Pingyangmycin as First-Line Treatment for Low-Flow Orbital or Periorbital Venous Malformations: Evaluation of 33 Consecutive Patients

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**IMPORTANCE** Low-flow orbital or periorbital venous malformation (OVM) is the most common periorbital vascular lesion that may produce an appearance defect, visual dysfunction, internal hemorrhage, and thrombosis. Intralesional injection of pingyangmycin as a minimally invasive, gentle intervention may have better outcomes in treating low-flow OVMs compared with other currently used methods.

**OBJECTIVE** To investigate the efficacy and safety of intralesional injection of pingyangmycin for treatment of low-flow OVM.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective, noncomparative, interventional case series was conducted in a single medical center. Thirty-three consecutive patients with low-flow OVMs undergoing intralesional injection of pingyangmycin were included in the study.

**INTERVENTIONS** Injections of 1 to 5 mL of a pingyangmycin 1.5-mg/mL mixture with lidocaine hydrochloride, 2%, were given. Each patient received 1 to 4 injections at an interval of 6 to 8 weeks between February 2002 and January 2013. Mixture volume was determined on a basis of 0.5 mL of solution per cubic centimeter of the lesion. The maximum dose for 1 injection was 8 mg. Clinical observations were well documented before and after treatment.

**MAIN OUTCOMES AND MEASURES** Reduction of lesion volume based on ultrasound-measured volume; overall appearance, including blue color and thickness of lesions before and after treatment; and adverse events were evaluated.

**RESULTS** Patients received a median of 2 (range, 1-4) intralesional injections of pingyangmycin. The mean pretreatment volume was 4.4 cm³ and posttreatment volume was 1.0 cm³ (t = 4.63; P < .001), with a mean decrease of 84% (range, 28%-100%). Marked to moderate improvement in the volume of the lesions was noticed in 31 eyes (94%); 25 of 33 (76%) with marked improvement and 6 of 33 (18%) with moderate improvement. Improvement occurred in 95% (18 of 19) of superficial lesions, 100% (3 of 3) of deep lesions, and 91% (10 of 11) of combined lesions. We noticed significant improvements in blue color and thickness on the basis of investigator scores from clinical photographs taken before and after treatment. None of the patients had recurrence noted at their final follow-up. Adverse events were limited to swelling of the conjunctiva and localized subcutaneous atrophy.

**CONCLUSIONS AND RELEVANCE** The results of intralesional pingyangmycin injection for treatment of low-flow OVM are encouraging and associated with a low risk of adverse events.

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Vascular malformations can be arterial, venous, lymphatic, or a random combination of these elements. Orbital or periorbital venous malformations (OVMs) are one of the most common forms of orbital vascular lesion; they involve orbital anatomical spaces and encase critical neurovascular structures. Although not common in the pediatric age group, OVMs may be congenital and enlarge slowly in proportion to the growth of the child and may be associated with episodes of internal hemorrhage and thrombosis.

There are many treatment options for low-flow OVMs documented in the literature, including laser therapy, sclerotherapy, electrochemical therapy, surgical resection, and a combination of these options. Surgical excision is seldom attempted because it usually leads to vision damage, massive bleeding, and deformity if the lesion is extensive or located in the deep orbit, and it is impossible to remove the lesions completely. The effects of laser therapy are limited, and this technique is effective only in patients with small superficial tumors. Sclerotherapy has been increasingly used for treatment of low-flow venous malformations. Different sclerosing agents have been used to treat OVMs, including alcohol, sodium morrhuate, and pingyangmycin. Alcohol is the most potent sclerosant available; its mode of action is to chemically injure the vascular endothelium and denature blood protein, resulting in intense thrombosis. A limiting factor may be that alcohol can cause serious complications, such as intolerable pain and necrosis. Sodium morrhuate is a detergent solution that acts specifically on venous endothelium, inducing sclerosis by damaging the endothelium via interference with cell membrane lipids. Complications associated with sodium morrhuate include pigmentation, skin necrosis, and risk for severe allergic reactions (anaphylaxis). Pingyangmycin was first used as an antitumor agent. It has been found to have a sclerosing effect on venous malformations located in several areas, including the maxillofacial region. The mechanism for pingyangmycin sclerotherapy involves direct destruction of endothelial cells, induction of inflammatory responses, and formation of a thrombus and fibrosis, leading to obstruction of the vessels.

