treating infantile hemangiomas, when associated with serious complications, systemic use glucocorticoids should be considered. The 595 nm PDL is effective in managing superficial vascular malformations in childhood, and could attempt to increase the treatment times to improve the outcomes.

REFERENCES

1. Dasgupta R, Fishman SJ. ISSVA classification. *Semin Pediatr Surg.* 2014;23:158–161.
2. George A, Mani V, Noufal A. Update on the classification of hemangioma. *J Oral Maxillofac Pathol.* 2014;18:S117–S120.
3. Nosher JL, Murillo PG, Liszewski M, et al. Vascular anomalies: a pictorial review of nomenclature, diagnosis and treatment. *World J Radiol.* 2014;28:677–692.
4. Masand P. Radiographic findings associated with vascular anomalies. *Semin Plast Surg.* 2014;28:69–78.
5. Blei F. Overgrowth syndromes with vascular anomalies. *Curr Probl Pediatr Adolesc Health Care.* 2015;45:118–131.
6. Wójcicki P, Wójcicka K. Epidemiology, diagnostics and treatment of vascular tumours and malformations. *Adv Clin Exp Med.* 2014;23:475–484.
7. Asai T, Suzuki H, Takeuchi J, et al. Effectiveness of photocoagulation using an Nd:YAG laser for the treatment of vascular malformations in the oral region. *Photomed Laser Surg.* 2014;32:75–80.
8. Hochman M. Infantile hemangiomas: current management. *Facial Plast Surg Clin North Am.* 2014;22:509–521.
9. Lee AH, Hardy KL, Goltsman D, et al. A retrospective study to classify surgical indications for infantile hemangiomas. *J Plast Reconstr Aesthet Surg.* 2014;67:1215–1221.
10. Sajan JA, Tibesar R, Jabbour N, et al. Assessment of pulsed-dye laser therapy for pediatric cutaneous vascular anomalies. *JAMA Facial Plast Surg.* 2013;15:434–438.

11. Goh CL. Flashlamp-pumped pulsed dye laser (585 nm) for the treatment of portwine stains—a study of treatment outcome in 94 Asian patients in Singapore. *Singapore Med J.* 2000;41:24–28.
12. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med.* 2008;358:2649–2651.
13. Laranjo S, Costa G, Paramés F, et al. The role of propranolol in the treatment of infantile hemangioma. *Rev Port Cardiol.* 2014;33:289–295.
14. Achauer BM, Chang CJ, Vander Kam VM. Management of hemangioma of infancy: review of 245 patients. *Plast Reconstr Surg.* 1997;99:1301–1308.
15. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med.* 2015;372:735–746.
16. Foerster SR, Canter CE. Pediatric heart failure therapy with beta-adrenoceptor antagonists. *Paediatr Drugs.* 2008;10:125–134.
17. North PE, Waner M, Buckmiller L, et al. Vascular tumors of infancy and childhood: beyond capillary hemangioma. *Cardiovasc Pathol.* 2006;15:303–317.
18. Greene AK, Rogers GF, Mulliken JB. Management of parotid hemangioma in 100 children. *Plast Reconstr Surg.* 2004;113:53–60.
19. Azizkhan RG. Complex vascular anomalies. *Pediatr Surg Int.* 2013;29:1023–1038.
20. Nozaki T, Nosaka S, Miyazaki O, et al. Syndromes associated with vascular tumors and malformations: a pictorial review. *Radiographics.* 2013;33:175–195.
21. Park KH, Jang YH, Chung HY, et al. Topical timolol maleate 0.5% for infantile hemangioma; it's effectiveness and/or adjunctive pulsed dye laser—single center experience of 102 cases in Korea. *J Dermatolog Treat.* 2014;29:1–3.
22. Kagami S, Kuwano Y, Shibata S, et al. Propranolol is more effective than pulsed dye laser and cryosurgery for infantile hemangiomas. *Eur J Pediatr.* 2013;172:1521–1526.
23. Kaune KM, Lauerer P, Kietz S, et al. Combination therapy of infantile hemangiomas with pulsed dye laser and Nd:YAG laser is effective and safe. *J Dtsch Dermatol Ges.* 2014;12:473–478.
24. Kwon SH, Choi JW, Byun SY, et al. Effect of early long-pulse pulsed dye laser treatment in infantile hemangiomas. *Dermatol Surg.* 2014;40:405–411.
25. Semkova K, Kazandjieva J. Rapid complete regression of an early infantile hemangioma with topical timolol gel. *Int J Dermatol.* 2014;53:241–242.
26. Villalba-Moreno AM, Cotrina-Luque J, Del Vayo-Benito CA, et al. Nadolol for the treatment of infantile hemangioma. *Am J Health Syst Pharm.* 2015;72:44–46.
27. Bencini PL, Tourlaki A, De Giorgi V, et al. Laser use for cutaneous vascular alterations of cosmetic interest. *Dermatol Ther.* 2012;25:340–351.
28. Becher GL, Cameron H, Moseley H. Treatment of superficial vascular lesions with the KTP 532-nm laser: experience with 647 patients. *Lasers Med Sci.* 2014;29:267–271.
29. Asai T, Suzuki H, Takeuchi J, et al. Effectiveness of photocoagulation using an Nd:YAG laser for the treatment of vascular malformations in the oral region. *Photomed Laser Surg.* 2014;32:75–80.
30. Marqués L, Núñez-Córdoba JM, Aguado L, et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. *J Am Acad Dermatol.* 2015;72:151–158.
31. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. *J Pediatr Orthop B.* 2004;13:349–357.
32. Swetman GL, Berk DR, Vasanawala SS, et al. Sildenafil for severe lymphatic malformations. *N Engl J Med.* 2012;366:384–386.
33. Danial C, Tichy AL, Tariq U, et al. An open-label study to evaluate sildenafil for the treatment of lymphatic malformations. *J Am Acad Dermatol.* 2014;70:1050–1057.