Embolization and sclerotherapy of maxillofacial arteriovenous malformations with the use of fibrin glue combined with pingyangmycin

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Objective. The objectives of this study were to document the results of using fibrin glue (FG) combined with pingyangmycin (PYM) for the embolism and sclerotherapy of maxillofacial arteriovenous malformations (AVMs).

Study Design. We reviewed the associated clinical data from December 2012 to June 2017 for 25 patients with maxillofacial AVMs. The major treatment method was direct percutaneous puncture and injection of FG combined with PYM. Treatment outcomes were assessed through physical examination, Doppler ultrasonography, computed tomography, and 3-dimensional computed tomography angiography scans. Follow-up time ranged from 12 months to 3 years after the last treatment (mean 21 months).

Results. Of the 25 lesions, 80% showed greater than 90% reduction, 12% showed greater than 75% reduction, and 8% showed greater than 50% reduction. Superficial skin necrosis or mucous ulcer occurred in 3 patients and healed without intervention. Regrowth was observed in 3 patients with extensive lesions involving multiple anatomic regions.

Conclusions. These data suggest that embolization and sclerotherapy with the use of FG combined with PYM are safe and effective for the treatment of small- to medium-sized, locally dilated maxillofacial AVMs. For AVMs involving multiple anatomic regions, combined application of this approach with other options should be considered. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:25−31)

Arteriovenous malformations (AVMs) are congenital, high-flow vascular malformations composed of anomalous capillary beds shunting blood from the arterial system to the venous system.[1] AVMs may remain stable from birth to early adulthood but are likely to progress before adulthood, particularly during adolescence.[2] As a result of the hemodynamic alteration between the arterial and venous systems, AVMs demonstrate local and perivascular hyperplasia or rapid expansion. Hormonal changes, trauma, or infection are potential triggers that stimulate expansion.[3-5] Typical manifestations of AVMs include pain, tissue expansion and destruction, ulceration, disfigurement, and bleeding.[6] Extensive AVMs may lead to heart failure in the later stages. The management of AVMs has always been a challenge for clinicians. Traditional therapeutic methods of AVM treatment include embolization, surgical resection, sclerotherapy, or a combination of these modalities. Some antiangiogenic drugs have also been developed in recent years, but their effect on AVMs remains to be confirmed.[7,8] In many cases, treatment is not curative, and the recurrence rate is high. Some therapeutic methods may cause serious complications despite positive effects. It is, therefore, necessary to explore new therapeutic modalities that both improve the efficacy of therapy and decrease the incidence of complications.

Pingyangmycin (PYM), also known as bleomycin A5, is a sclerosant for the treatment of venous malformations (VMs) and has been extensively used in China. Since 2005, we have developed a new technique to improve the effects of PYM sclerotherapy: the combination of fibrin glue (FG) with PYM for the embolism and sclerotherapy of VMs. In 2008, we reported the

Statement of Clinical Relevance

The clinical results revealed that embolization and sclerotherapy with the use of fibrin glue combined with pingyangmycin could obliterate the nidus, feeding arteries, and draining vessels of localized maxillofacial arteriovenous malformations and that this advantage may reduce the recurrence rate.

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Received for publication May 26, 2019; returned for revision Dec 17, 2019; accepted for publication Feb 5, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.02.003

preliminary results of the use of this technique in 7 patients with VMs.[9] Later, we applied this method to treat larger and high-flow maxillofacial VMs. Our clinical results showed that intralesional injection of FG in combination with PYM is very effective in the treatment of VMs. Since 2012, we have attempted to treat maxillofacial AVMs by using this technique. Results have shown that injection of FG in combination with PYM effectively blocks the nidus, the abnormal feeding and outflow vessels of the medium-sized, locally dilated maxillofacial AVMs, with acceptable complication rates.