Research has shown that pingyangmycin used as a single agent has a positive effect on certain types of orbital vascular malformation, such as cavernous hemangiomas and distensible venous malformations. We therefore believed that patients undergoing intralesional injection of pingyangmycin might have similar or even better outcomes in treatment of low-flow OVMs because pingyangmycin is thought to be a milder treatment for such lesions, producing fewer adverse events. In the present study, which we believe to be the largest case series, we present our results on treatment of low-flow OVMs using intralesional injection of pingyangmycin.

Methods

This was a single-center, retrospective, noncomparative interventional case series of patients with low-flow OVMs who underwent intralesional injection of pingyangmycin. Approval was obtained from the institute’s ethics committee, and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained before each patient was enrolled in the study. All procedures were performed at the Department of Ophthalmology, Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine between February 14, 2002, and January 15, 2013. Patients with low-flow OVMs who came to the clinic for their initial treatment and had at least 1 follow-up examination were included. Participants did not receive financial compensation.

Diagnosis of low-flow OVMs is based on history, clinical manifestations, and imaging appearances. Generally, in superficial lesions, a dark blue lesion beneath the skin or conjunctiva is noticed first; in deep lesions, proptosis might be the only symptom. To differentiate OVMs from other orbital vascular lesions, the Valsalva maneuver and any other posture that may cause elevation of venous pressure should be performed. Doppler ultrasonographic examination is necessary to determine the velocity of blood flow in the lesion. Computed tomography or magnetic resonance imaging is needed as well to determine the range of the lesions. Treatment is required to relieve the pain caused by thrombosis or to resolve cosmetic or functional problems.

Eligibility of Patients

All patients who came to the clinic underwent a detailed preoperative assessment, including the history of previous interventions, course of the disease, Valsalva maneuver, 3-dimensional reconstructed computed tomography or magnetic resonance imaging with and without contrast, and Doppler ultrasonography. Photographs were taken to record and estimate the coloration and thickness of the lesions. The distensibility of the lesions was judged by compression of the jugular vein during computed tomography or magnetic resonance imaging; patients with distensible lesions were excluded. The velocity of the blood flow was measured using Doppler ultrasonography. Patients with high-blood flow vascular malformations, such as arteriovenous malformations; no-flow vascular malformations, such as lymphatic malformations; and low-flow malformations, such as cavernous hemangiomas, were excluded. Patients who had previously received treatment or had received other therapeutic modalities were also excluded. Low-flow OVMs were classified anatomically into 4 different groups: (1) superficial lesions that typically consist only of visible vascular malformations of the conjunctiva or lid, (2) deep lesions that usually have no surface manifestations and are entirely retrobulbar, (3) combined lesions that have both superficial and deep components, and (4) complex lesions that involve the orbit, periorbital, and intracranial tissues and may involve multifocal sites.

Treatment Protocol

Superficial lesions were treated by percutaneous injection, whereas deep lesions were treated following transluminal or transconjunctival orbitotomy to completely expose the surface of the lesions under direct vision. Before treatment, sterilization was performed with povidone-iodine. A mixture of 8 mg of pingyangmycin powder (8 mg in powder form per am-
Pingyangmycin for Periorbital Venous Malformations

Outcome Measures
Data on the location of the malformation, age at initial treatment, number of injections, dose, adverse events associated with therapy, and duration of follow-up were retrieved from patient records and analyzed. Patients were asked to visit the clinic 1 week, 1 month, 3 months, 6 months, and 1 year after their last treatment, and photographs were taken by one photographer using the same background.

The primary outcome was the reduction in volume of each patient’s lesion as measured before treatment and 3 months after treatment. An ultrasound-based method of calculating volume was used to estimate the volume of lesions before and after treatment.

Table 1. Clinical Characteristics of Included Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (55)</td>
</tr>
<tr>
<td>Eye</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15 (46)</td>
</tr>
<tr>
<td>Left</td>
<td>18 (54)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>23.8 (11.2)</td>
</tr>
<tr>
<td>Follow-up, mean (SD), mo</td>
<td>7.9 (8.3)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Eyelid, upper or lower</td>
<td>17 (52)</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Intraconal</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Glabella</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Inner canthus</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>19 (58)</td>
</tr>
<tr>
<td>Deep</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Combined</td>
<td>11 (33)</td>
</tr>
</tbody>
</table>

Results

Clinical Features of Patients
Thirty-three patients underwent intralesional injection of pingyangmycin between February 14, 2002, and January 15, 2013 (Supplement eTable 1). Their ages ranged between 4 and 45 years (mean [SD], 23.8 [11.2] years). There were 15 (45%) male patients and 18 (55%) female patients. Follow-up duration ranged from 2 to 48 months (7.9 [8.3] months). All patients had venous malformations confined to the periorbital or orbital area, among which 15 (45%) were right-sided and 18 (55%) left-sided. Seventeen patients (52%) had upper or lower eyelid involvement; 9 (27%) of these had conjunctiva involvement, 2 (6%) had glabella involvement, and 1 (3%) had inner canthus involvement, and 4 (12%) lesions were located intraconally. Nineteen (58%) patients had superficial lesions, 3 (9%) had deep lesions, and 11 (33%) had combined lesions (Table 1).

