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ORIGINAL ARTICLE

Clinical Evaluation of Color Doppler Ultrasound in Selecting the Optimal Treatment Modality for Infantile Hemangioma[△]

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Key words: color Doppler ultrasound; infantile hemangioma; Nd:YAG laser;
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Objective We investigated the efficacy and safety of 1064 nm Nd: YAG laser, intense pulsed light (IPL), and lauromacrogol injection in the treatment of hemangioma, in order to evaluate the value of color Doppler ultrasound guidance in choosing the optimal treatment modality.

Methods Infantile patients who were clinical diagnosed as hemangiomas were randomly divided into group A, who had color Doppler ultrasound examinations before the treatment, and group B who had the treatment without ultrasound evaluation. Patients in the group A were assigned into subgroups according to the depth of lesion by sonography: group A-1 for those who had a lesion depth <1.2 mm, and took intense pulsed light therapy; group A-2 for those who had a lesion depth ≥1.2mm and < 3 mm, and took long pulse 1064 nm Nd:YAG laser therapy; group A-3 for those who had a lesion depth ≥3mm and <5 mm, and were treated by IPL combined with long pulse 1064 nm Nd:YAG laser treatment; Group A-4 for those who had a lesion depth ≥5 mm, and took lauromacrogol injection therapy. Patients in the group B took long pulse 1064 nm Nd:YAG laser treatment without preoperative ultrasound evaluation. The efficacy and adverse reactions of the treatments between the groups were evaluated and compared statistically.

Results Totally 113 patients with 128 skin lesions were enrolled in this study, 85 in the group A (mean age 6.8±7.9 months) and 28 in the group B (mean age 6.9±9.9 months). The mean depth of hemangioma was 3.3±1.1 mm in the group A, ranging from 0.5-7.8 mm, with 0.8±0.4 mm, 2.2±0.4 mm,

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4.2±0.6 mm and 6.2±0.7 mm in group A1, A2, A3 and A4, respectively. The cure rates and effective rates in the group A were significantly higher than those in the group B (cure rates: 64.5% vs 56.3%, $U=3.378$, $P=0.045$; effective rates: 89.5% vs 78.1%, $U=4.163$, $P=0.041$). The adverse effect rates of the group A (vesicle 20.0%, pigmentation 46.9%, scarring 17.7%) were lower than those of the group B (vesicle 21.9%, pigmentation 60.4%, scarring 25.0%). Incidences of pigmentation and scarring were statistically significantly different ($U=3.884$, $P=0.034$, and $U=4.016$, $P=0.032$ respectively) between the two groups.

Conclusion With the guidance of color Doppler ultrasound, the efficacy and safety of long pulse 1064 nmNd:YAG laser, intense pulsed light, and lauromacrogol injection in the treatment of infantile hemangioma have better outcomes compared to laser treatment alone without preoperative ultrasound examination.

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HEMANGIOMA is one of the most common vascular tumors in children. Infantile hemangiomas are benign proliferations of endothelial cells. They can be clinically classified as superficial, deep, and mixed according to the location of the vascular proliferation, whether in the dermis, hypodermis, or both. The incidence of hemangioma in the early neonatal is about 5%-10%, and 30% in preterm infants.^{1,2} Although it is possible for infantile hemangioma to regress completely, about 40% to 50% of patients persist residual lesions, such as telangiectasias, scar, skin atrophy, fibrofatty tissue residues, and other beauty defects.^{3,4} Clinically, there are still 20% to 30% of hemangiomas that cannot regress completely. Some severe hemangiomas with rapid proliferation may lead to serious dysfunction, and even be life-threatening.² Therefore, in recent years, more experts prefer treatments rather than observation.

Application of laser in the treatment of hemangioma has been more commonly used than ever due to the development of laser technology. Although the effect of long pulse 1064nm Nd: YAG laser treatment is deep and fast, it is very easy to leave an obvious scar. In order to reduce complications, the present study applied color doppler ultrasound prior to treatments to assess the physical volume, composition, depth, and velocity of blood flow in the hemangioma, and compared their outcomes with that of the laser treatment without ultrasound guidance, in order to establish the rationale of using ultrasound to optimize the treatment for patients with hemangioma.

PATIENTS AND METHODS

Case selection

This study was carried out in the Department of Dermatology, the First Affiliated Hospital of Nanjing Medical University from July 2014 to July 2015. Patients were recruited from outpatient clinics. The inclusion criteria: 1.

