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*Original Article*

# Combination of propranolol and sclerotherapy for treatment of infantile parotid hemangiomas

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**Abstract:** We aimed to evaluate the efficacy of combination of propranolol and sclerotherapy in treating parotid hemangiomas. Twenty-six parotid hemangiomas patients were subjected to combined treatment from January 2009 and June 2014. The effects of the therapy modality were evaluated. Nineteen patients were females and 7 were males. The median age of treatment initiation was 4.96 months. Twelve lesions were located on the left side parotid glands, while thirteen lesions affected the right side. One infant had bilateral lesions. One to six (average 2.04) injections were performed and the mean period for propranolol was 8.94 months. All the patients got satisfied aesthetic outcomes. No complications of propranolol or sclerotherapy occurred during the whole medication period. The study demonstrated that combination of propranolol and sclerotherapy was an effective and safe method for infantile parotid hemangiomas. Larger-scale studies should be performed to further investigate the long-term efficacy and results of the present combined method for infantile parotid hemangiomas.

**Keywords:** Parotid hemangiomas, propranolol, sclerotherapy, complication

## Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors of infancy, with a prevalence of 1-10% in newborns and infants. The prevalence differs among races, since Caucasians have a higher incidence while the incidence in Africa infants is somewhat lower. The nature pathological course of IH includes three phases. The first phase is proliferative phase during the first half year of life, where IHs initiate and grow rapidly. Following proliferative phase is involuting phase, where tumor growth slows and vessels become prominent. Then IHs turn into involuted phase, where fibrofatty tissue finally replaces the tumor mass.

IHs prefers to locate in the head and neck. In our previous investigation, we found more than 57% of these neoplasms settled on the craniomaxillofacial regions [1]. The salivary glands are the common organs involved by the lesions. It has been estimated ninety percent of salivary gland hemangiomas arise in parotid glands [2]. Parotid hemangiomas have more complicated characteristics than the lesions of truck or arms and legs. The fast proliferating parotids hemangiomas with huge volume occupy severe shunting, causing high load for heart [3]. Obstruction of the external auditory canal is very common with parotid hemangiomas and causes minor to moderate conductive hear loss. Airway compromise is the severest complication requested for emergent treatment or tracheotomy. Furthermore, the deep IHs have a longer proliferating phase [4]. Thus the treatment modality of parotid glands should be more aggressive and intensive than small and superficial lesions.

Propranolol has been recommended as the first-line treatment for problematic IHs. We have treated IH patients using this agent for more than four years and get outstanding results [1]. Sclerotherapy are also effective in causing regression of IHs, although there is a risk of ischemic necroses and scar formation. Based on our experience that parotid IHs need more aggressive and intensive modality, we com-

bined oral propranolol and endovascular sclerotherapy to treat parotid IHs.

## Materials and methods

The ethics committee of Xinhua Hospital, affiliated to Shanghai Jiaotong University School of Medicine, approved this study. All parents in this research were informed of the purpose and provided with written informed consent. This research was conducted between January 2009 and June 2014. The inclusion criteria were as follows: infants were newly diagnosed with IHs and did not receive any treatment including corticosteroids, propranolol or surgery. The contraindications for use of propranolol included: a history or risk of asthma, reactive airway disease, impaired renal or liver function, heart defects or arrhythmia, hypotension, central nervous system disorders, neonates under the age of 1 month, or allergy to propranolol or sclerotherapy agents. Infants who withdrew from follow-up within 6 months were also excluded from the study.