Safety
The adverse events reported were conjunctival swelling in 2 patients (6%), subcutaneous atrophy in 1 (3%), and transient blurred vision in 1 (3%) patient (patient 13) during injection, which resolved 10 minutes later. In patient 7 (Figure 1), swelling of the conjunctiva was observed 3 days after the initial injection of pingyangmycin; however, it had subsided at the 1-month follow-up, and a second injection was performed with good cosmetic outcome. Only patient 6, who had very large combined multiple OVMs, experienced moderate pain during the injection; because she felt the pain was tolerable, opiates were not used. No systemic or functional ocular complications have been observed.

Efficacy
All patients showed decreased volume of their lesions and improvement in clinical symptoms. The mean volume of the lesions before treatment was 4.4 cm³ and after treatment, 1.0 cm³ (t = 4.63; P < .001), with a mean decrease of 84% (range, 28%-100%). Degrees of reduction in the volume of the lesions are...
presented in Table 2. Moderate to marked improvement in the volume of the lesions was noticed in 94% (31 of 33) of the eyes (76% [25] with marked improvement and 18% [6] with moderate improvement); there was 95% (18 of 19) improvement in superficial lesions, 100% (3 of 3) in deep lesions, and 91% (10 of 11) in combined lesions. No significant differences were found between these 3 lesion subtypes (P = .11). There were significant improvements in the blue coloration and thickness of OVMs as well based on the scores of investigators from clinical photographs taken before and after treatment (Table 3). Patient 3 and patient 11 are shown as examples (Supplement [eFigure 1 and eFigure 2, respectively]). Patient 12 had a lesion with significant extension to the frontal, glabella, upper eyelid, and canthus areas (Supplement [eTable 1]). Although the lesion showed a reduction in volume of 28%, outcomes with respect to blue color and thickness remained poor owing to atrophy of subcutaneous tissues, such as fat and muscles, caused by long-term compression of the lesion preoperatively. After treatment, the reduction in volume of the lesion made the blueness and unevenness of skin surface more apparent (Supplement [eFigure 3]). The median number of pingyangmycin treatments was 2 (range, 1-4) (Supplement [eFigure 4]). None of the patients experienced recurrence.

**Discussion**

Orbital and periorbital venous malformations are congenital malformations rather than neoplasms. Pathologically, they consist of thin-walled vascular channels with deformity of smooth muscle; they have been classified as high-flow, low-flow, and no-flow malformations. Low-flow venous malformations are nondistensible lesions that usually exist at birth as dysmorphic vessels and increase in size with age. They may be localized or extensive and frequently require intervention because of cosmetic or functional ocular concerns, as well as potential risks of pain, thrombosis, or hemorrhage due to the low blood flow. Figure 2 shows an example of a giant intra-
conal venous malformation in a 4-year-old child that caused a proptosis of 4 mm in the right eye. A 94.6% reduction in volume was shown by magnetic resonance imaging, and the proptosis resolved after 1 intralcal injection of pingyangmycin. In our study, OVMs often appeared to be located in the upper or lower eyelid (52%), in which the compression of lesions may lead to deformation or atrophy of eyelid muscle, causing ptosis, visual axis occlusion, or eyelid retraction.

Several interventions, such as percutaneous absolute ethanol sclerotherapy, carbon dioxide laser ablation, surgical excision, or a combination of these treatments have been used to treat OVMs, with variable results. However, the use of absolute ethanol sometimes leads to unendurable pain and is associated with the risk of optic nerve injury due to the inflammation that occurs after treatment, whereas laser therapy and surgical excision are applicable only for superficial lesions.

We searched for literature on various interventions on OVMs in PubMed (January 1, 1999, to December 31, 2013). Although there were a few studies, most focused on high-flow OVMs. Two studies mentioned low-flow OVMs; however, low-flow was not separated from high-flow OVMs in descriptions of the treatment procedure or outcomes. Various interventions used for OVMs are listed in the Supplement (eTable 2). Pingyangmycin provides a milder form of sclerotherapy and is less likely to cause adverse events such as subcutaneous atrophy, venous occlusion, and pain.

