A clinical study of ultrasound-guided intralesional injection of bleomycin A5 on venous malformation in cervical-facial region in China

Rui Hou, DDS,[a] Jun Guo, MD,[b] Kaijin Hu, DDS,[a] Yaowu Yang, DDS,[a] Lei Wang, DDS,[a] Liang Kong, DDS,[a] Guicai Liu, DDS,[a] and **Delin Lei, MD,[a]** *Shaanxi, China*

Objectives: **To evaluate the therapeutic outcome of ultrasound-guided intralesional injection of bleomycin A5 on treatment of venous malformation (VM) in cervical-facial region.**

Methods: **Seventy-five patients (32 male, 43 female), ranging in age from 13 to 60 years old, suffering from VM in cervical-facial region were admitted to and treated at our hospital between June 2006 and February 2007. Of all the patients, 54 malformations were located in the facial region, eight in the submental region, 10 in the submandible region, and three in the cervical region; all were treated by ultrasound-guided intralesional injections of bleomycin A5. The size of the lesions ranged from 6 × 9 mm to 32 × 39 mm. Injection of bleomycin A5 on venous malformation was then carried out through the inspection of ultrasonography. Repeated course of bleomycin A5 injection was administrated for larger malformations. The amount was 8 mg each time. The therapeutic interval was two to four weeks. The therapeutic outcome on venous malformation was evaluated by physical examination and ultrasonography with Doppler according to the Shou standards, including four grades; cured, basically cured, improved, and invalid. The complications were also observed during and after injection.**

Results: **The duration of follow-up ranged from 6 to 24 months. The average times of treatment were 1.64 times. Among them, 42 patients (56%) received only one time of treatment, 21 (28%) patients received two times, nine (12%) patients received three times, and three (4%) patients received four times. According to criteria of therapeutic outcome, the results showed cured in 63 patients (84%), basically cured in 10 patients (13.33%), improved in two patients (2.67%), and none ineffective. Seventy-one patients (94.67%) had local swelling in injection region for several days and two patients (2.67%) developed temporary dizziness after treatment. There were no other complications recorded.**

Conclusions: **Intralesional injection of bleomycin A5 establishes a promisingly effect way for patients suffering from VM in the cervical-facial region under ultrasound guidance. (J Vasc Surg 2010;51:940-5.)**

Venous malformations (VMs) are one type of vascular malformation formerly referred to as "cavernous hemangiomas." They are also the most common vascular anomalies in the cervical-facial region, which usually involve multiple anatomical regions including the skin, mucosa, and critical neuromuscular structures. If left untreated, it will increase gradually and finally affect appearance and organ functions. Intraoral VMs can bleed, distort dentition, cause speech problems, or even obstruct the upper airway, thus increasing the difficulty of treatment.

A variety of techniques have been used in the treatment of VMs. The main therapies include laser therapy, surgical excision, and sclerotherapy. Laser therapy is effective for small superfacial VMs. When it is sometimes used for deep lesions, skin flap elevation is required.[1,2] Complete surgical resection is often difficult and often involves massive bleeding, severe scars, and injury of the facial nerves. Sclerotherapy is an optional approach for treating this disease. The main advantages are no external scarring and few complications as compared with surgical treatment. Therefore, sclerotherapy is selected as the first choice for VMs in the face and neck.[3-6]

There have been attempts to use many sclerosants, including sodium morrhuate, absolute ethanol, and bleomycin. All these sclerosing agents have their particular advantages and limitations.[3-6] Sodium morrhuate can promote thrombosis and occlude the vascular venous vessels in the lesions; however, it might cause complications such as ulceration and hematuria if a high dose is injected. Although absolute alcohol is widely used in the treatment of large VMs because of its low cost, antiseptic quality, wide availability, and ease of use, ethanol sclerotherapy may result in a wide range of complications, mainly severe pain immediately after injection, skin necrosis, neuropathy, and facial nerve injury.