MATERIALS AND METHODS

Twenty-five patients with maxillofacial AVMs (most were small- to medium-sized, locally dilated AVMs) were chosen and treated with embolism and sclerotherapy by using FG combined with PYM from December 2012 to June 2017 at the Air Force Military Medical University−affiliated Stomatologic Hospital, Xi'an, Shaanxi, China. Of the 25 lesions treated, 22 were small- to medium-sized, locally dilated AVMs, and 3 were AVMs involving multiple anatomic regions. Twenty-two of these patients underwent direct puncture of the nidus and injection of FG combined with PYM, and 3 underwent both direct puncture and transarterial injection because of the larger size and obvious supplying arteries of their AVMs. Each patient received 1 to 5 scleroembolization procedures (mean 3 procedures) over the course of treatment, depending on the type, size, and response of the lesion. Six patients underwent surgical excision of the thickened fibrous connective tissue and residual lesions in addition to the above treatment (Table I). Institutional review board approval was obtained for this study from our treating hospital, and all patients involved in this study gave their informed consent.

For most patients, the procedure was performed routinely under regional anesthesia in the ward therapeutic room. Fibrin Sealant (FIBINGLUEAAS; Shanghai RAAS Blood Products Co., Ltd., Shanghai, China), also known as *FG*, was applied for embolization. This material consists of fibrinogen and thrombin prepared from human plasma. The mixture of these 2 components simulates the last phase of blood coagulation. The administered dose of PYM (Pingyangmycin; Jilin Aodong Pharmaceutical Industry group Yanji Co., Ltd) was 8 mg. PYM powder was dissolved in a solution (2 mL) containing dexamethasone (5 mg, 1 mL) and 2% lidocaine (1 mL), and then 1 mL of the solution was infused into fibrinogen (2 mL) and thrombin (2 mL) solutions, respectively. Equal volumes (3 mL) of the 2 components were simultaneously injected into the lesions by using 2 syringes and a sterile connected mixing system. Repeat injections were typically performed at 4-week intervals. The required number of embolization and sclerotherapy procedures per patient was dependent on the type, size, and therapeutic response of the lesions. A small incision was made in the submandibular area to expose the external maxillary artery and the anterior facial vein in patients who required external maxillary artery injection. One patient underwent transarterial injection via percutaneous direct puncture into the superficial temporal artery. To ensure the accuracy and effectiveness of treatment, scleroembolization was performed under the guidance of color Doppler ultrasonography. For lesions with thickened fibrous connective tissue and residual lesions after scleroembolization, surgical resection was routinely carried out under sedation or general anesthesia in the operating room.

Treatment outcomes were evaluated by physical examination and Doppler ultrasonography, computed tomography (CT), and 3-dimensional computed tomography angiography (3-D CTA) scans. Response rates were graded as follows: reduction greater than 90%, reduction of 75% to 90%, reduction of 50% to 75%, and reduction less than 50%. Follow-up time ranged from 12 months to 3 years after final treatment (mean follow-up time = 21 months).

Table I. Summary of lesions location, treatment methods, outcome, and complications in 25 patients

Parameter	*No. of patients (%)*
Sites	
Facial/zygomatic	3 (12)
Facial/cheek	5 (20)
Facial/ parotideomasseteric	2 (8)
Facial/frontal	1 (4)
Upper lip	5 (20)
Lower lip/chin	2 (8)
Paranasal/nasal dorsum/suborbital	2 (8)
Submental/submandibular/neck	5 (20)
Treatment method	
Direct puncture	22 (88)
Direct puncture/transarterial	3 (12)
Operation after embolization	6 (24)
Size reduction (%)	
Greater than 90%	20 (80)
Greater than 75%	3 (12)
Greater than 50%	2 (8)
Complications	
Superficial skin necrosis	1 (4)
Superficial mucous ulcer	2 (8)

RESULTS

The anatomic areas affected by AVMs, treatment methods, outcomes, and complications of the treatment are summarized in Table I, and the outcomes in typical cases are shown in Figures 1−3. Of the 25 study patients, 19 were males and 6 were females, and they