Previous studies have described successful experience with pingyangmycin as first-line therapy in the management of vascular malformations in the maxillary region. It has also been shown that pingyangmycin can have very promising effects on 2 specified kinds of OVM: cavernous hemangiomas and distensible venous malformations in the periorbital area. Pingyangmycin used as a single agent can significantly shrink the volume of orbital cavernous hemangiomas, even with a single intralcal injection. More notably, the proptosis swelling and pain associated with high-flow OVMs can be almost relieved by the use of pingyangmycin mixed with fibrin glue or lipiodol emulsion. These agents may increase the local residence time of pingyangmycin, thus increasing the efficacy of the treatment.

Unlike cavernous hemangioma and high-flow OVMs, low-flow OVMs are characterized by slow blood flow. This allows
Pingyangmycin to remain in the target venous malformations longer, thus shrinking the lesions to a greater extent and avoiding damage to noninvolved vessels.15 The results of previous studies13-15 have raised the possibility that pingyangmycin may play a similar or better role in the treatment of low-flow OVMs. Therefore, we sought to evaluate the efficacy and safety of intralesional injection of pingyangmycin in the management of low-flow OVMs, with mean follow-up of 8 months for 33 consecutive patients, on the basis of correctly distinguishing the orbital vascular diseases present.

Fluoroscopic guidance has proved to be useful in verifying the location and drainage of deep lesions.24 In our study the superficial surfaces of deep lesions could be fully exposed using a transcutaneous or transconjunctival surgical approach, and the injection was performed under direct vision to avoid injection into surrounding tissues. This procedure has been used successfully in other studies.15

In the present study, we used various outcome measures, including measurement of lesion resolution and masked assessments of photographs by 3 independent investigators, which helped to minimize bias. Patients experienced significant reduction in the volume of their lesions after treatment. Approximately 76% of the OVMs showed obvious reduction in volume at the end of the study, 18% (n = 6) had a moderate response, and 6% (n = 2) had a slight response, which coincides with the findings of other studies.13,25 We recommend the use of transconjunctival incision in deep low-flow OVMs. The advantage of this technique is the ease of exposure of the lesion, allowing accurate injection of pingyangmycin and thus reducing the lesion volume more effectively. This method has not been used previously in the treatment of OVMs.22 Examination and scoring of serial photographs revealed significant improvement in the thickness and blue coloration of the lesions in most cases. In the present study, a 29-year-old patient showed minimal response to the intervention because the lesions had been compressed by a large area of venous malformation; the uneven skin and lack of normal tissue became more evident after a decrease in the volume of the lesion, which led to a poor cosmetic result. Therefore, a combination of pingyangmycin injections with other interventions, such as surgical or laser procedures, may be an alternative for some patients.

The most common serious adverse event associated with the use of pingyangmycin is pulmonary fibrosis.26-28 However, intralesional injection of pingyangmycin was generally well tolerated in the present study. The patients remained systemically stable because the doses that we used were far below those that may cause toxic effects. However, among 9 patients with conjunctival lesions, 2 patients (22%) (patients 6 and 7) experienced a period of conjunctival swelling and associated pain after the initial pingyangmycin injection. Patient 7 demonstrated complete resolution at her first follow-up 4 weeks after treatment and developed no more swelling during the second injection. Patient 6, in whom the lesion extended to involve the frontal, glabella, upper and lower eyelid, conjunctiva, and maxillofacial areas, experienced severe swelling of the conjunctiva 2 days after the first injection and was referred to the Department of Oral and Maxillofacial Surgery for further treatment. The degree of swelling of the conjunctiva showed an 80% reduction at her 48-month follow-up examination.

The study limitations are the heterogeneous patient population, small sample, and use of a single center. Although scoring was performed by 3 independent investigators, measurement bias was a potential limitation. In addition, we failed to obtain more than 6 months’ follow-up data from some of the patients, mainly as a result of their inadequate adherence. Patients were asked to revisit the clinic and the risk of recurrence was emphasized; however, some patients did not consider recurrence to be possible after 6 months. Finally, the risk of central retinal artery occlusion and optic nerve injury, although small, cannot be discounted. Safety cannot be proved by the absence of catastrophic adverse effects in this study of a small group of patients. The risk of central retinal artery occlusion and optic nerve injury with intralesional injections was avoided in the present study, which does not mean it is not a clinical practice with potentially serious adverse events.

Conclusions

On the basis of our findings, intralesional injection of pingyangmycin is a safe and effective treatment of all types of low-flow OVMs. Significant reductions were shown in the volume of the lesions and blue coloration; reductions in thickness were remarkable as well. Adverse events were inevitable, but most were mild and tolerable. Multicenter research with a larger number of participants may help to confirm these results.


