

# Sclerosing Therapy as First Line Treatment for Low Flow Vascular Lesions of the Orbit

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- **PURPOSE:** To evaluate the outcome of sodium morrhuate 5% injections in patients with low flow vascular lesions, which consist of orbital lymphangiomas, and in one patient with intraosseous cavernous hemangioma.
- **DESIGN:** Prospective, interventional consecutive case series.
- **METHODS:** Intralesional sodium morrhuate 5% was injected under direct visualization or under radiographic guidance to six patients with orbital lymphangiomas and one patient with intraosseous cavernous hemangioma. Comprehensive eye examination and follow-up imaging studies were performed. **MAIN OUTCOME MEASURES:** Lesion size was evaluated by orbital imaging and clinical examination, visual acuity, exophthalmos, and posttreatment complications.
- **RESULTS:** Seven patients (four female, three male; average age, 33 years) were included. Six patients were diagnosed with orbital lymphangioma, and one patient was diagnosed with intraosseous cavernous hemangioma. Patients received an average of  $2.6 \pm 2$  intralesional injections of sodium morrhuate, with a range of one to six injections and a mean volume of  $0.9 \pm 0.8$  ml (range, 0.2 to 2.1 ml). Lesions showed a decrease in size an average of 50% (33%) and ranged from minimal (10%) to near total resolution (85%). Visual acuity and intraocular pressure remained unchanged; exophthalmos decreased an average of  $1.5 \pm 1.8$  mm. Complications included one case of orbital hemorrhage that resolved spontaneously and transient keratopathy in all patients with anterior orbital lesions.
- **CONCLUSION:** Intralesional sclerosing therapy with sodium morrhuate 5% is effective in tumor debulking in patients with orbital lymphangioma and is not associated with vision-threatening complications. It may be a better alternative to surgery for low flow orbital tumors, which includes lymphangioma. (Am J Ophthalmol 2006;141:333–339. © 2006 by Elsevier Inc. All rights reserved.)

**O**RBITAL LYMPHANGIOMAS ARE BENIGN UNENCAPSULATED hamartomatous tumors that are composed of vascular channels.<sup>1,2</sup> Although benign in nature, they tend to invade and intertwine with surrounding tissues, which makes treatment difficult.<sup>1,3</sup> Histologically, lymphangiomas are composed of irregular vascular channels that are lined with a single layer of attenuated endothelial cells.<sup>1,2,4,5</sup> Orbital lymphangiomas are rare, comprising approximately 2% of all orbital biopsy samples; most tumors, however, are diagnosed by neuroimaging and are never operated.<sup>1,6</sup>

Clinically, lymphangiomas are associated with decreased vision, ocular pain, decreased extraocular motility, proptosis, displaced globe, and ptosis.<sup>1,3,7,8</sup> Symptoms typically are present in childhood, which poses a particular problem because amblyopia may develop secondarily.<sup>7,9,10</sup> Ocular emergencies such as spontaneous intraorbital hemorrhages may occur, which leads to optic neuropathies and permanent visual disturbances.<sup>1</sup> Lymphangiomas tend to affect female patients more than male patients, although this predilection is mild.<sup>1,3,11,12</sup>

Orbital lymphangiomas present a treatment challenge, and conservative approaches are preferred.<sup>7,10,13</sup> Radiotherapy is unsuccessful because of the slow turnover rate of the tumor.<sup>14</sup> Successful surgical excision has been reported<sup>3,15</sup>; however, the procedure often is difficult because of the intricate architecture of the lesion and the associated risk of hemorrhage.<sup>16</sup> Complications such as cicatrization, residual tumor, and symptomatic recurrence have been reported.<sup>1,3,6,17</sup> Further, multiple surgical resections may be needed to obtain a satisfactory result.

Alternatives to surgical excision include observation, needle decompression, carbon dioxide laser debulking, and systemic corticosteroids, all of which displayed varied success in the past.<sup>10,18–20</sup> The use of sclerosing agents for the treatment of lymphangiomas have been used in previous experiments. Intralesional injections of OK-432, a sclerosing agent made of group A *Streptococcus pyogenes* of human origin, were introduced in one patient with improvement, although complications such as increased intraocular pressure were noted.<sup>17</sup> In another study, sodium tetradecyl sulfate was injected in three patients; one

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patient experienced a decrease in the size of the lymphangioma; however, the other two patients showed minimal results.<sup>18</sup> Alcohol and Ethibloc (Ethnor Laboratories/Ethicon, Neuilly, France) injections have also been described in orbital venous malformations. It is important to consider the characteristics of orbital lymphangiomas to invade nearby tissues that will make sclerosing therapy more difficult.