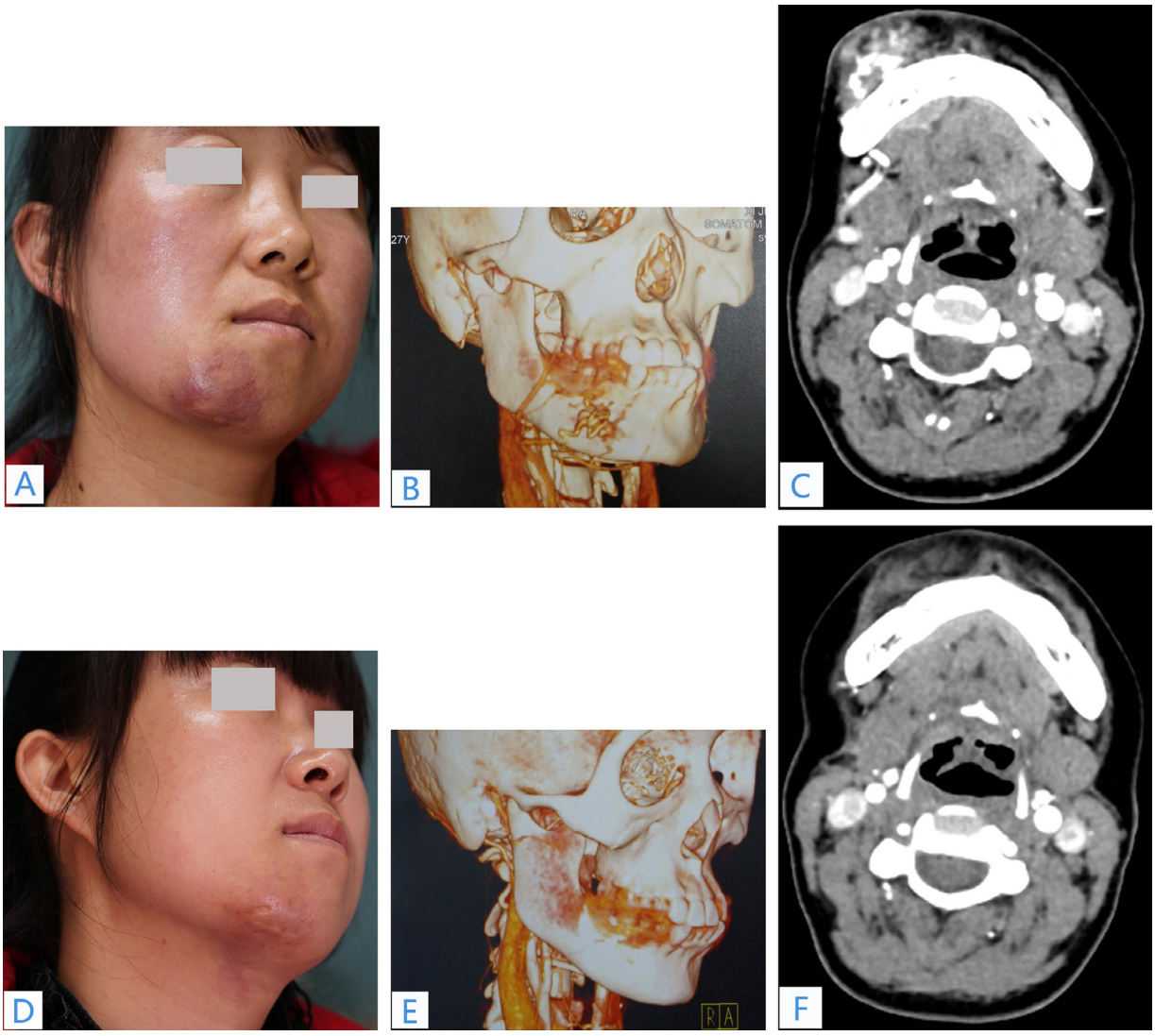

Fig. 1. Arteriovenous malformation (AVM) in the chin. Facial appearance, 3-dimensional computed tomography angiography (3-D CTA) and computed tomography (CT) scans before treatment (**A, B**, and **C**); Facial appearance, 3-D CTA, and CT scan after treatment (**D, E**, and **F**).

ranged in age from 19 to 74 years (mean 29 years). The average diameter of the lesion nidus was about 3.5 cm. An obvious reduction in pulsation, redness, swelling, and warmth was evident in all patients. Twenty of 25 lesions (80%) showed greater than 90% reduction; 3 (12%) showed greater than 75% reduction; and 2 (8%) exhibited greater than 50% reduction after treatment.