Children patients with clinical diagnosis of hemangioma; 2. Without contraindications of laser treatment, such as local bleeding, ulcers, and infection; 3. Untreated in the past three months. The exclusion criteria: 1. Lauromacrogol allergy for children who accept the injection treatment; 2. Voluntary withdraw because of serious side effects after the treatment, such as severe erythema, itching. The study was approved by the institutional ethics committee. After being informed details on adverse reactions and prognosis for the treatment, the guardians signed the consents. The enrolled patients were assigned into group A or group B by simple randomization. Patient whose programmed number was divisible by 5 was assigned into group B, and all the other enrolled patients were assigned into group A.

Pretreatment ultrasound evaluation

All patients in Group A had ultrasound examinations before treatment by the same sonographer in the Department of Ultrasound. Ultrasound device (Philips, IU22, Netherlands) with a linear array probe (L12-5MHz) was used. We observed the size, boundary, internal echoic texture, blood flow distribution and flow velocity for hemangiomas, and measured the maximum dimension perpendicular to the skin as the depth of the lesion.

Treatments plans

Patients in group A were subsequently grouped according to the depths of hemangioma measured by ultrasound. group A-1: depth <1.2 mm, intense pulsed light(IPL) therapy; group A-2: depth ≥1.2 mm and <3 mm, long pulse 1064 nm Nd:YAG laser treatment; group A-3: depth≥3 and <5 mm, or blood flow velocity ranging from 15 cm/s to 30 cm/s, combination of IPL and long pulse 1064 nm Nd:YAG laser treatment. The above three treatments were performed for 3-5 times continuously, with an interval of 3-4 weeks. group A-4: depth ≥5 mm, or blood

flow velocity >30 cm/s, lauromacrogol injection therapy, two injections for a course, 1-3 courses in total with an interval of 2 weeks. Patients in group B underwent long pulse 1064 nm Nd:YAG laser therapy for 5 times without preoperative ultrasound, using the same parameters as in the treatment for the group A-2.

Procedures of the treatments

IPL and Nd:YAG long pulse laser treatment

After routine disinfection of the lesion area, frozen ultrasound gel was applied. The operator and the assistant wore protective garment, and patients wore eye masks to prevent laser damage. For IPL (Lumenis one, Lumenis Ltd., USA), parameter settings were: dual pulse, both 3.0ms in width, pulse interval 40ms, energy density 14-16 J/cm². For 1064 nm Nd:YAG laser therapy (Lumenis one long pulse Nd:YAG treatment, Lumenis Ltd., USA), parameter settings were: single pulse, wavelength of 1064 nm, pulse width 12 ms, adjustable for 0.1-300 ms, energy density 88-92 J/cm², adjustable for 3-300 J/cm², treatment spot size 4-6 mm, adjustable for 3 mm, 5 mm, 7 mm, or 10 mm. The therapeutic energy was adjusted according to the response of lesion to the treatment. The treatment performance persisted till the lesion surface appeared gray-like changes. For immediate pallor, the treatment performance subsided for a few minutes as appropriate.

Lauromacrogol injection therapy

Each lesion had injections of lauromacrogol (Shaanxi Tianyu Pharmaceutical Co., Ltd., China) at two or three points, with 0.5-0.6 ml for each injection volume.

Post treatment management

All patients proceeded with the same post treatment management. Cold compression for 20-30 min after laser treatment to reduce local redness and swelling. Parents were instructed not to pierce, but to keep clean and use topical erythromycin ointment to protect and prevent from infection if blister appeared, till vesicles was self-absorbed. For lauromacrogol injection, compression was applied for a few minutes till the bleeding stopped. We informed the parents to avoid rubbing if local swelling occurred after the treatment in the early 1-3 days. An appropriate treatment was performed if erosion and exudation appeared. Patients were followed up for at least three months.

Efficacy evaluation

Two dermatologists evaluated the treatment effects three months after the last treatment by visual observation. Treatment effects were categorized as cured, significant

effective, effective, or ineffective. Cured: hemangioma area subsided $\geq 95\%$, the residual lesion had lighter color, no obvious scar, no recurrence in 3 months, no local physiological dysfunction; significant effective: the affected skin area subsided 60% to 94%, or accompanied with a slight scar; effective: affected skin area subsided 20% to 59%, or accompanied with a mild to moderate scar; ineffective: no changes in the affected skin area, or accompanied with obvious scars. The cure rate was defined as the percentage of cured patients in total number of cases, and the effective rate was defined as the percentage of the cured and the significantly effective ones together in the total included lesions.