Bleomycin is a glycopeptide antibiotic produced by the bacterium Streptomyces verticillus. Usually, it is used as an antineoplastic drug to treat many kinds of cancer, such as lymphoma, cervical cancer, head and neck cancer, and testicular cancer. Bleomycin A5, also named pingyangmycin, is the most commonly used sclerosing agent for the treatment of vascular anomalies in China. Histological in-

From the Department of Oral and Maxillofacial Surgery[a] and the Department of Image Diagnoses,[b] School of Stomatology, the Fourth Military Medical University.

Competition of interest: none.

Reprint requests: Dr. Kaijin Hu, School of Stomatology, the Fourth Military Medical University, ChangLe West Road 145 Xi'an, Shaanxi 710032, China (e-mail: hukaijin@fmmu.edu.cn).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2009.11.038

Table. Puig's classification scheme

Type	
I	Isolated malformation without peripheral drainage
II	Malformation that drains into normal veins
III	Malformation that drains into dilated veins
IV	Malformation that represents dysplastic venous ectasia

vestigation shows that bleomycin A5 can cause injury and detachment of endothelial cells and lead to narrowing or occlusion of the vessels.[7] Compared with sodium morrhuate and absolute ethanol, bleomycin A5 will not result in ulceration and necrosis in skin and mucosa. There are also no reports on hematuria and neuropathy. In addition, bleomycin A5 sclerotherapy has no great pain or nerve injury, which makes it especially suitable for treating VMs in the cervical-facial region. Therefore, intralesional injection of bleomycin A5 on VMs in cervical-facial region has been a routine therapy and has proven to be effective[3,5,7-11] in China.

However, traditional direct percutaneous treatment through aspiration of the blood could not really confirm the needle tip within the lesions. It still has a risk of complications, including intravascular injection, and is incapable of treating some lesions in deep tissues. Also, it is sometimes difficult to orientate the needle into the lesion. Therefore, it is necessary to look for other, more effective methods with relatively minimal side effects.

Ultrasonography with Doppler is an effective diagnostic tool to rate the blood stream. It allows an unambiguous classification as to venous, arterial, or lymphatic malformation,[12] which is a simple noninvasive method to distinguish slow-flow from fast-flow vascular malformation. Therefore, if ultrasound guidance technique is used in the treatment of VMs, the outcome might improve.

In this study, we present our experience and clinical outcome in treating 75 patients suffering from VMs in cervical-facial region with bleomycin A5 through ultrasound-guided intralesional injection.

PATIENTS AND METHODS

Patients admitted to our hospital were those with VMs in cervical-facial region. Patients chosen for bleomycin A5 treatment are non-allergic to the bleomycin A5 in the past and with no systematic disease. Each of them had small to middle sized VMs, and there was no drainage venuous from the lesion or the drainage venuous was less and their diameters were smaller by ultrasonography. Therefore, these VMs belonged to type I and type II lesions[13,14] according to Puig's classification system of VMs, which based on anatomical and hemodynamic features (Table).

There were 75 VMs patients treated at our hospital between June 2006 and February 2007. Thirty-two were male, while 43 were female, ranging in age from 13 to 60 years old. Diagnosis was confirmed by history, clinical presentations, physical examination, and ultrasonography with Doppler (GE Logiq 400 CL PRO, Milwaukee, Wisc). Of all the patients, 54 malformations (72%) were located in the facial region, including 32 (42.67%) in parotid region, four (5.33%) in orbital area, 16 (21.33%) in nasal-labial area, and two (2.67%) in frontotemporal area. The others involved eight (10.67%) in the submental region, 10 (13.33%) in the submandible region, and three (4%) in the cervical region. The lesion was measured clinically and confirmed by ultrasonography, with a maximum of 32×39 mm, and a minimum of 6×9 mm.

The powder of bleomycin A5 (TianjinTaihe Pharmaceutical Co. Ltd, Tianjin, China), 8 mg in dose, was dissolved by solution containing dexamethasone (5 mg, 1 mL; Shanghaitongyong Pharmaceutical Co. Ltd, Shanghai, China) and lidocaine 2% (4 mL; Beijingzizhu Pharmaceutical Co. Ltd, Beijing, China). If the size of malformations was less than 10×15 mm by ultrasonography, dexamethasone and lidocaine were reduced to half dose, while the injected bleomycin A5 dose remained 8 mg each time.

