

Clinical Study of Sclerotherapy of Maxillofacial Venous Malformation Using Absolute Ethanol and Pingyangmycin

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Purpose: The purpose of this study was to evaluate the outcomes of sclerotherapy of maxillofacial venous malformations by use of absolute ethanol and pingyangmycin (bleomycin A₅ hydrochloride).

Patients and Methods: We treated 23 consecutive patients with maxillofacial venous malformations by sclerotherapy with a combination of absolute ethanol and pingyangmycin under local anesthesia. The size of the lesions ranged from 2 cm × 2 cm to 12 cm × 10 cm. Venography showed the presence of large venous lakes. Venograms were obtained during the first procedure before and after injection of absolute ethanol (0.5-2.5 mL) to confirm the site of the nidus and assess the effect of sclerosis of the nidus and draining veins. Subsequently, 8 to 16 mg of pingyangmycin dissolved in 40 mL of saline solution was infused into the nidus by a dynamic infusion pump at a rate of 1 mL/min. If necessary, this procedure was repeated once in 2 or 4 weeks. The clinical outcomes and complications were evaluated.

Results: The duration of follow-up ranged from 6 to 37 months, with a mean of 20.3 months. Only 1 procedure was required in 3 patients, and the procedure was required to be repeated twice in 9 patients, 3 times in 7, and 4 times in 4. All the patients were satisfied with the treatment results, and excellent clinical results were obtained in 9 patients. There was no skin necrosis or nerve damage.

Conclusions: Percutaneous sclerotherapy with the combined use of absolute ethanol and pingyangmycin is a safe and effective treatment for maxillofacial venous malformations.

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Venous malformation (VM) is a common vascular disease of the face and neck.¹ VM is usually present at birth and grows proportionally with the body. Clinical presentations vary from simple varicosities to complex anomalies involving several tissue planes. Over the years, a variety of techniques have been used in the treatment of VM, including irradiation, electroco-

agulation, cryotherapy, laser therapy, copper implantation, surgical excision, and sclerotherapy.²⁻⁵ However, there are no effective ways to treat some of the larger lesions of VMs that grow without obvious boundaries and in complex anatomic sites. Surgical excision is useful only in the case of localized and limited lesions. Aggressive excision can lead to loss of motor function, nerve damage, or massive bleeding.^{5,6} Laser therapy (Nd:YAG [neodymium:yttrium-aluminum-garnet]) is effective for small superficial VMs and sometimes can be used for deep lesions after skin flap elevation.^{4,6} Sclerotherapy is an optional approach for treating this disease and is advantageous in that there is no external scarring. There have been attempts to use many sclerosants, including boiling water, sodium morrhuate, absolute ethanol, sodium tetradecyl sulfate, and bleomycin.^{5,9} Bleomycin is an established antineoplastic drug, and it is currently used as a sclerosing agent and exhibits a high incidence of residual disease.¹⁰ Pingyangmycin is bleomycin A₅ hydrochloride, commonly used in China for chemotherapy of oral cancer, and is now also used as a sclerosant. Absolute alcohol, the most destructive and reliable sclerosant, is widely used in the treat-

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ment of VM because of its low cost, antiseptic quality, wide availability, and ease of use. However, ethanol sclerotherapy often requires general anesthesia because the procedure is very painful and may cause coagulation disorder and skin necrosis if excessive alcohol is used for the treatment of large VMs.^{5,11,12} In this study we used absolute alcohol in combination with pingyangmycin in the sclerotherapy of 23 patients with VMs and obtained good clinical results.

Patients and Methods

From July 2002 to June 2005, 23 consecutive patients (12 male and 11 female patients) were referred to the department of oral and maxillofacial surgery for the treatment of maxillofacial VM. Their ages ranged from 2 to 38 years, with a mean of 21 years. Diagnosis of VM was confirmed by clinical presentation, ultrasonography, and intranidal venography. In all cases the lesion appeared during childhood and could enlarge when the lesion site was placed in a dependent position. The lesions were easily compressible, and blood samples could be obtained on needle puncture. No prior surgery was attempted. Of the patients, 5 underwent sclerotherapy with sodium morrhuate (2 cases) or pingyangmycin (3 cases) and presented with recurrent lesions. The lesion sites included cheek (9 cases), parotid region (2 cases), infraorbital region (1 case), scalp (1 case), chin (1 case), submandibular region (1 case), buccal and infraorbital regions (3 cases), and buccal and parotid regions (5 cases). The sizes of the lesions were measured clinically and confirmed by venograms, with a maximum of 12 cm × 10 cm and a minimum of 2 cm × 2 cm. Ultrasonography showed that all the lesions had 1 or more large venous lakes. Given the risk of tissue necrosis, VMs that mainly affected the superficial dermis or those without evident venous lakes were excluded from this therapy.