Safety assessment

The post-treatment safety assessment was performed 3 months after the last treatment, and all patients were assessed using the same evaluation criteria. Two dermatologists made visual observations on adverse reactions of the lesion before and after treatment and made records, which included vesicles, infections, pigmentations, scars and bleeding. The severity of adverse reaction was evaluated as following categories: 1. no local adverse reactions; 2. mild local adverse reactions, with little influence on the appearance of skin; 3. moderate local adverse reactions, with a great impact on the appearance of skin; 4. serious local adverse effects.

Statistical Analysis

Statistical analyses were performed using SPSS (version 16.0) software. The size of hemangioma in the group A was compared to that of the group B by students' t test. Treatment efficacy and adverse reactions of each treatment group were expressed as percentage. The significance of differences between group A and group B was analyzed using Wilcoxon rank-sum test. $P < 0.05$ was considered statistically significant.

RESULTS

Group of patients and color Doppler ultrasound results

There were 113 patients enrolled in the study, aged from 45 days to 6 years old, 73 cases were female and 40 cases were male. 98 patients were under 1 year old, and the other 15 patients aged from 1 to 6 years old. There were 14 patients with multiple skin lesions, thus totally 128 lesions received treatments. Detailed characteristics of the patients and the size, location, depth, velocity of lesions in this study were listed in Table 1. The diameter of the lesions ranged from 0.2 mm to 63 mm. There was no significant

difference in the mean size of hemangioma between the two groups ($9.00 \pm 5.63 \text{ cm}^2$ in group A and $8.82 \pm 5.33 \text{ cm}^2$ in group B, $t=0.235$, $P>0.05$). Locations distributed in the head, face or neck for 58 lesions, limbs or the trunk for 70 lesions. The maximum and minimum depths were 9 mm and 0.5mm respectively. The colors of lesions were bright red, purple red and deep red.

The efficacy of the treatment

The efficacy of the treatment for group A, subgroups of group A and group B are shown in Table 2. The cure rate of group A (62/96, 64.6%) was significantly higher than that of group B (18/32, 56.3%, $U=3.378$, $P=0.045$); the overall effective rate of the treatment in group A (86/96, 89.6%) was significantly higher than that of group B (25/32, 78.1%, $U=4.163$, $P=0.041$). The treatment effects of group A and

group B in typical cases were illustrated in Fig. 1.

Assessment of adverse reactions

The common adverse reactions after treatments were vesicles, pigmentations, and scarring. As shown in Table 3, the adverse effects rates of group A (46.8% pigmentation, 17.7% scarring) were significantly lower than those of group B (60.4% pigmentation, $U=3.884$, $P=0.034$; 25.0% scarring, $U=4.016$, $P=0.032$). Infection occurred in one case of A-3 group, which was related to improper post-treatment care, but was controlled with topical mupirocin, twice a day for one week. There was one case in the A-4 group who encountered slight bleeding, and received hemostasis by compression. We also informed the parent not to rub, and the patient recovered with no sequela.

Table 1. Characteristics of patients and lesions in group A, subgroups of group A and group B[§]

Groups	No. of patients	Sex male/female	Age (months)	No. of lesions	Characteristics of lesions						
					Location (n)			Size (mm)		Depth by US (mm)	Velocity of blood by US (cm/s)
					Head, face neck	trunk	Limb	D1	D2		
A	85	31/54	6.8±7.9	96	45	32	19	0.2-63	0.2-50	3.3±1.1	15.39±10.82
A-1	21	8/13	6.8±7.8	22	11	6	5	0.2-38	0.2-34	0.8±0.4	6.02±3.86
A-2	28	10/18	6.6±9.8	36	14	11	11	4.2-54	3.2-25	2.2±0.4	12.01±4.62
A-3	30	12/18	6.9±6.4	32	17	12	3	5.2-63	6.2-50	4.2±0.6	21.25±8.11
A-4	6	1/5	7.5±6.3	6	3	3	0	15.0-23	12-25	6.2±0.7	41.46±3.36
B	28	9/19	6.9±9.9	32	13	7	12	0.8-45	0.2-46	-	-
In total	113	40/73	6.9±8.4	128	58	39	31	0.2-63	0.2-50	-	-

§: Plus-minus values are means±SD.