Before treatment, each patient underwent intramuscular injection of promethazine hydrochloride, an antiallergic drug, to prevent hypersensitivity. First, the lesion was again confirmed by ultrasonography. The suitable puncture pathway was also determined through multiple scanning. Then, a puncture needle was pricked into lesions under ultrasound guidance. After multiple scanning and the aspiration of the blood confirmed its intralesional position, the injection of bleomycin A5, filled in the externally connected syringe, was carried out through the inspection of ultrasonography. A multi-point injection was used so as to uniformly distribute bleomycin A5 in the lesion area. At last, the surrounding region of malformations and the injection pinhole were pressed for three to five minutes in order to prevent spilling or bleeding. Repeated course of bleomycin A5 injection was administrated for larger malformations. The therapeutic interval was two to four weeks.

All patients were monitored for vital signs and symptoms, general examination of blood, hepatic, and renal function tests, and chest X-ray during the course of their treatment. The therapeutic effect on VMs was evaluated by physical examination and ultrasonography with Doppler according to the Weidong Shou standards.[8]

Cured. Lesions disappear completely and the color of skin and mucosa are normal without functional disturbance. No recurrence has been observed on follow-up visit.

Basically cured. Lesions disappear basically. The color of skin and mucosa are normal or pigmentary lightly without functional disturbance. The appearance is asymmetrical and the patient needs observing.

Improved. The reduction of lesions is more than 50%, but the lesion did not disappear completely and needed other treatment or plastic surgery.

Invalid. The reduction of lesions is less than 50% after three to five times treatment.

All patients were observed for development of any local side effects (such as hyperemia, edema, pain, ulceration, and effusion in the injection region and surrounding tissue) or general side effects (such as fever, gastrointestinal reac-

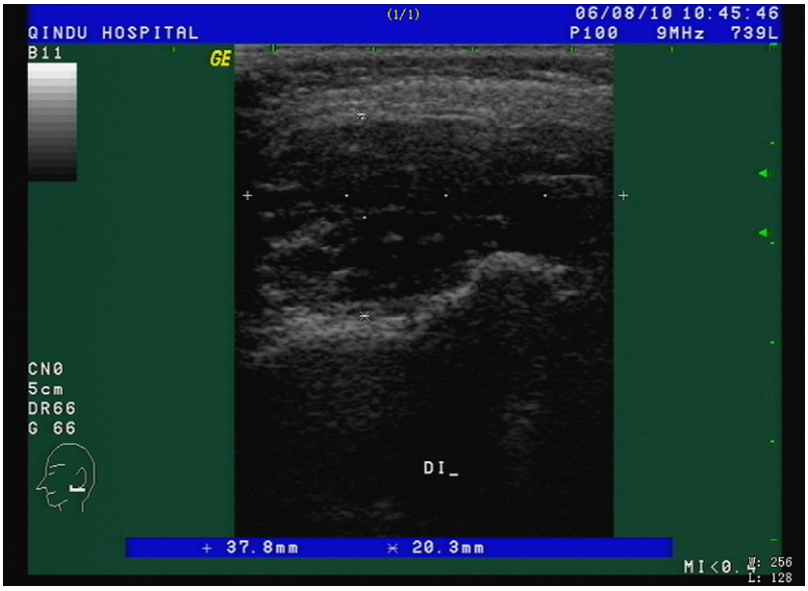

Fig 1. The ultrasonography image showed the lesion was 37.8 × 20.3 mm at the first visit on Aug. 10, 2006.

tions, pulmonary fibrosis, cutaneous reaction, and hypersensitiveness) during and after injection.