In the first procedure, percutaneous ethanol sclerotherapy was performed under the guidance of a venogram. By use of 7- to 9-gauge needles, contrast media were injected into the engorged vascular lesion with the patient under local anesthesia, and the lateral and frontal craniofacial projections were then obtained. After analysis of the nidus and draining veins on venograms, approximately one fourth to one third of the cavity volume of absolute ethanol (0.5-2.5 mL) was injected into the vascular nidus with manual compression of the surrounding region and the draining veins. The compression was maintained for 5 minutes to fix the ethanol in the nidus. Thereafter a lateral venogram was obtained again to determine the effect of sclerosis of the lesion. Finally, 40 mL of saline solution, mixed with 8 to 16 mg of pingyangmycin (Taihe Pharmaceutical Co, Ltd, Tianjin, China) and 10



FIGURE 1. Dynamic pump with 40 mL of pingyangmycin solution being infused.

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mg of dexamethasone, was administered via a dynamic pump at a rate of 1 mL/min (Fig 1). Antibiotics and painkillers were administered for 3 to 5 days after this procedure to control edema and pain. Repeated courses of ethanol injection and pingyangmycin infusion were administered for large malformations. The interval of sclerotherapy was 2 to 4 weeks. This time allowed for the swelling to subside. The patients were then followed up once at 2 to 3 months after sclerotherapy and examined with ultrasonography and occasional needle aspiration to evaluate any possible residual VM. If residual lesions persisted, the treatment would be repeated. The follow-up interval was 6 to 37 months, with a mean of 20.3 months. The clinical results were determined by reduction in the lesion size and patient satisfaction based on our consensus, and the results were rated by use of 4 grades: excellent ($\geq 80\%$ reduction in size), good ($\geq 60\%$ but $< 80\%$ reduction in size), fair ($\geq 40\%$ but $< 60\%$ reduction in size), and poor ($< 40\%$ reduction in size).

Results

On the basis of the results of the venogram, we categorized VMs into 2 morphologic types: 1) lobulated, which comprised rounded clusters of confluent vascular lakes with few connections to adjacent normal veins, and 2) varicose, which comprised irregular dilated conducting veins. The distribution of the 2 morphologic types was as follows: lobulated in 18 cases (Fig 2) and a combination of lobulated and varicose in 5 cases (Fig 3). The venous outflow from the malformations was minimal in 10 cases (Fig 2) and moderate in 13 (Fig 3). A total of 58 procedures were performed in the 23 cases. Only 1 treatment procedure was required in 3 patients, and the procedure was required to be repeated 2 times in 9 patients, 3 times in 7, and 4 times in 4. The total volume of absolute ethanol that was used ranged from 1 to 8 mL,