Patients were administrated hospitalization and received electrocardiogram (ECG) and cooler Doppler echocardiography to exclude heart defects. Magnetic resonance imaging (MRI) was scheduled to assist diagnosis in some deep lesions and to estimate of tumor volume prior to medication. Before the initiation of propranolol treatment, detailed history inquiry and physical examination by a pediatrician was scheduled to rule out pulmonary disease. Then patients were treated with propranolol, given as two separate doses (given at 8 am and 8 pm) under ECG monitoring. The total dosage of first day was 0.5 mg/kg/day and increased to 1 mg/kg/day on the second day. Endovascular sclerotherapy was scheduled 2 to 3 days after initiation of propranolol without obvious heart rate and blood pressure decrease. Prepare the instruments for injection: a 5 $cm^3$ syringe, two 10 $cm^3$ syringe, a tee joint and a scalp vein needle (0.55 mm). The agent for injection included 1 $cm^3$ lidocaine mixed with 4 $cm^3$ saline (Syringe A), 4 $cm^3$ absolute ethyl alcohol (Syringe B), 4 $cm^3$ Lauromacrogol (10 ml: 100 mg, Tianyu Pharmaceutical, Shanxi, China) and 3.5 mg Betamethasone (Schering-Plough Labo N.V.) mixed with 5 mg methotrexate (Pude pharma, Shanxi, China) (Syringe C). Under general anesthesia and disinfection, the operator punctured the needle of syringe A into the lumen of vessels from unaffected skin. Aspirated the venous blood slightly to ensure the tip of needle be in the lumen of target vessel and no observed pulse of blood. Kept the position of needle and replaced the Syringe A with Syringe B. Injected small volume of absolute ethyl alcohol into the lumen of target vessels gently following a slight aspiration. After several repetitive protocols, the volume of blood flowed back to the tube get decreased and micro-thrombus could been observed. Thereafter replaced Syringe B with Syringe C and injected the mixture into the vessels. Multiple punctures were performed to ensure sclerosis of the majority of lesions. Dressing for compression was not recommended to avoid pressure induced migration of the micro-thrombus. On the second day after sclerotherapy, oral propranolol (1 mg/kg/day) was conducted and continued at least 6 months. Discharge from hospital was scheduled on the second or third day after sclerotherapy. Repeat endovascular sclerotherapy were performed at > 3-4 months interval. The patients were followed up in outpatient clinic.

## Results

Twenty-six patients with infantile parotid hemangiomas were enrolled in our study, including 19 female infants and 7 male infants. Twelve lesions were located on the left side parotid glands, while thirteen lesions affected the right side parotid glands. One infant suffered with bilateral parotid gland hemangiomas. One patient had slight airway stenosis. The average age of treatment initiation was 4.96 months (range from 1.6 to 11.9 months). The mean lesion areas of MRI scanning (calculated on lesions' maximum horizontal plane and coronal plane) were (9.30±5.37) $cm^2$ and (8.78±4.62) $cm^2$, respectively. The mean volume of absolute ethyl alcohol and lauromacrogol-betamethasone-methotrexate mixture for each sclerotherapy was 2.67 $cm^3$ and 3.32 $cm^3$, respectively. The average number of sclerotherapy was 2.04 (range from 1 to 6 times) (**Tables 1** and **2**).

Obvious improvement in the color (changing from intense-red to red or purple) of the superficial parts of IHs could be observed several days after initiation of therapy. Upon first follow-up 4 weeks after discharge, laboratory blood tests including complete blood count, fasting