RESULTS

All 75 patients completed the treatment and achieve the ideal effect. The follow-up range was 6 to 24 months, and the mean follow-up time was 10.3 months. The average times of treatment were 1.64 times. Among them, 42 patients (56%) received only one time of treatment, 21 (28%) patients received two times, nine (12%) patients received three times, and three (4%) patients received four times. According to the follow-up visit, 84% (63 patients) were cured, 13.33% (10 patients) were basically cured, 2.67% (two patients) were improved, and 0% were ineffective.

Seventy-one patients (94.67%) had local swelling in injection regions but the swelling disappeared after three to five days without any special treatment. Two patients (2.67%) had momentary dizziness after treatment and felt better in 30 minutes.

There were no other local reactions and general reactions found during and after the treatment.

Typical case. Male, 14 years old, with a clinical diagnosis of VMs in left parotideomasseteric region. The first visit was on Aug. 10, 2006. The lesion is 37.8 × 20.3 mm, confirmed by ultrasonography (Fig 1). Injection of bleomycin A5 (8 mg) on VMs was carried out under ultrasound guidance. On Aug. 24, 2006, the lesion reduced to 22.5 × 10.0 mm (Fig 2) and the patient was given the second treatment; on Oct. 8, 2006, the lesion reduced to 14.5 × 8.3 mm (Fig 3) and the patient was given the third treatment. The lesion disappeared after three sessions, and the color of skin was normal without functional disturbance. No recurrence has been observed on follow-up visit on Jul. 25, 2007 (Fig 4).

DISCUSSION

The mechanism of bleomycin A5 on VMs is its injury to endothelial cells and occlusion of the vessels. After proper injections, the fibrous degenerated gradually and the lesions are under regression without necrosis and obvious scar. This minimally invasive treatment is easy to carry out and has an affirmatory effect. Therefore, it has an extensive application in clinics in China from the 1990s to now.[3,5,7-11] Zheng et al reviewed 3824 patients suffering from hemangiomas and VMs in cervical-facial region who underwent bleomycin A5 treatment in 31 reports published from 1991 to 2003 in China.[9] However, only 1335 patients were evaluated on therapeutic effect because both VMs and hemangiomas patients were included, as bleomycin A5 also has a therapeutic effect on hemangiomas.[7,11] In addition, there were also some reports using different classifications. Among them, 932 patients (69.81%) were cured, 263 patients (10.70%) were basically cured, 103 (7.72%) patients were improved, and 37 patients (2.77%) were ineffective. The effective rate was 97.23%.

However, single injection of bleomycin A5 without ultrasound guidance has been faced with many problems. The routine percutaneous treatment will make the drug disperse into surrounding tissues so that the drug concentration in lesion area will decrease significantly, which reduces the therapeutic effect. In addition, a lot of VMs in clinic are in deep region, adjacent to many important tissues such as parotid gland, facial nerve, and cervical vessels. Usually, the intralesional injection is based on clinical examination and injection into the lesion with aspiration of blood, which has a high risk, especially in treating lesions in deep regions. Sometimes misjudgement may lead to side effects and intravascular injection will result in serious complication. Therefore, Yamaki[15] first treated seven patients