Minor complications were observed during the course of treatment. Some patients complained of hotness of the body and numbness of the treatment area immediately after injection of FG combined with PYM, but the sensation disappeared within a few minutes. Bluing of skin or mucosa occurred occasionally after direct puncture injection. Sudden whitening or blackening occurred commonly after transarterial injection, indicating tissue ischemia or obstruction of draining veins. Superficial skin necrosis occurred, and a thin crust formed on the forehead of one of the patients who underwent superficial temporal artery frontal branch injection and resolved on its own. Superficial mucous ulceration occurred in 2 of the patients and healed without intervention. Regrowth was observed in 3 patients with extensive lesions involving multiple anatomic regions. These patients underwent incomplete treatments and subsequent change of treatment plan.

DISCUSSION

Several options exist for the management of AVMs, and each has advantages and disadvantages. Transcatheter superselective arterial embolization is a common treatment modality for AVMs and can be used as either

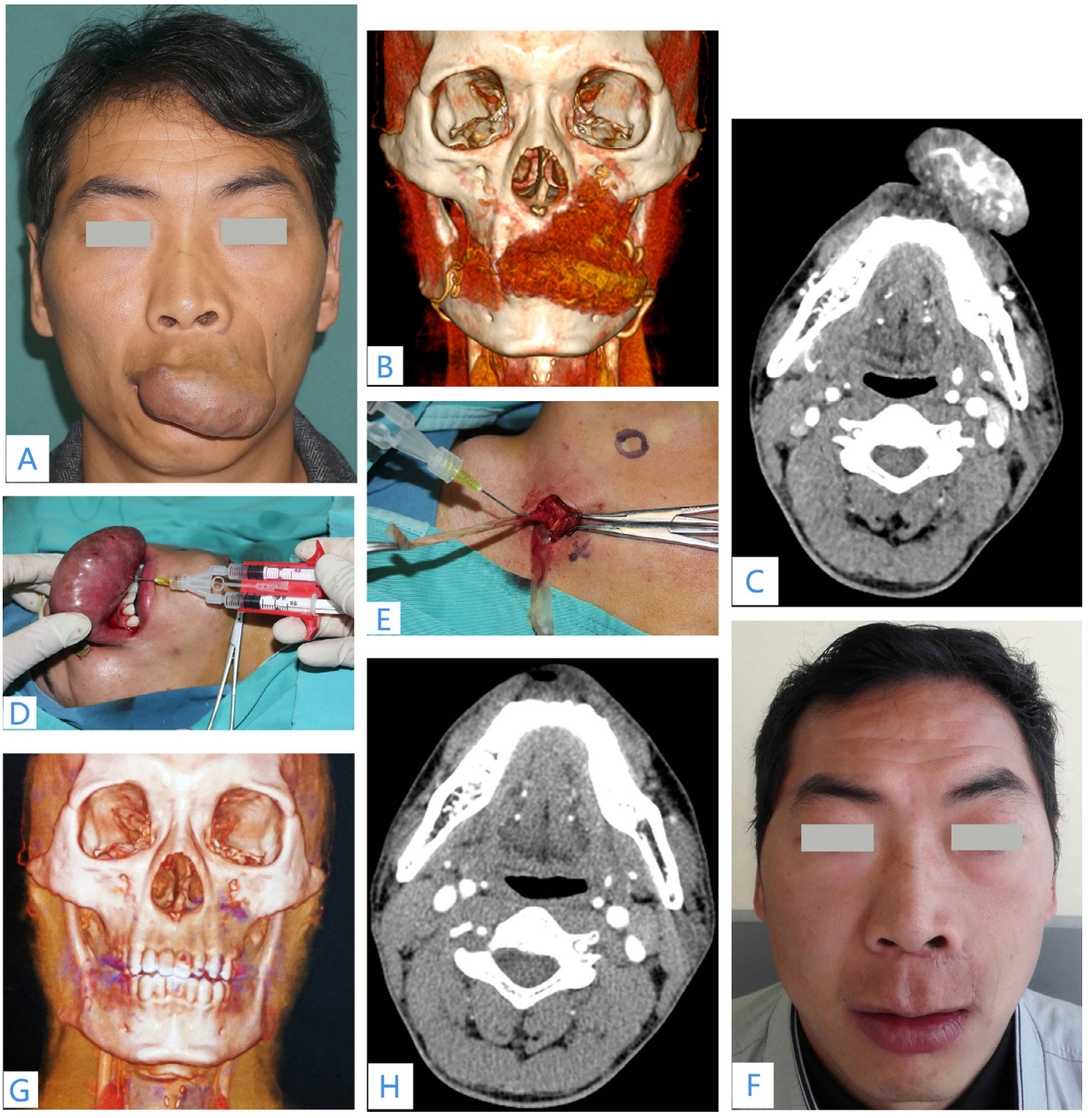

Fig. 2. Arteriovenous malformation (AVM) in the upper lip and paranasal area. **A**–**C**, Facial appearance, 3-dimensional computed tomography angiography (3-D CTA) and computed tomography (CT) scans before treatment. **D**, Direct puncture and injection of fibrin glue (FG) combined with pingyangmycin (PYM). **E**, Injection of FG combined with PYM through external maxillary artery. **F**–**H**, Facial appearance, 3-D CTA, and CT scan after treatment.

complete or adjuvant therapy. Various embolic materials,[10-13] such as Onyx Glue, N-butyl-2-cyanoacrylate, polyvinyl alcohol, absolute ethanol, Gelfoam, and coils, are used. With skilled operating technique and proper determination of indication, intravascular embolization may cure part of the AVMs. Additionally, embolization can be used as a preoperative procedure to control hemorrhage during surgery and to prevent bleeding from large nonresectable AVMs. Recent advances have included the use of Onyx (ethylene-vinyl alcohol copolymer) and absolute ethanol for embolization. The use of Onyx has enabled partial or complete control of lesions in anatomically challenging areas of the head and neck and has also enabled embolization in extensive lesions with multiple niduses without a large number of coils.[10,14] Absolute ethanol embolization has proven to be effective and safe and may help achieve curative effects in the management of infiltrating-diffuse extracranial AVMs in the head and neck.[13] The mechanism of this procedure is that