**Table 1.** Summary of patients' characteristics and treatment details (Part 1)

| Patient No. | Gender | Side involved | Age at first treatment onset (mons) | Imaging examination | Lesions on other sites |
|---|---|---|---|---|---|
| 1 | male | R | 10 | B Ultrasound | None |
| 2 | male | R | 4.4 | MRI | None |
| 3 | female | L | 4.8 | MRI | None |
| 4 | female | R | 7.2 | MRI | Superficial lesion on the ipsilateral face |
| 5 | female | L | 3.4 | MRI | None |
| 6 | female | L | 7.9 | MRI | Deep lesion under the right sternocleidomastoid muscle (1.08 cm × 2.85 cm) |
| 7 | male | R | 5.2 | MRI | None |
| 8 | male | L | 3.6 | MRI | None |
| 9 | female | L | 3 | MRI | None |
| 10 | female | R | 11.9 | B Ultrasound | None |
| 11 | female | R+L | 8.1 | MRI | Bilateral parotid glands |
| 12 | female | R | 1.7 | MRI | Slight airway stenosis |
| 13 | female | R | 5.2 | MRI | None |
| 14 | female | R | 1.8 | MRI | None |
| 15 | male | R | 5.2 | MRI | None |
| 16 | female | L | 4.1 | MRI | None |
| 17 | female | L | 4.2 | B Ultrasound | None |
| 18 | female | R | 1.6 | MRI | Superficial lesion on the ipsilateral face |
| 19 | female | L | 5.6 | MRI | None |
| 20 | male | L | 3.6 | MRI | None |
| 21 | female | L | 4.2 | MRI, B Ultrasound | None |
| 22 | female | R | 2.8 | MRI, B Ultrasound | None |
| 23 | female | L | 3.5 | MRI | None |
| 24 | female | R | 5.6 | MRI | None |
| 25 | female | L | 5.5 | MRI | None |
| 26 | male | R | 8.8 | MRI | None |

**Table 2.** Summary of patients' characteristics and treatment details (Part 2)

| Patient No. | Area on maximum horizontal plane ($cm^2$) | Size on maximum horizontal plane (cm×cm) | Area on maximum coronal plane ($cm^2$) | Size on maximum coronal plane (cm×cm) | Color Doppler Echocar-diography | No. of injections | Total duration of Pro (mons) | Follow-up after last injection (mons) | Compli cations |
|---|---|---|---|---|---|---|---|---|---|
| 1 | / | / | / | / | Negative | 1 | 6 | 10 | no |
| 2 | 5.75 | 2.10×3.37 | 4.92 | 4.35×1.85 | Negative | 2 | 11 | 12 | no |
| 3 | 10.8 | 2.29×4.07 | / | 4.50×2.48 | Negative | 2 | 11 | 12 | no |
| 4 | 13.23 | 4.48×3.21 | 9.86 | 3.39×4.32 | Negative | 1 | 8 | 15 | no |
| 5 | 4.4 | 2.98×1.76 | 3.71 | 3.16×1.56 | Negative | 1 | 11 | 16 | no |
| 6 | 23.37 | 6.01×4.19 | 18.3 | 5.92×3.47 | Stenosis of left subclavian artery ostial | 3 | 8 | 13 | no |
| 7 | 4.5 | 3.19×1.85 | 4.78 | 4.13×1.58 | Persistent left superior vena cava | 3 | 9 | 9 | no |
| 8 | 11.75 | 4.70×2.64 | 12.48 | 5.50×2.60 | Slightly faster of left pulmonary artery blood flow | 1 | 11.5 | 20 | no |
| 9 | 6.81 | 4.44×2.58 | 6.34 | 4.10×1.77 | Patent foramen ovale | 1 | 7, on going | 7 | no |
| 10 | / | / | / | / | Negative | 2 | 5 | 10 | no |
| 11 | 3.66 | 2.60×2.03 | 4.9 | 2.71×2.91 | Patent foramen ovale | 3 | 6 | 6 | no |
| 12 | 8.17 | 2.90×4.32 | 10.71 | 3.80×3.98 | Patent foramen ovale | 3 | 15 | 18 | no |
| 13 | 10.71 | 5.06×3.24 | 11.89 | 4.09×4.15 | Negative | 1 | 8, on going | 8 | no |
| 14 | 12.9 | 4.97×4.02 | 9.82 | 2.99×5.34 | Atrial septal defect | 1 | 12, on going | 12 | no |
| 15 | 21.34 | 7.16×2.97 | 20.64 | 7.89×3.33 | Negative | 1 | 9 | 10 | no |
| 16 | 6.11 | 2.91×1.92 | 9.9 | 4.36×3.27 | Slightly faster of pulmonary artery blood flow | 2 | 7, on going | 7 | no |
| 17 | / | / | / | / | Negative | 1 | 6, on going | 6 | no |
| 18 | 6.18 | 3.56×2.18 | 5.97 | 2.41×3.41 | Negative | 4 | 12 | 8 | no |
| 19 | 2.45 | 2.11×1.27 | 3.91 | 3.50×1.16 | Negative | 1 | 6, on going | 6 | no |
| 20 | 11.59 | 4.69×3.67 | 12.64 | 5.39×2.77 | Negative | 2 | 13 | 7 | no |
| 21 | 10.26 | 3.97×4.00 | 8.09 | 3.51×2.19 | Negative | 2 | 10 | 10 | no |
| 22 | 7.99 | 3.01×3.90 | 5.44 | 3.51×2.22 | Negative | 4 | 12 | 12 | no |
| 23 | 12.22 | 5.30×3.13 | 9.06 | 4.68×2.22 | Negative | 6 | 10 | 6 | no |
| 24 | 3.26 | 1.70×2.51 | 4.89 | 1.81×3.25 | Negative | 1 | 8, on going | 8 | no |
| 25 | 7.05 | 4.16×1.36 | 3.44 | 2.49×1.87 | Atrial septal defect | 1 | 5, on going | 5 | no |
| 26 | 12.22 | 4.38×4.04 | 14.64 | 3.97×5.13 | Negative | 3 | 6 | 15 | no |