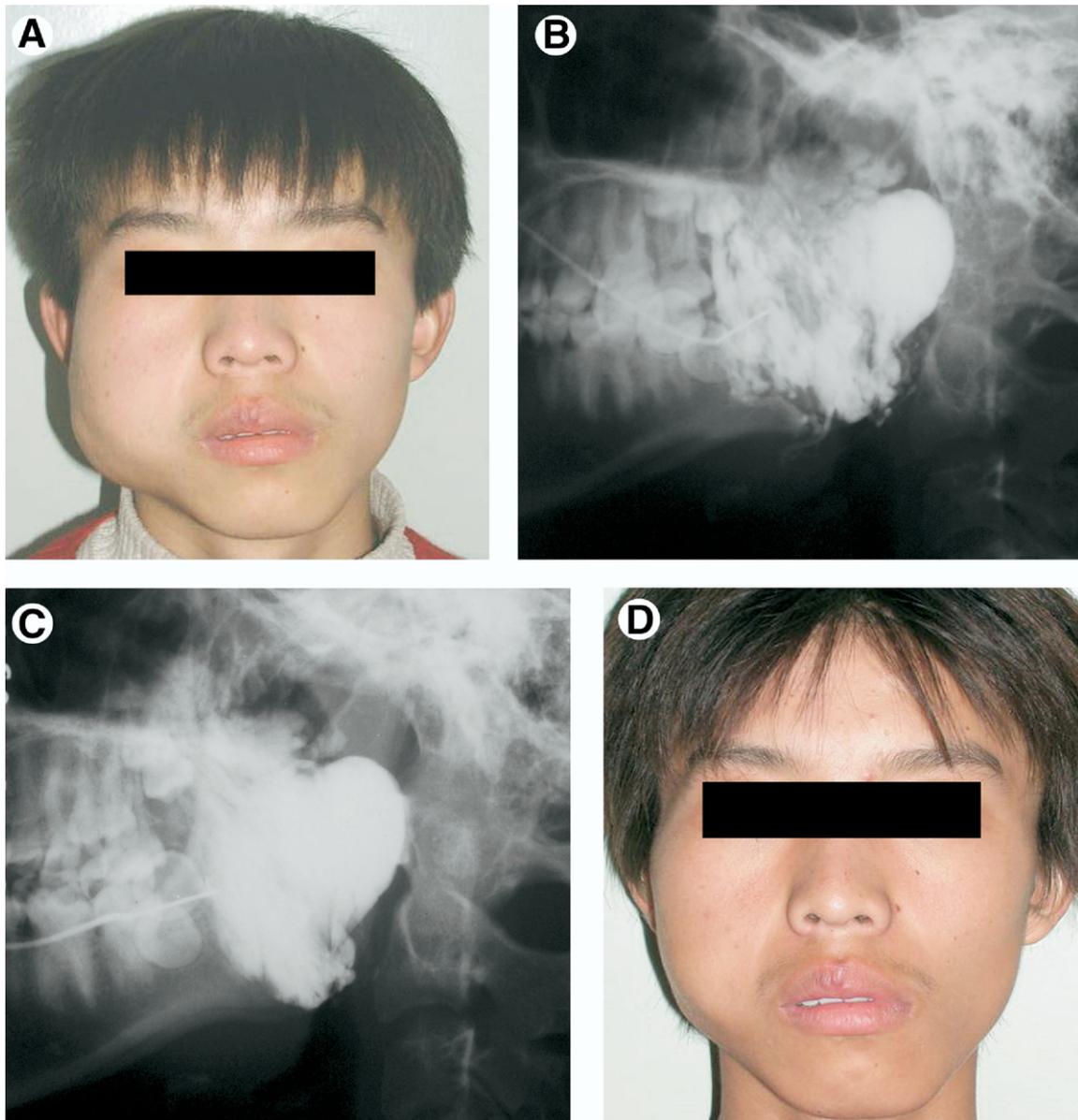


FIGURE 2. A, Photograph of a 17-year-old boy with right cheek and parotid VM. B, The percutaneous venogram showed a lobulated VM with minimal venous outflow. C, After ethanol injection, the outflow disappeared on the venogram. D, Photograph of patient 37 months after 4 sclerotherapy procedures.

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with a mean of 2.8 mL, and the overall dose of pingyangmycin ranged from 8 to 56 mg, with a mean of 22 mg (Table 1). All the patients had remission or alleviation of their symptoms. Excellent results were obtained in 9 patients (Figs 2, 4), with a follow-up period ranging from 12 to 37 months (mean, 23 months). The other 14 patients also presented good results, with a follow-up period ranging from 6 to 36 months (mean, 20 months), and were satisfied with the cosmetic appearance. All the patients had mild to moderate swelling and pain, and the symptoms were treated well within 3

to 5 days. No skin necrosis or neuropathy occurred in these cases.