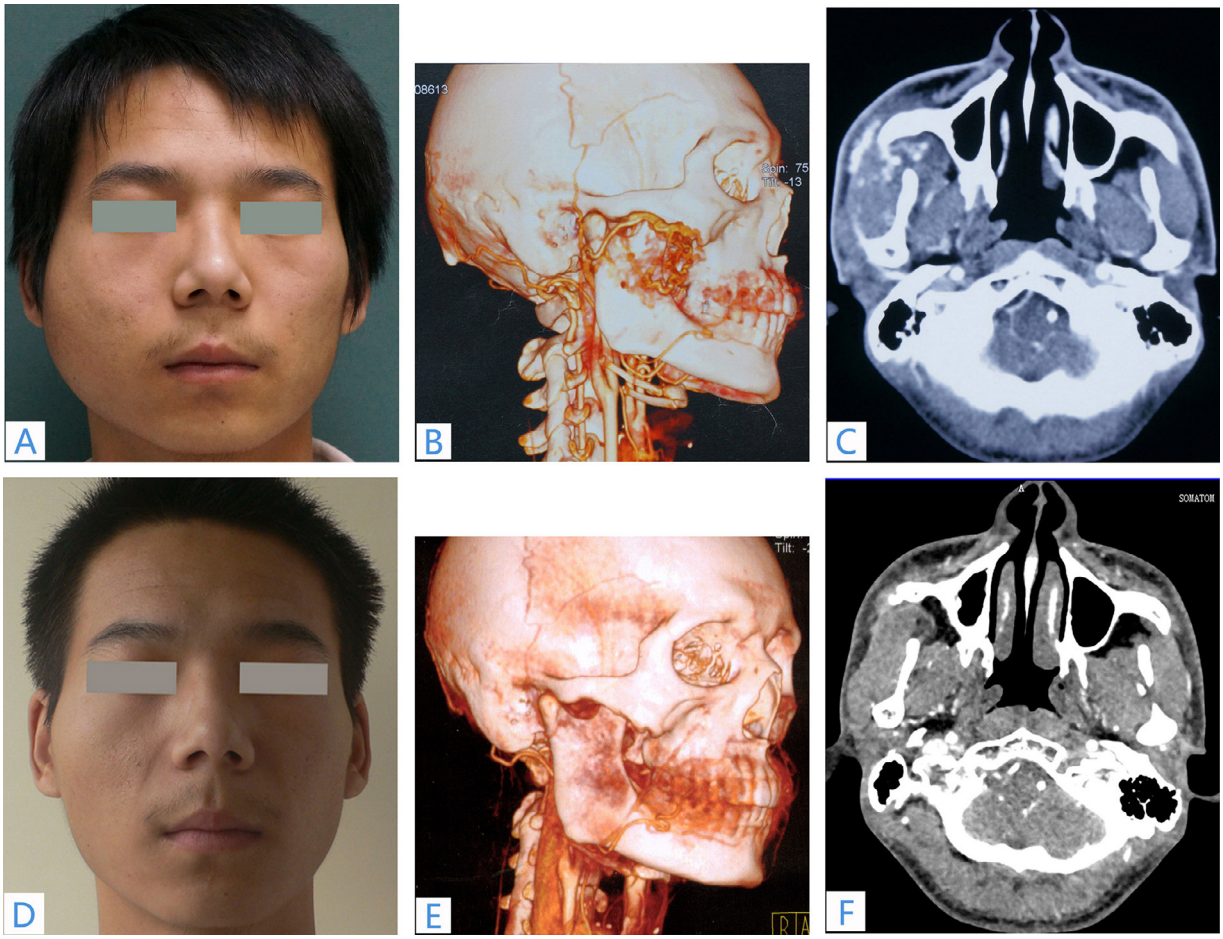

Fig. 3. Arteriovenous malformation (AVM) in the right facial and zygomatic areas. **A**–**C**, Facial appearance, 3-dimensional computed tomography angiography (3-D CTA), and computed tomography (CT) scans before treatment. **D**–**F**, Facial appearance, 3-D CTA, and CT scans after treatment.

absolute ethanol has a direct denuding effect on the vascular wall and clumping of damaged erythrocytes and denatured proteins, which results in complete and permanent obliteration of the vessel lumen.[13,15-17] However, the use of embolization has not yet been proven to be curative because of its associated high rate of re-expansion and complications, including local skin ulceration, mucosal sloughing, distal soft tissue necrosis, and neurologic damage.[2,18] Theoretically, this results from collateralization and recruitment of new vessels to support an undetected portion of the nidus.[1] Repeated embolizations may, therefore, improve patient outcomes.

Surgery is a significant option for the management of AVMs[19,20] and is usually recommended for the treatment of well-localized lesions that can be resected completely. Surgery also can be used to control life-threatening hemorrhage and to improve serious functional and cosmetic deformities. For diffuse or unresectable AVMs, however, surgical treatment may not be a judicious choice. Unreasonable excision and ligation of the feeding artery may lead to accelerated growth and further deterioration of the disease. In general, preoperative embolization combined with surgical excision may improve the chances of achieving a cure.[21,22]

The traditional approach of transcatheter interventional embolization through the femoral artery aims to obstruct the feeding arteries and results in an ischemic environment that favors collateralization and angiogenesis.