blood glucose, aspartate transaminase, alanine transaminase and thyroid function tests were undertaken and no obvious abnormality was happened. Thereafter, oral propranolol was recommended to continue. The mean period for propranolol was 8.94 months, including 8 patients who were still taking propranolol. All the patients got satisfied aesthetic outcomes. No complications of propranolol or sclerotherapy occurred during the whole medication period. Long-term outcomes were convincing in the aesthetic improvement (**Figures 1**-**3**). There was no relapse after propranolol cessation (**Figures 1**-**3**).

## Discussion

IHs are benign tumors, and the majority are small in size and self-limiting. The small lesions located at non-important sites don't need positive intervention. However, in some cases, severe or life-threatening problems can arise. IHs originated from orbits may compromise eyeball and visual nerve, causing visual impairment. Airway hemangiomas usually obstruct the airway. Rapid proliferating lesions on the faces involve severe disfigurement which may be troublesome for reconstruction. Ulceration of parotid IHs during the early proliferative phase happened in 59 percent patients, which is much higher than 5 percent of all cutaneous hemangiomas. The characteristics of parotid glandhemangiomamakeitmorecomplicated.Parotid IHs often cause deformity of adjacent structures, narrowing of external auditory canal or subglottis. High blood volume circulating in the large lesions may contribute to congestive heart failure [5]. It has been reported that 30 to 35 percent of parotid lesions became problematic. Deep hemangiomas may proliferate until 2 years of age [4]. Compared with hemangiomas at other sites, the need for intervention is somewhat greater for parotid hemangiomas [6]. Therefore, we thought that parotid IHs need more aggressive and intensive modality.

Oral prednisolone and interferon were once the most commonly used agents to treat IHs and got satisfied outcomes during the past decades. But some clinicians have reported that drug therapy for parotid hemangiomas is less predictable since they are notorious for large growth and resistant to drugs [3, 7]. Buckmiller et al. reported that regrowth was frequently seen 3-6 weeks after intralesional steroid injection [8]. Resistance to pharmacologic treatment may be caused by increased metabolism and secretion of the drugs by the parotid gland [5]. Besides increased metabolism and secretion, the volume of lesions is another factor related to sensitivity to drugs. Larger lesions appeared less likely to respond to pharmacological therapy. However, contrary findings described good response of parotid hemangiomas to interferon and corticosteroid [9, 10]. There are unacceptable side effects after high dose and long term usage of prednisolone. After utilization of propranolol in treating IHs, we have stopped systemic corticosteroid or interferon for IH patients.