CASE REPORTS

Case 1

A 17-year-old boy had a recurrent VM in the right cheek and parotid areas. The symptoms had been alleviated after 6 therapeutic procedures with sodium morrhuate injection at the age of 6 years, but they gradually recurred during the past 4 years. The size of the mass was approximately 8 cm × 8 cm. Examina-

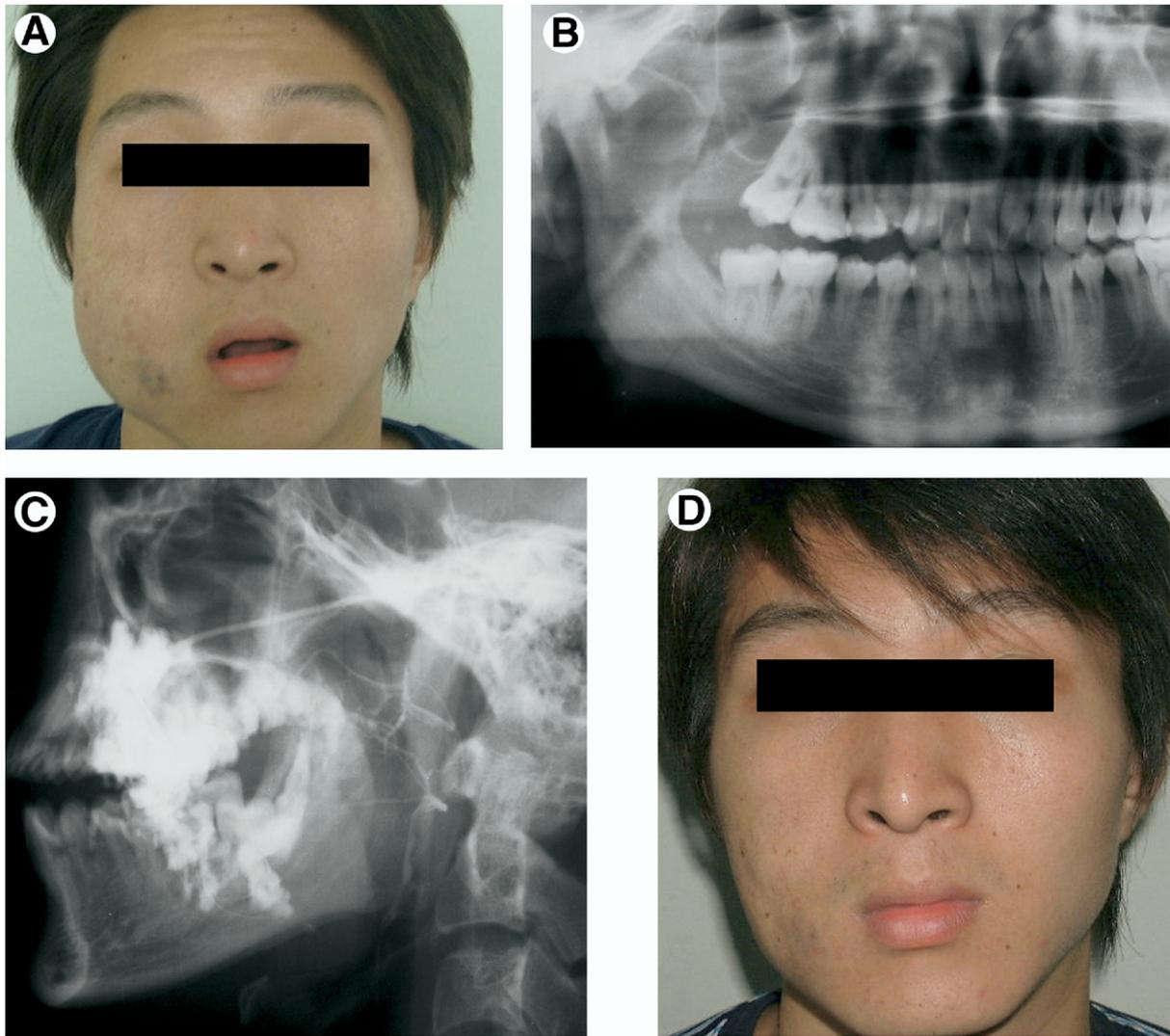


FIGURE 3. A, Photograph of 19-year-old man with right cheek VM. B, Panoramic tomography showed phleboliths, compression of the right ramus, and distortion of the dentition. C, The intralesional venogram showed the malformation. D, Photograph of patient 36 months after 3 sessions of sclerotherapy.