Table 2. Efficacy of the treatments for lesions of hemangioma in group A, subgroup of group A and group B

Groups	No. lesions	Effects of the treatments <i>n</i> (%)				
		Cured	Significant effective	Effective	Ineffective	Overall effective rate
A	96	62 (64.5)	24 (25.0)	6 (6.3)	4 (4.2)	86 (89.5)
A-1	22	14 (63.6)	6 (27.3)	2 (9.1)	0 (0)	20 (90.9)
A-2	36	24 (66.6)	8 (22.2)	1 (2.8)	3 (8.3)	32 (88.8)
A-3	32	22 (68.8)	7 (21.9)	2 (6.2)	1 (3.1)	29 (90.6)
A-4	6	2 (33.3)	3 (50.0)	1 (16.7)	0 (0)	5 (83.3)
B	32	18(56.3) [†]	7 (21.9)	3 (9.4)	4 (12.5)	25 (78.1) [*]
In total	128	80(62.5)	31 (24.2)	9 (7.0)	8 (6.3)	111 (86.7)

*Significant different as compared to group A ($U=4.163$, $P=0.041$).

[†]Significant different as compared to group A($U=3.378$, $P=0.045$).

Case 1. A boy of 8 months in Group A-1. A. The lesion located in the waist, 8 mm×4 mm in size, 1mm in depth, hypoechoic, no color blood flow signal. B. The skin lesion subsided more than 95% after 3 times IPL (intense pulse light) treatments. The residual lesion was pale without obvious scar, which was determined as cured.

Case 2. A girl of 3 months and 5 days in Group A-2. A. The lesion located in the left upper limb, 15 mm×12 mm in size, 2.5 mm in depth, hypoechoic under ultrasound, with low velocity blood flow spectrum (7.6 cm/s). Long pulse 1064 nm Nd: YAG laser treatments were performed for 5 times. B. The Skin lesion subsided more than 85%. The residual lesion was pale without obvious scar, which was determined as significant effective.

Case 3. A girl of 4 months and 10 days in group A-3. A. The lesion located in the right wrist, 11 mm×5 mm in size, 3.5 mm in depth, slightly hyperechoic, with maximum blood flow velocity 21.6 cm/s. The patient received strong long pulse 1064 nm Nd:YAG laser treatment, combined with IPL (intense pulsed light) treatment for 4 times. B. the skin lesion subsided more than 95%. The residual lesion had slight pigmentation, with no obvious scar, which was determined as cured.

Case 4. A boy of 8 months and 12 days in Group A-4. A. The lesion located behind the left ear, 13 mm×12 mm in size, 6.3 mm in depth, slightly hyperechoic, with maximum blood flow velocity 34 cm/s. Injection of polyalcohol (0.5 ml) was administrated at 2 points once a week for a course. B. The regression was about 65% with no obvious scar, which was determined as significant effective.

Case 5. A girl in 5 months and 5 days in group B. A. The lesion located on the back around left scapula, 15 mm×12 mm in size. Long pulse 1064 nm Nd: YAG laser treatment (pulse width 12 ms, energy 90 J/cm², spot 6 mm) was performed for 4 times. B. The regression was about 73%, with a slight pigmentation, and no obvious scar, which was determined as significant effective.

Figure 1. Photographs of the typical cases in group A and group B before and after the treatment.

Table 3. Comparison of adverse reactions in the group A and group B

Groups	No. of lesions	Adverse reactions				
		Vesicle n(%)	Pigmentation n(%)	Scar n(%)	Bleeding n(%)	Infection n(%)
A	96	18 (20.0)	45 (46.9)	17 (17.7)	1 (1.0)	1 (1.0)
A-1	22	4 (18.1)	12 (54.5)	2 (9.1)	0	0
A-2	36	7 (19.4)	18 (50.0)	7 (19.4)	0	0
A-3	32	7 (21.9)	14 (43.8)	6 (18.8)	0	1 (3.1)
A-4	6	0	1 (16.7)	2 (33.3)	1 (16.7)	0
B	32	7(21.9)	19(60.4)*	8(25.0)†	0	0
In total	128	25(19.5)	64(50.0)	25(19.5)	1(0.7)	1 (0.7)

*Significant difference between group A and B (U=3.884, P=0.034).

†Significant difference between group A and B (U=4.016, P=0.032).

DISCUSSION

In recent years, laser therapy has become an important method for the treatment of superficial infantile hemangioma. The principles of laser treatment are based on the absorption of selective photothermal effect that causes heating of the vessel wall thus destroy the abnormal blood vessels.⁵ Adjustable long pulse width 1064 nm Nd: YAG laser for the treatment of hemangioma has a rapid onset and significant effect. Currently the parameters in treatment of hemangioma using 1064 nm Nd: YAG laser are mostly based on physician's clinical experience.⁶ For deep hemangiomas, it requires a combination with other treatments to reach complete therapeutic effect due to limitations of laser penetrating depth.