Surgical management was one option for parotid IHs. With further understanding of IH pathology and available medical treatments, necessary of parotidectomy declined. Due to the proximity of facial nerve, surgical resection is arduous. Parotid IHs are usually encapsulated and infiltrate adjacent tissues, making complete resection difficult, increased blood lose and coursing facial nerve injury. Furthermore, incomplete resection resulted in regrowth of IHs [11]. Thus surgical intervention should be limited during proliferative phase while be considered to correct the remarkable disfigurement after involution.

Propranolol is now widely used to treat IHs at any locations and favorable outcomes have been proved in most IH cases. Previously, we reported our preliminary experience on treatment of IHs in Chinese individuals and explored its underlying mechanism based on hemangiomas stem cells [12]. Since Chinese individuals have a twofold greater sensitivity to effects of propranolol than Whites [13], we utilized low-dose propranolol in treating IHs and acquired satisfied outcomes. Due to the fact that drug therapy for parotid IHs is less predictable, and the rapid enlargement of tumors brings remarkable deformity, social pressure and psychological suffering to patients and parents, we think earlier and more aggressive modality should be undertaken. Some authors argued that parotid IHs could regress completely without intervention. However, none can predict when they begin to regress, what extent they will involute and how long they may take to finish regression. In most cases, even full involution occurs, there exists lax skin, fibrofatty tissue and telangiectasias. If early intervention can effectively