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tion showed that the mass was compressible with mild tenderness (Fig 2A). A percutaneous venogram of the lesion with 8 mL of 60% Urografin (Sunrise Haipu Pharmaceutical Co Ltd, Shanghai, China) showed a lobulated VM with minimal venous outflow (Fig 2B). Thereafter 2.5 mL of absolute ethanol was slowly injected into the nidus with manual compression of the surrounding area. Twenty minutes later, a lateral projection of the venogram was obtained again with the same amount of contrast media, which confirmed the disappearance of the venous outflow (Fig 2C). After this, 40 mL of saline solution with 16 mg of pingyangmycin and 10 mg of dexamethasone was infused via the previously mentioned method. Oral antibiotics were administered for 72 hours postoperatively to diminish any inflammatory reactions. Dur-

ing the next 6 months, 3 sets of injections were administered. The overall doses of ethanol and pingyangmycin were 5 mL and 56 mg, respectively. The lesion was almost completely obliterated after the 4 sclerotherapy procedures. The boy was very satisfied with the results (Fig 2D), and there were no complications or recurrence during the 37-month follow-up period.

Case 2

A 19-year-old man had a VM in the right cheek. The lesion became evident at the age of 3 years. He had received multiple sessions of laser therapy and sclerotherapy in other hospitals, but the lesion had recurred and grown gradually. Clinical examination showed a diffused soft mass with a small area of

Table 1. RESULTS OF SCLEROTHERAPY OF 23 PATIENTS WITH MAXILLOFACIAL VM

Case No.	Gender	Age (yr)	Position	Size (cm)	Procedure	Dose of Absolute Ethanol (mL)	Dose of Pingyangmycin (mg)	Interval of Follow-Up (mo)	Outcome
1	M	19	Buccal	6 × 4	3	3	24	36	Good
2	F	36	Buccal and infraorbital	4 × 5	3	4.5	24	13	Excellent
3	M	38	Parotid and buccal	4 × 6	3	2	24	24	Good
4	F	22	Buccal	4 × 4	2	1.5	16	26	Good
5	F	20	Buccal	3 × 4	3	2	20	22	Good
6	F	25	Buccal	2 × 2	1	2	8	36	Excellent
7	M	17	Buccal and parotid	8 × 8	4	5	56	36	Excellent
8	M	17	Buccal and parotid	8 × 5	3	2.5	24	36	Good
9	F	15	Buccal	3 × 3	1	2	16	25	Good
10	M	29	Buccal	2 × 2	1	1	8	37	Excellent
11	M	9	Parotid	4.5 × 5.5	2	2	16	13	Excellent
12	F	19	Buccal	5 × 5	2	2	16	36	Excellent
13	F	23	Buccal and infraorbital	5.5 × 3	3	2	24	11	Excellent
14	F	2	Frontal and parietal scalp	12 × 2	3	3	15	25	Good
15	F	24	Buccal	4 × 5	2	2	8	6	Good
16	M	14	Buccal and infraorbital	8 × 8	4	6.5	40	12	Good
17	M	19	Buccal and parotid	10 × 8	4	5.5	36	12	Excellent
18	M	22	Submandibular	5 × 6	2	2	24	13	Good
19	M	18	Parotid	5 × 6	2	2	24	25	Good
20	F	21	Buccal	3 × 4	2	2	16	24	Good
21	M	37	Buccal, infraorbital, and parotid	12 × 10	4	8	40	12	Good
22	F	18	Chin	4 × 3	2	1	16	23	Good
23	M	19	Infraorbital	2 × 2	2	2	16	12	Excellent

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discolored dermis in the right cheek (Fig 3A). The mass became more engorged in a dependent position. Panoramic tomography showed multiple phleboliths in the affected region. The right ramus was compressed, and the local dentition was distorted (Fig 3B). For the venogram, 6 mL of Urografin was injected and the malformation exhibited a combined lobulated and varicose morphology. The outflow was moderate (Fig 3C). Thereafter 1.5 mL of ethanol and 8 mg of pingyangmycin were administered. After 3 sets of sclerotherapy with a total of 3 mL of ethanol and 24 mg of pingyangmycin, the buccal mass evidently decreased. During the 36-month follow-up period, the patient was satisfied with the good cosmetic results and no recurrence was detected (Fig 3D).