[2,6] Similarly, incomplete resection and ligation of the feeding arteries may cause local tissue hypoxia and stimulate regrowth of new vessels. Currently, to moderate the limitations of both embolization and resection, direct percutaneous puncture sclerotherapy has been applied. This procedure utilizes particular, usually liquid, embolic materials, or sclerosing agents. The embolic materials are directly injected, with or without sclerosing agents, into the nidus of AVMs via a percutaneous route. The advantage of this technique is that it may obliterate the nidus and draining vessels more effectively, and, thus, the lesion can be better

controlled. Absolute ethanol, Onyx Glue, and PHILTM have been used for this procedure, and the resultant therapeutic effects have been favorable.[6,13,15]

FG is a natural hemostatic agent derived from plasma coagulation proteins. It is also known to be a fibrin sealant and has been extensively used as a hemostatic agent, a sealing agent, an adhesive agent, and a targeted delivery system for specific medications. FG also has applications in the management of vascular malformations, but fewer reports have been published to this effect.[9,23,24] Scleroembolization using FG combined with PYM is a procedure in which both FG and PYM are directly injected into the nidus of AVMs via a percutaneous or arterial route. Application of PYM alone is insufficient to achieve a sclerosing effect because of the high flow rate of blood through the AVMs, which makes combined application of FG and PYM essential for treatment. FG exhibits a period of fluidity immediately after injection, and this characteristic allows FG and PYM to fully penetrate the nidus and the draining veins. The coagulating and embolizing functions of FG are beneficial to the retention of PYM in the dysplastic cavity and vessels of the AVMs, thus enhancing the sclerosing effect of PYM. For the small and localized AVMs in this study, direct puncture of the nidus and injection of the sclerosing agent were performed. For the large AVMs in this study, with multiple niduses, both direct-puncture and transarterial injection were performed to ensure full coverage.