The purpose of the current study was to evaluate the outcome of intralesional sodium morrhuate 5% injections (Glenwood, LLC, Englewood, New Jersey, USA) for the treatment of low flow vascular lesions, particularly orbital lymphangiomas, and cavernous hemangioma of bone. Sodium morrhuate is an effective sclerosing therapy in other disease such as venous malformations, esophageal varices, and varicose veins.<sup>21-26</sup>

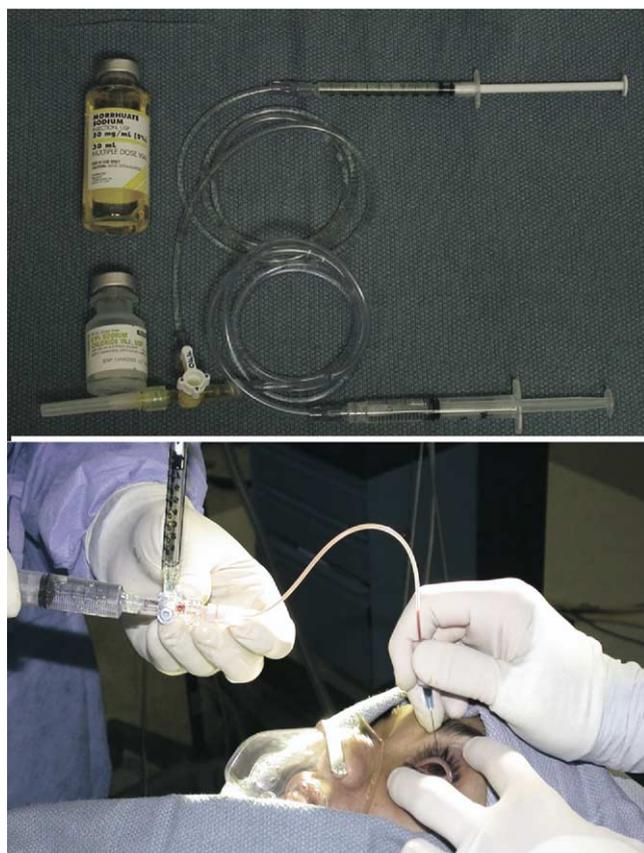
## MATERIAL AND METHODS

A PROSPECTIVE STUDY OF SIX PATIENTS WITH CLINICALLY or radiographically significant orbital lymphangiomas and one patient with cavernous hemangioma of the bone at the Jules Stein Eye Institute was conducted from January 2001 to July 2004. Patients were given 0.1-ml aliquots of sodium morrhuate 5% intralesionally or into the lymphatic cystic spaces to debulk the tumor in a nonsurgical manner. The main outcome measures for comparison purposes were lesion regression that was evident by clinical examination and radiographic studies, functional and cosmetic outcome, and comprehensive eye examination. All treatments were performed by three of the authors (R.A.G., R.M.S., T.C.) over the period that ranged from 2001 to 2004 at the Jules Stein Eye Institute. The study was approved by the local institutional review board.

Six of the patients received injections for very anterior lesions that were visible clearly at the level of the conjunctiva. Each patient received from one to six injections in total that were spaced 1 month apart, with each injection involving a volume of 0.1 ml of sodium morrhuate 5%. One patient had a more posterior lesion that was accessed with fluoroscopic guidance. There was always an attempt to withdraw fluid from the lesion before the injection.

A cavernous hemangioma of bone was encountered and embolized under radiographic guidance before the operation; however, operatively a significant amount of blood loss was noted, and the case was closed. Two weeks later the case was readdressed. On dissection to the level of the bony tumor, the vascular lesion within was noted, and three separate 0.1-ml aliquots were injected with a long 25-gauge needle. Instantaneously the vascular lesion showed involution, which allowed a blood-free complete dissection of the bony tumor.

Cosmetic outcome was graded by scores of 1 to 3. A score of 1 is defined as worsening of lesion appearance; a



**FIGURE 1.** Preparation of sodium morrhuate before intralesional injection in a patient with orbital lymphangioma. (Top) Five-inch 30-gauge needle is placed at the end of a three-way stopcock, and a 1-ml syringe that contains sodium morrhuate is placed in the remaining port. (Bottom) A 1.5-inch 25-gauge needle on a 3-way stopcock was placed superomedially until it was found intralesionally under radiographic guidance.

score 2 is defined as no change to minimal change in lesion; and a score of 3 is defined as a significant decrease in size of lesion. Comprehensive eye examination was performed before the first treatment and at 1 day, 1 week, and 1 month after first injection and every 3 months thereafter. Clinical postoperative evaluation and MRI scans were obtained and evaluated for a change in size or position of tumor.