Case 3

A 19-year-old woman had a soft mass in the right masseteric muscle area. The lesion became evident over the last 3 years and became more engorged

during biting (Fig 4A). We injected 8 mL of contrast media for the venogram, and the malformation was shown to be mainly lobulated with a mild venous outflow (Fig 4B). Thereafter 2 mL of ethanol and 16 mg of pingyangmycin were administered. Three months after this treatment, the mass disappeared and further treatment did not appear necessary. The patient was very satisfied with the outcome (Fig 4C), and no recurrence was detected during the 36-month follow-up period.

Discussion

Vascular malformation is a lesion that grows progressively with age and exhibits a normal rate of endothelial cell turnover. According to the channel abnormality, vascular malformations are subdivided into capillaries, veins, arteries, lymphatics, or a combination of these vessel types. Capillary malformations,

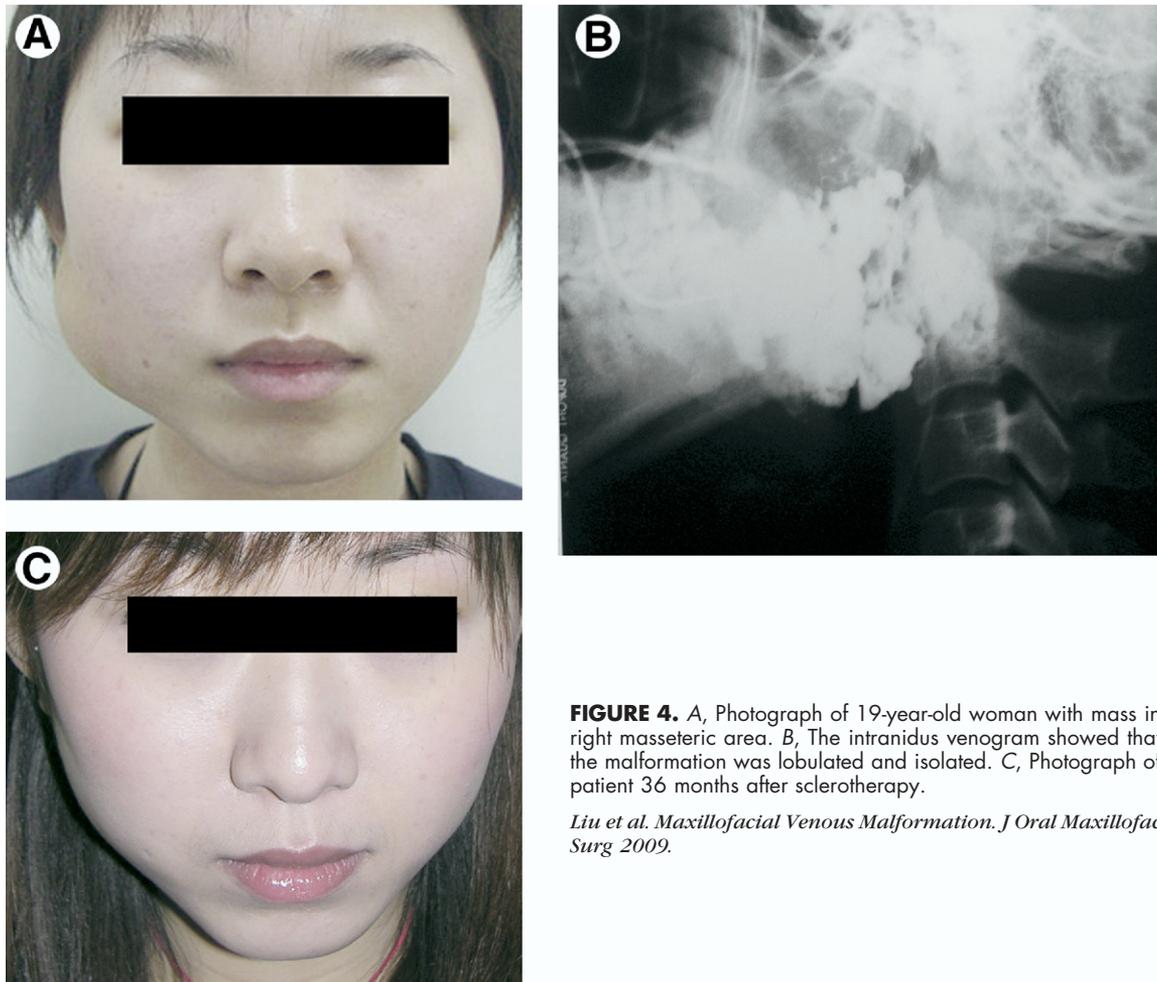


FIGURE 4. A, Photograph of 19-year-old woman with mass in right masseteric area. B, The intranidus venogram showed that the malformation was lobulated and isolated. C, Photograph of patient 36 months after sclerotherapy.

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lymphatic malformations, and VMs are slow-flow lesions, whereas arterial malformations, arteriovenous fistulas, and arteriovenous malformations are fast-flow lesions.^{5,13,14} Among all the vascular anomalies, VMs are the most common, particularly in the craniofacial region. Although they may be observed at birth, most lesions do not become clinically apparent until late infancy or early childhood.¹¹⁻¹⁴

Most VMs can be diagnosed easily by careful history and physical examination. They are soft, compressible, nonpulsatile masses. They may become more engorged with the Valsalva maneuver or when the involved area is in a dependent position.^{5,13} Symptoms vary with the size and location of the lesion. Patients frequently experience firmness and discomfort in the early morning, presumably as a result of stasis and microthrombosis within the lesion.^{6,13} Intraoral VMs can bleed, distort dentition, cause speech problems, or obstruct the upper airway. Ultrasonography is a simple noninvasive method to distinguish slow-flow from fast-flow vascular malformations, and we commonly use this method.⁶ Plain films can exhibit phlebitis in the mass and possible distortion of

bony structures in the vicinity. Magnetic resonance imaging (MRI) and intranidus venography are the most accurate imaging techniques for delineating VMs. These anomalies exhibit high signal intensity on spin-echo T2-weighted MRI sequences, which can be used to define the extent of the lesions and evaluate treatment outcomes.^{5,6,13} Our hospital is not equipped with an MRI machine, and hence, we were unable to perform MRI scans in most of our patients. However, intranidus venograms can illustrate the extent and morphologic characteristics of the nidus and draining veins, which are helpful for treatment considerations.