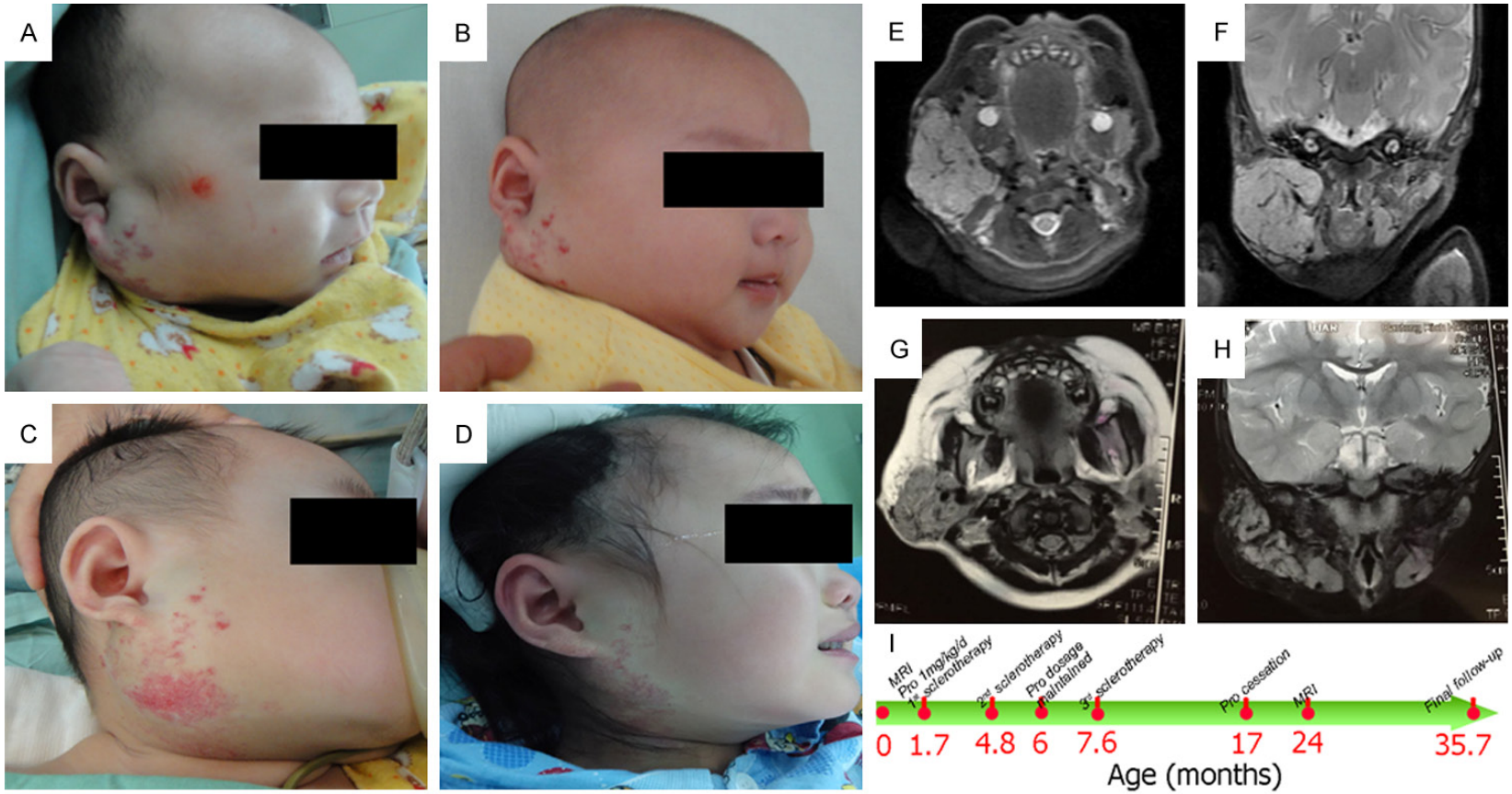


**Figure 1.** A female patient with right parotid hemangioma. The lesion proliferated rapidly. Elevated temperature of affected area was detected and MRI showed flowing-void effect in the lesion. The dosage of propranolol was 1 mg/kg/day. After age of 6-month-old, the daily dosage of propranolol maintained and did not add with body weight increase. The patient took propranolol for 15 months and received 3 times' sclerotherapy. A. The 54-day-old infant before treatment. B. Three months after taking propranolol and first sclerotherapy. The infant received second sclerotherapy. C. Near three months after second sclerotherapy. The infant received third sclerotherapy. D. Fourteen months after third sclerotherapy. E, F. MRI imaging of the lesion before treatment. G, H. MRI imaging of the lesion 22 months after initial treatment. I. The schematic of diagram of the whole treatment.