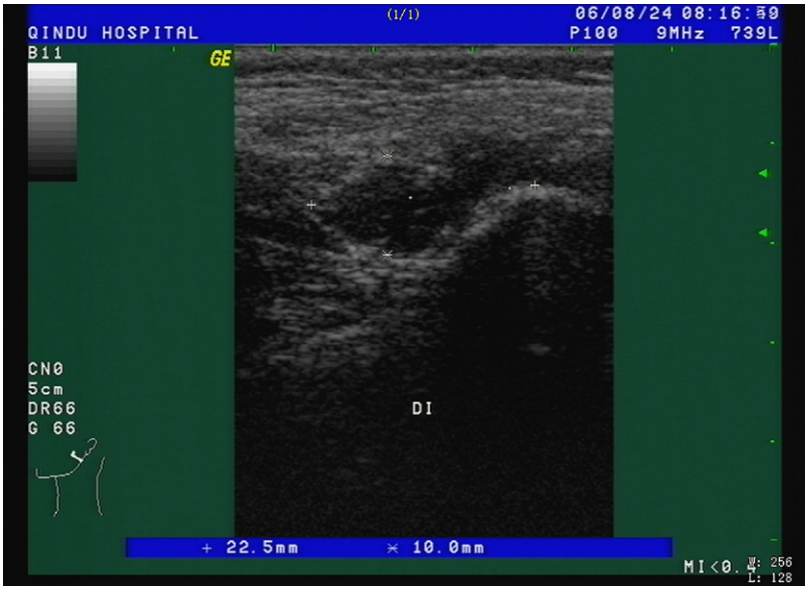

Fig 2. The ultrasonography image showed the lesion was 22.5 × 10.0 mm after the first injection of pingyangmycin on Aug. 24, 2006.

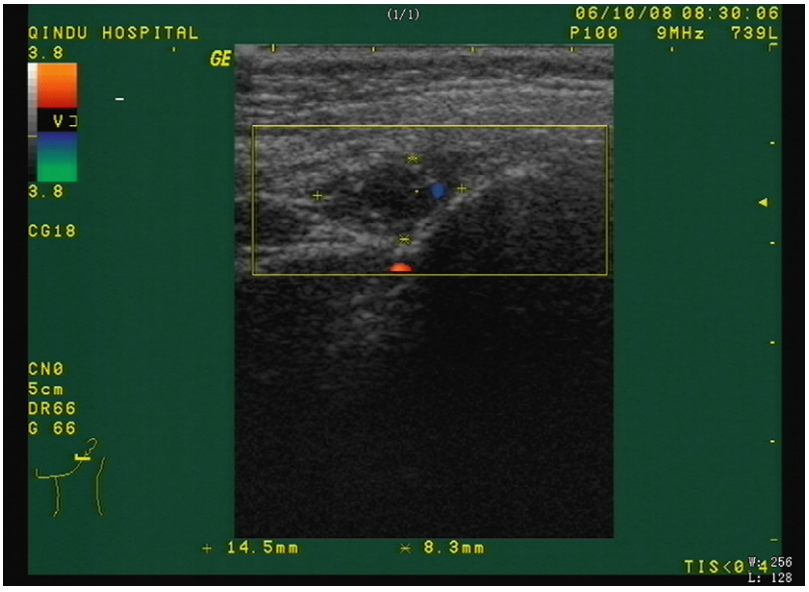

Fig 3. The ultrasonography image showed the lesion was 14.5 × 8.3 mm after the second injection of pingyangmycin on Oct. 8, 2006.

with VMs in cervical-facial region by intralesional injection of absolute alcohol under ultrasound guidance. Yamaki has researched this method in depth and reports many advantages of it. For example, it will prevent intra-arterial injection accidents.[15-17]

Bleomycin A5 has also been used to treat VMs in cervical-facial region for more than 10 years in our hospital.[5,7] We found there were some factors that affect the outcomes; for example, the size and location of the malformations, the number and the diameter of the drainage venuous, different treatment schemes, and whether there was ultrasound guidance. In this study, we evaluated the therapeutic outcome of injection of bleomycin A5 on treatment of venous malformation in cervical-facial region. The malformations were small to middle sized which had no drainage venuous or the drainage venuous was less and their diameters were smaller by ultrasonography. One or multiple times of injection of 8 mg bleomycin A5 in dose