Management of low-flow VMs is difficult. Surgical resection may be hazardous because of major blood loss and incomplete resection. For anatomic reasons, VMs encase critical neuromuscular structures and have no evident limited boundary, thus increasing the difficulty of surgical treatment; consequently, high recurrence, scar, and facial paralysis are well documented.⁸ Sclerotherapy is selected as the first choice for VMs in the face and neck because it is advantageous in that there is no external scarring and there are few complications as compared with surgical

treatment. Sclerosing agents such as sodium morrhuate and ethanol are commonly used for this purpose. 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.⁹ Ethanol is a simple and reliable sclerosing agent that can directly damage endothelial cells, denature hematic proteins, and form thrombus. However, ethanol sclerotherapy is very painful and requires detection of the lesion volume before injection. Swelling, tissue sloughing, and neuropathy are the reported complications of ethanol sclerotherapy.¹¹⁻¹³ Cutaneous or mucosal necrosis presumably results from extravasation or reflux of the sclerosing agent into the subcutaneous or submucosal tissue.⁹ In our series superficial VMs or those without large venous lakes were excluded from this therapy. Another sclerosing agent, bleomycin, has also been commonly used for VM treatment over the past few years. Pingyangmycin is similar to bleomycin and can serve as a useful sclerosant. Intralesional pingyangmycin injection can damage endothelial cells by forming a deoxyribonucleic acid-Fe²⁺-pingyangmycin complex, cleaving deoxyribonucleic acid strands, interrupting cell proliferations, and leading to vessel wall hyperplasia or vessel occlusion.^{9,10} Mild swelling and pain can be well tolerated by the patients. In some patients mild fever may develop after injection of this drug, which can be controlled with relative ease. This can be useful to treat superficial VMs to minimize the risk of ulceration and for those proximal to important neurovascular structures. Pulmonary fibrosis, bone marrow suppression, or immunosuppression might occur only if the dose is considerably high (>500 mg).⁹ Direct percutaneous injection of pingyangmycin provides a reliable effect for small-sized lesions of VMs. However, for large lesions in the face and neck, it is difficult to obtain good clinical results because pingyangmycin is diluted soon after injection.