Recently, intense pulsed light (IPL) technology has been applied in interventional treatment for hemangiomas because of its minimal or non-invasive advantage.⁷⁻⁸ IPL is emitted by polychromatic incoherent light source, with a pulse width between 515-1200 nm. The bigger the pulse width, the higher the energy density to heat the blood vessel. A plurality of pulses allow the cooling of epidermis, while maintaining the heat underneath to built up and damage blood vessels. Long pulse 1064 nm Nd: YAG laser is well absorbed by haemoglobin, and penetrates to maximum 5-7 mm in depth. The energy transferred and absorbed results in tissue heating, and causes necrosis of vascular endothelial. Theoretically, when laser energy changes the oxygenated hemoglobin in red blood cells to methemoglobin, the absorption of the Nd:YAG laser by hemoglobin increases 3-5 folds, which makes it possible to set the laser at a lower fluency, and thereby reduce adverse effects while keep a good therapeutic effect.⁹ Laser or IPL is difficult to reach deep subcutaneous tumors for the limitation in penetration. Auromacrogol injection into the target vessel can destroy endothelial cells of blood vessels in hemangioma, causing vascular occlusion,¹⁰ which could make up the limitation of laser therapy in penetration and effectively achieve therapeutic purposes. However, selecting the most appropriate treatment modality for a specific individual patient from many alternative treatment options, and optimizing treatment parameters are the main issues that physicians have to face.

Color Doppler ultrasound has been used in comprehensive evaluation of hemangioma, such as identifying the composition, depth, distribution and direction of blood vessels, and velocities of blood flow. The technology is non-invasive, safe, simple, and has been used in the diagnosis of hemangioma since 1984.¹¹⁻¹³ Despite plenty of

literature on ultrasound imaging of hemangioma, there have been very few reports on the application of US in quantitatively analyzing hemangioma and guiding the treatment.¹⁴⁻¹⁸

All hemangioma lesions in our study showed as a solid tumor in sonography, and were hypoechoic for small lesions, and heterogeneous for large ones. The internal texture of infantile hemangioma is more complex in sonography. It could be heterogeneously hypoechoic, anechoic or hyperechoic lesions with rich blood supply. These observations in our study were consistent with Dubois' study,¹⁹ where 70 infantile hemangiomas were studied for the sonographic characteristics; among them, 59 hemangiomas were found to have very rich arterial blood supply; the other 11 lesions were post-treated, and showed less abundant blood supply.

In this study, ultrasound was used to help choosing optimal treatment according to the tumor depth in sonography. Based on the blood flow velocity and vascular diameter, we set parameters for laser therapy, such as pulse width and pulse energy interval, and adjusted parameter settings appropriately, in order to alleviate suffering of children. Our therapeutic targets are to damage the hemangioma without unnecessary overtreatments, and to achieve as good therapeutic effects as we can.

Previous studies have indicated that understanding the features of hemangioma before laser treatment was helpful to achieve good outcome.¹⁴⁻¹⁸ In the present study, we evaluated hemangiomas with ultrasound and select treatment modality according to features of the hemangioma on sonography. The effective rate was better than those using Nd:YAG laser treatment (78.1%) alone without sonography evaluation. The overall effectiveness rate (89.5%) in our study was also superior to that in the previous report.²⁰ In addition, the adverse reactions in the group A with pre-treatment sonography occurred less frequently compared to the group B without pre-treatment sonography. These results support the above ideas and indicate that ultrasound guidance is helpful to achieve a better therapeutic outcome for infantile hemangioma patients.

Sonography can accurately determine the blood flow velocity and the depth of hemangioma, so we can choose the type of laser and adjust the energy to deliver. By doing so, some side effects caused by excessive energy can be prevented. In addition, ultrasound imaging of the target lesion provided comprehensive morphological and vascularity information for physicians who operate the treatment, which is helpful to avoid normal tissue damaging, as well as a variety of adverse reactions, such as erythema, swelling,

and even scars from overtreatment.

In conclusion, this study suggested that the application of color Doppler ultrasound in selecting treatment modality for hemangioma in children achieved better treatment efficacies and less adverse reactions. The morphological and vascularity assessments of the tumor by sonography help to select treatment modality, laser type and appropriate parameters, and consequently achieve a better outcome.

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