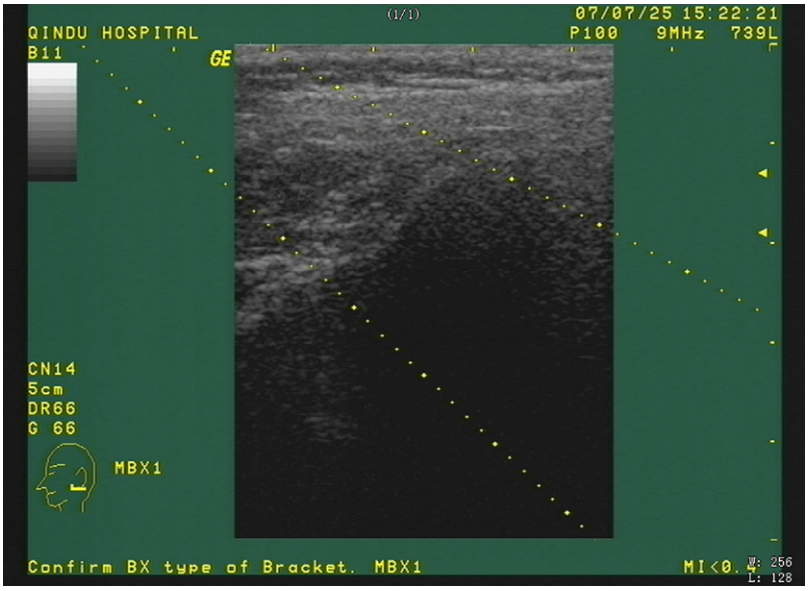

Fig 4. The ultrasonography image showed the lesion disappeared completely on follow-up visit nearly 10 months later (Jul. 25, 2007).

on malformation were carried out through the inspection of ultrasonography with therapeutic intervals of two to four weeks.

Through ultrasonic inspection, the range of lesions, the tissue plane occupied, and the relationship between lesions and surrounding tissues could be determined so that the effects of treatment could be improved by ensuring the precise injection position. After the follow-up visit, the results showed each grade of the therapeutic effect was improved comparing with the review results of Zheng,[9] which were 84% cured, 13.33% basically cured, 2.67% improved, and none ineffective. The effective rate reached 100%, which was also improved compared with the previous results[3,5,7,10-11,13-14] by routine treatment.

Considering the treatment times, the review of Zheng[9] showed that there were 302 patients who received one time of treatment, 266 patients received two times, a few received seven to eight times, and one even received 17 times, according to the reports that had such treatment time statistics. In this study, 63 patients (84%) received only one or two times of treatment, which suggests that on the one hand, the treatment time could be reduced under ultrasound guidance; on the other hand, the patients only suffered from VMs, and perhaps the sizes of VMs in this study were relatively smaller compared with others in former reports.

Considering the complications recorded, the review of Zheng[9] showed that of all the 3824 patients, two patients had anaphylactic shock (0.005%), 232 patients had fever (6.07%), 171 patients had gastrointestinal reactions (4.47%), 62 patients had local ulceration (1.62%), three patients had local cutaneous reaction (0.008%), and none had pulmonary fibrosis. While under ultrasound guidance, the treatment complications were reduced. For example, Yamaki[16] reported only swelling (75%) and local pain (82%) after treatment of patients with VMs in cervical-facial region by intralesional injection of absolute alcohol, though he had not used bleomycin A5, and these complications disappeared five to seven days later. Although the chances for complications may be raised in local tissue when bleomycin A5 is put in the wrong place with high dose, we observed that only transient local swelling (94.67%) and momentary dizziness (2.67%) were present in this study, as experienced doctors performed the whole operation under ultrasound guidance (R.H., J.G., Y.Y.).

These encouraging results were mainly relevant with the precise injection of bleomycin A5 into lesions under ultrasound guidance, which made the drug concentrations centralize in lesion areas so as to improve the therapeutic effect and reduce the complications. Moreover, the reduced complications were also relevant with the use of dexamethasone and the antiallergic drug before treatment. We have not mentioned the lesion recurrence in the study, for it may be associated with the fact that most lesions were relatively small and the time of follow-up interval was relatively short.

However, there are some weaknesses in this study. First, there was no control group in this report. We only did a retrospective study, not a prospective one. Second, there was a lack of the authors being blinded to the results. Therefore, a controlled, blinded study should be recommended in the future.

Although ultrasonic inspection was used each time, several advantages of this special treatment were found. First, the therapeutic effect was improved. The final results could suggest that the efficiency of utilizing bleomycin A5

was enhanced and the curative course shortened. Second, the treatment is safe. It has the ability to prevent the injury on the important tissues through the pricking path, which not only reduces the occurrence of complications but also enlarges the routine treatment range. Third, the treatment is minimally invasive compared with surgery. The application of this technique establishes a promisingly effect way for patients suffering from VMs.