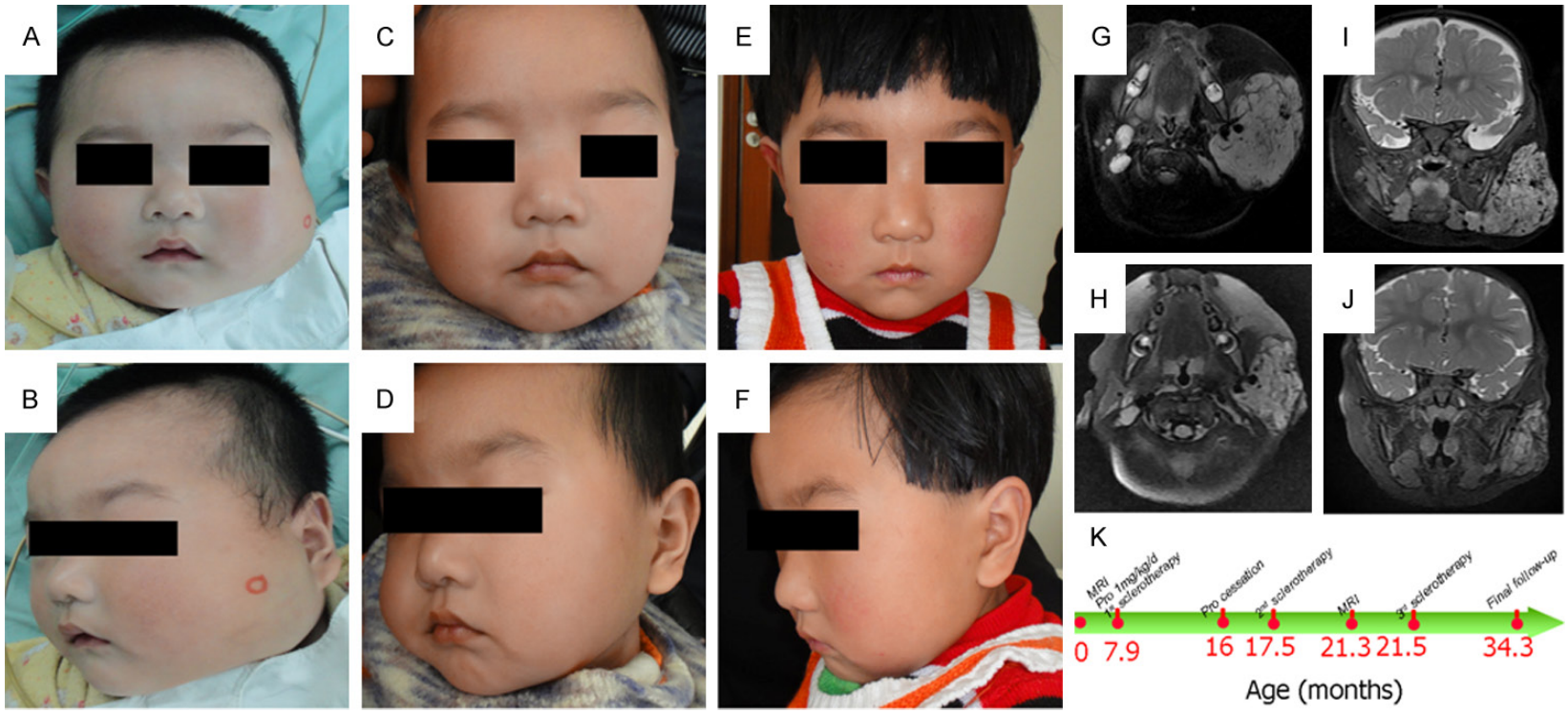


**Figure 2.** A female patient with left parotid hemangioma. The patient took propranolol for 8 months and received 3 times' sclerotherapy. A, B. The 7.9-months-old infant before treatment. C, D. The infant received second sclerotherapy 9.6 months after first sclerotherapy. Four months later, the patient received third sclerotherapy. E, F. Thirteen months after third sclerotherapy. G, I. MRI imaging of the lesion before treatment. H, J. MRI imaging of the lesion 13.4 months after initial treatment. K. The schematic of diagram of the whole treatment.