Our clinical results confirmed that embolization and sclerotherapy by using FG combined with PYM effectively obliterates the nidus, the feeding arteries, and the draining vessels of maxillofacial AVMs, especially in the case of localized AVMs. This therapeutic modality presents several advantages. With the use of PYM, the endothelial cells of dysplastic vessels can be damaged, and these vessels may be occluded permanently, thereby achieving a curative effect. FG is a natural, human-sourced embolic agent and is typically absorbed within 2 weeks after intralesional injection. Unlike other liquid embolic agents, such as n-butylcyanoacrylate glue, Onyx, or PHILTM, the risk of focal and perivascular inflammation is minimal after FG injection. As PYM is a mild sclerosing agent, it can destroy the endothelial cells in the nidus of the AVMs but rarely causes severe complications, such as tissue necrosis, neurologic damage, or systemic adverse reactions. In addition, most small, localized lesions may be cured without surgery by using this method. This is an important consideration for maxillofacial AVMs, given the aesthetic importance of this anatomic area.

Potential complications of embolization and sclerotherapy by using FG combined with PYM include allergic reactions, tissue ischemia, and abnormal embolism. Rational injection method and FG/PYM dose can help reduce the risk of abnormal embolization. In the process of treatment, we usually inject 3 mL of FG/PYM initially, and then we ask the patient whether he or she has any abnormal feeling; we also observe and try to detect any abnormal signs in the patients. If all goes well, we continue the injection. In our studies, we have not observed any serious complications. Bluishness and sudden whitening or blackening of skin or mucosa are sometimes observed, but these side effects disappear within a few minutes to several days. Because of the rich blood supply in the maxillofacial region, tissue necrosis caused by insufficient blood supply rarely occurs after injection of FG combined with PYM. The direct puncture and injection method is safer than transarterial injection. Sudden whitening or blackening usually occurs after external maxillary artery injection. Sometimes, the jelly-like mixture of FG and PYM can be found in the anterior facial vein after external maxillary arterial injection. This demonstrates that FG and PYM can penetrate the nidus and the draining veins and embolize the abnormal vascular network of the AVMs. However, sudden skin blackening often implies obstruction of draining veins and potential tissue necrosis. Keeping the anterior facial vein open, local puncture, and bloodletting are helpful for the prevention of possible local tissue necrosis.

In most cases, it is beneficial to eliminate the lesion if FG migrates into the vascular network of the AVMs. However, if FG migrates into vital blood vessels (e.g., internal jugular vein, pulmonary artery, ophthalmic artery, or internal carotid artery), serious complications may occur. To reduce the risk of abnormal migration of FG, we have excluded patients whose lesions communicated with vital blood vessels before treatment, as demonstrated by the results of Doppler ultrasonography and 3-D CTA. Embolization by using FG combined with PYM should be applied cautiously in the superficial temporal artery or its branches. For lesions located in the upper third of the facial area, the safer option is direct puncture and injection. Caution also should be exercised in the treatment of lesions where the nidus communicates directly with significantly dilated draining veins because FG clots may travel to the lungs and cause serious and sometimes fatal pulmonary embolism.

CONCLUSIONS

Our data suggest that embolization and sclerotherapy by FG combined with PYM is a safe and effective approach for the treatment of small- to medium-sized, locally dilated maxillofacial AVMs. For AVMs involving multiple anatomic regions and superficial skin, this method is not effective in eliminating all lesions, so application of this treatment in combination with other treatment options should be considered.

ACKNOWLEDGMENTS

We are grateful to Dr. Hollie Walsh and Dr. Hai Zhang from the University of Washington School of Dentistry, Seattle, WA, for their wise guidance, critical comments, and editing of the manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (Grant No. 81470757).

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