AUTHOR CONTRIBUTIONS

Conception and design: RH, KH, DL
Analysis and interpretation: RH, JG, GL
Data collection: JG, LW, LK
Writing the article: RH, YY
Critical revision of the article: YY, LW, LK
Final approval of the article: KH, DL
Statistical analysis: GL
Obtained funding: N/A
Overall responsibility: KH

REFERENCES

1. Derby LD, Low DW. Laser treatment of facial venous vascular malformations. Ann Plast Surg 1997;38:371-8.
2. Yildirim I, Cinar C, Aydin Y, Cayci C. Sclerotherapy to a large cervicofacial vascular malformation: a case report with 24 years' follow-up. Head Neck 2005;27:639-43.
3. Zhao JH, Zhang WF, Zhao YF. Sclerotherapy of oral and facial venous malformations with use of pingyangmycin and/or sodium morrhuate. Int J Oral Maxillofac Surg 2004;33:463-6.
4. Lee CH, Chen SG. Direct percutaneous ethanol instillation for treatment of venous malformation in the face and neck.Br J Plast Surg 2005;58:1073-8.
5. Yang Y, Sun M, Hou R, Yan Z, Wang L, Cheng X, et al. Preliminary study of fibrin glue combined with pingyangmycin for the treatment of venous malformations in the oral and maxillofacial region. J Oral Maxillofac Surg 2008;66:2219-25.
6. Berenguer B, Burrows PE, Zurakowski D, Mulliken JB. Sclerotherapy of craniofacial venous malformations: complications and results. Plast Reconstr Surg 1999;104:1-11; discussion 12-5.
7. Yang Y, Sun M, Cheng X, Hu X, Zhang P, Ma Q, et al. Bleomycin A5 plus dexamethasone for control of growth in infantile parotid hemangiomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:62-9.
8. Shou WD, Ye BF, Shou BQ, Xu MY, Meng ZY, Yang Z. Clinical analysis of intralesional injection of Pingyangmycin in hemangiomas and vascular malformations in 520 patients [Chinese]. Journal of Practical Stomatology 2001;17:312-4.
9. Zheng JW, Chen CJ, Zhang ZY. Intralesional injection of pingyangmycin for hemangiomas and vascular malformations in oral and maxillofacial region: a systematic review of the Chinese Literature [Chinese]. China Journal of Oral and Maxillofacial Surgery 2003;1:102-5.
10. Liu Y, Liu D, Wang Y, Zhang W, Zhao F. Clinical study of sclerotherapy of maxillofacial venous malformation using absolute ethanol and pingyangmycin. J Oral Maxillofac Surg 2009;67:98-104.
11. Wang LL, Gao QH, Liu K, Wang XY, Wang CM, Wen YM. Intralesional pingyangmycin therapy for 51 infantile patients with parotid gland hemangioma. Shanghai Kou Qiang Yi Xue 2009;18:142-6.
12. Urban P, Philipp CM, Poetke M, Berlien HP. Value of colour coded duplex sonography in the assessment of haemangiomas and vascular malformations. Med Laser Appl 2005;20:267-78.
13. Puig S, Aref H, Chigot V, Bonin B, Brunelle F. Classification of venous malformations in children and implications for sclerotherapy. Pediatr Radiol 2003;33:99-103.
14. Puig S, Casati B, Staudenherz A, Paya K. Vascular low-flow malformations in children: current concepts for classification, diagnosis and therapy. Eur J Radiol 2005;53:35-45.
15. Yamaki T, Nozaki M, Fujiwara O, Yoshida E. Duplex-guided foam sclerotherapy for the treatment of the symptomatic venous malformations of the face. Dermatol Surg 2002;28:619-22.
16. Yamaki T, Nozaki M, Sasaki K. Color duplex-guided sclerotherapy for the treatment of venous malformations. Dermatol Surg 2000;26:323-8.
17. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. J Vasc Surg 2008;47:578-84.

Submitted Jul 12, 2009; accepted Nov 1, 2009.