All these sclerosing agents have their particular advantages and limitations. The best choice is a combination of the advantages of each sclerosing agent and reduction of their limitations. Zhao et al¹⁵ exhibited good clinical results by using pingyangmycin and iodinate oil to treat VMs, as this method prolonged the treatment time of pingyangmycin in lesions. In this study we used ethanol and pingyangmycin to treat VMs. First, intranasal ethanol injection promoted thrombosis formation in the nidus and draining veins, thus reducing the blood flow speed and increasing the effective time of pingyangmycin in the lesion. Second, intralesional pingyangmycin infusion via a

dynamic pump further prolonged the pingyangmycin treatment time. Dexamethasone was added to the pingyangmycin solution to prevent allergy and to alleviate post-treatment edema. The overall volume of absolute ethanol was low, ranging from 1 to 8 mL, and only 0.5 to 2.5 mL of ethanol was used in 1 treatment session, thus decreasing the probability of associated complications. The dose of pingyangmycin was also low, ranging from 8 to 56 mg. Good clinical results were obtained in all cases, with 39% of VMs (9/23) being completely or almost completely obliterated. The complications were mild. Severe complications such as skin necrosis and neuropathy were not encountered. Therefore we believe that this method is safe and effective for VMs in the craniofacial region.

References

1. Takahashi S, Mulliken JB, Kozakewich HP, et al: Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 93:2357, 1994
2. Fishman SJ, Mulliken JB: Hemangiomas and vascular malformations of infancy and childhood. *Pediatr Clin North Am* 40:1177, 1993
3. Kane WJ, Morris S, Jackson IT, et al: Significant hemangiomas and vascular malformations of head and neck: Clinical management and treatment outcomes. *Ann Plast Surg* 35:133, 1995
4. Derby LD, Low DW: Laser treatment of facial venous vascular malformations. *Ann Plast Surg* 38:371, 1997
5. Lee CH, Chen SG: Direct percutaneous ethanol instillation for treatment of venous malformation in the face and neck. *Br J Plast Surg* 58:1073, 2005
6. Yildirim I, Cinar C, Aydin Y, et al: Sclerotherapy to a large cervicofacial vascular malformation: A case report with 24 years' follow-up. *Head Neck* 27:639, 2005
7. Shou BQ: The effect of relatively large dose of sodium morrhuate injection in the treatment of cavernous hemangioma in the oro-facial region. *J Oral Maxillofac Surg* 2:16, 1992
8. Karaca C, Barutcu A, Yilmaz M, et al: Treatment of hemangiomas and vascular malformations by electrothrombosis. *Eur J Plast Surg* 20:192, 1997
9. 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* 33:463, 2004
10. Mathur NN, Rana I, Bothra R, et al: Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck. *Int J Pediatr Otorhinolaryngol* 69:75, 2005
11. Goyal M, Causer PA, Armstrong D: Venous vascular malformations in pediatric patients: Comparison of results of alcohol sclerotherapy with proposed MR imaging classification. *Radiology* 223:639, 2002
12. Puig S, Aref H, Chigot V, et al: Classification of venous malformations in children and implications for sclerotherapy. *Pediatr Radiol* 33:99, 2003
13. Berenguer B, Burrows PE, Zurakowski D, et al: Sclerotherapy of craniofacial venous malformations: Complications and results. *Plast Reconstr Surg* 104:1, 1999
14. Choi YH, Han MH, O-Ki K, et al: Craniofacial cavernous venous malformations: Percutaneous sclerotherapy with use of ethanolamine oleate. *J Vasc Interv Radiol* 13:475, 2002
15. Zhao JH, Zhao YF, Wang SP, et al: Treatment of cavernous hemangioma in oral and maxillofacial regions with pingyangmycin and oleum iodisatum emulsion. *J Compr Stomatol* 2:127, 2002