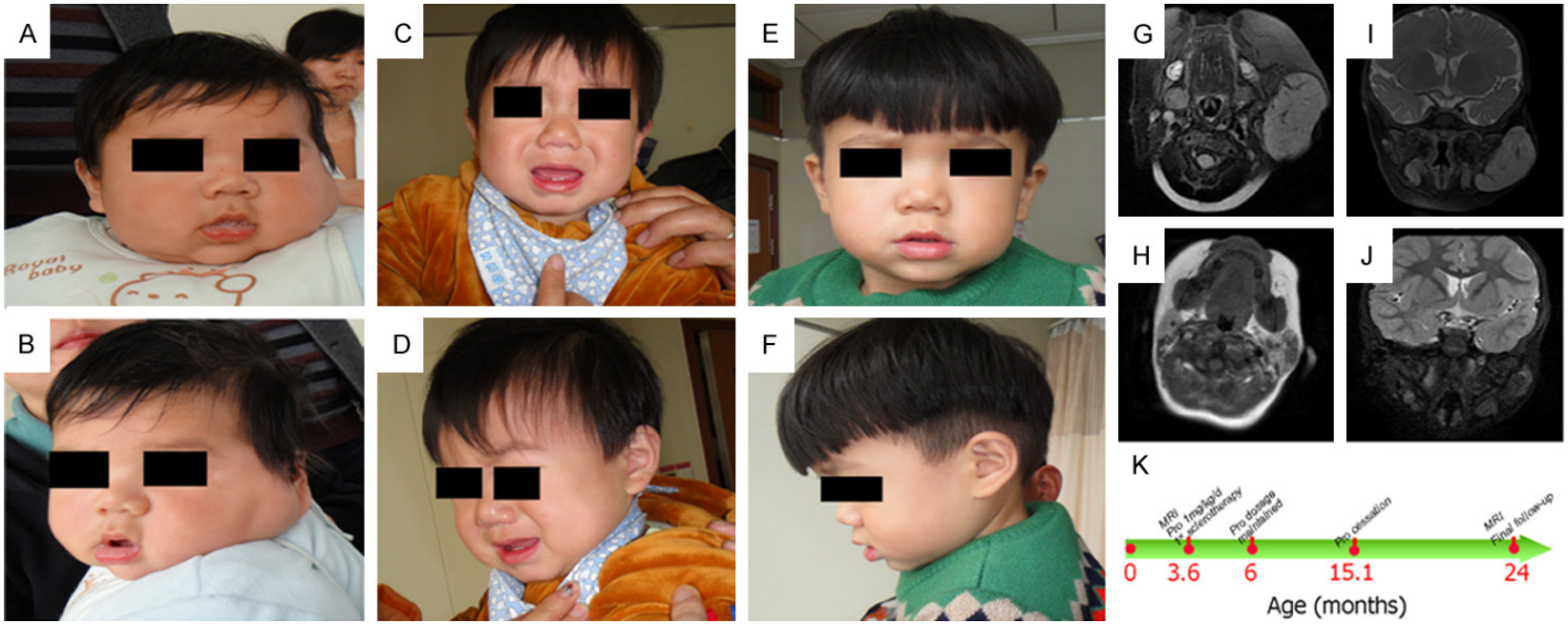


**Figure 3.** A male patient with left parotid hemangioma. The patient took propranolol for 11.5 months and received once sclerotherapy. A, B. The 3.6-months-old infant received propranolol and sclerotherapy. C, D. About 9 months after sclerotherapy. E, F. Twenty months after sclerotherapy. G, I. MRI imaging of the lesion before treatment. H, J. MRI imaging of the lesion 20 months after initial treatment. K. The schematic of diagram of the whole treatment.

prevent fast growth, it is possible to minimize the residual sequelae. Thus we combined of propranolol and sclerotherapy to treat and early control parotid IHs. The results showed that all the patients with the combined therapy modality undertook complete regression. Follow-up after six month indicated no relapse happened.

Sclerotherapy can cause thrombosis and obliteration of vascular lumina. With advantages such as low toxicity, low allergic reaction, high efficiency, micro-invasion and facility in use, sclerotherapy has been widely described in treating vascular malformation and tumors. We noticed the phenomenon that the temperature was elevated and MRI showed flowing-void effect in some lesions, indicating micro-arteriovenous fistula in IHs. The micro fistulas may be one factor that contributes to rapid growth of IHs and the reason of inefficiency of systemic or local applied steroid. Previous studies have confirmed sclerotherapy during proliferative phase could block growth rate and accelerate regression process. But there exists complications when being applied in lesions with extended arteriovenous shunts, causing irreversible occlusion of vessels and subsequent necrosis. Combination of oral corticosteroids and sclerotherapy has been reported in treating IHs [14]. Combination of two modalities might reduce the overall therapy duration and side effects encountered with either of the drug. Propranolol could induce vasoconstriction during the first several days. Reduction of blood flow in the tumors may facilitate sclerotherapy since lower blood fluid dynamics is beneficial to stabilize microthrombus. Furthermore, most part of a lesion was sclerosed, there remains un-sclerosed fraction which may be the target of propranolol. This is the reason we started oral propranolol before sclerotherapy and our purpose of this combined method is to early control growth of parotid IHs. Even though, caution must be kept in mind to avoid undesirable sclerosis. Betamethasone was used with lauromacrogol to reduce inflammation, protect facial nerve and promote regression. Methotrexate could target on endothelial cells and inhibit high proliferation. In the present research, all patients got satisfied outcomes and no complication occurred. However, we have not conducted randomized controlled trials of propranolol with our combined method. Larger-scale studies should be performed to further investigate the different efficacy between propranolol treatment and present combined method in infantile parotid hemangiomas.

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## Disclosure of conflict of interest

None.

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