• **INJECTION TECHNIQUE:** A technique of intralesional microinjection was performed. For anesthetic purposes, one drop of proparacaine is instilled into the eye, which is followed by a cotton swab that has been soaked in 4% lidocaine that is placed directly on the lesion and the immediately surrounding conjunctiva. A 0.5-inch 30-gauge needle is placed at the end of a three-way stopcock, and a 1-ml syringe is placed in the remaining port that contains sodium morrhuate (Figure 1). The needle is placed into the visible lesion, and clear fluid is withdrawn. With the needle remaining in the intralesional space, the lever on the stopcock is rotated, and small aliquots of 0.1

ml of sodium morrhuate 5% are injected. The cornea is then irrigated with balanced salt solution (BSS) fluid, and direct pressure is held on the lesion for 2 minutes.

- **ANGIOGRAPHIC GUIDANCE:** For anesthetic purposes, monitored intravenous anesthesia care was induced. Under fluoroscopic guidance, a 1.5-inch 25-gauge needle on a 3-way stop-cock was placed superomedially until it was found intralesionally (Figure 1). Contrast was injected just before the sclerosing agent. The contrast agent pooled locally, and 0.5 ml of sclerosing agent sodium morrhuate 5% was injected.

- **STATISTICAL ANALYSIS:** Paired samples nonparametric Wilcoxon signed-rank test were used to evaluate posttreatment change in numeric variables as visual acuity, intraocular pressure, and exophthalmos. The Pearson bivariate correlation was used to evaluate correlation between disease duration, number of injections, and total volume of sodium morrhuate to percentage decrease in lesion size, which was estimated by imaging studies and clinical examination. Statistical analysis was performed with Microsoft Excel software (Microsoft Corporation, Redmond, Washington, USA) and SPSS software (SPSS, Inc, Chicago, Illinois, USA) programs. Conversion of Snellen acuity to logarithm of the minimum angle of resolution values was performed.

## RESULTS

SEVEN PATIENTS (THREE MALE, FOUR FEMALE; MEAN AGE, 33 years) were followed after sclerosing therapy for orbital lymphangioma (six patients) or intraosseous hemangioma (one patient); the mean duration of orbital tumor was 17 months. Six patients underwent previous debulking of lesion (one of these patients underwent four surgeries and required a skin graft); in one patient, no previous treatment was performed. Three of the six patients with anteriorly presenting orbital lymphangiomas had a history of poor visual acuity in the eye of the affected side that was the result of optic neuropathy and coexisting amblyopia. Demographics of study population are summarized in the Table.

Patients received an average of  $2.6 \pm 2$  intralesional injections of sodium morrhuate, with a range of 1 to 6 injections and a mean volume of  $0.9 \pm 0.8$  ml (range, 0.2 to 2.1 ml). Lesion size, which was estimated clinically and by imaging studies, decreased an average of  $50\% \pm 33\%$  and ranged from minimal regression (10%) to near complete resolution (85%). Interestingly, percentage decrease in size was not correlated with total amount of sodium morrhuate that was injected or change in exophthalmos.

Four of the six patients with predominantly anterior lesions had a 3+ score on cosmetic outcome, with near

**TABLE.** Demographics of Seven Patients Who Underwent Sclerosing Therapy With Sodium Morrhuate for Orbital Lymphangioma at the Jules Stein Eye Institute, 1999-2004

| Variable                      | Measure                     |
|-------------------------------|-----------------------------|
| Gender (n)                    |                             |
| Male                          | 3 (43%)                     |
| Female                        | 4 (57%)                     |
| Age (y)*                      | $33 \pm 15$ (17 – 57)       |
| Diagnosis (n)                 |                             |
| Lymphangioma                  | 6 (86%)                     |
| Intraosseous hemangioma       | 1 (14%)                     |
| Side (n)                      |                             |
| Right                         | 3 (43%)                     |
| Left                          | 4 (57%)                     |
| Disease duration (mo)*        | $17 \pm 12$ (4 – 38)        |
| After treatment (n)           |                             |
| Debulking                     | 6 (86%)                     |
| None                          | 1 (14%)                     |
| Visual acuity                 |                             |
| Before injections             | 20/90 [20/25 - CF]          |
| After injections              | 20/80 [20/25 - CF]          |
|                               | <i>P</i> = not significant  |
| Intraocular pressure (mm Hg)* |                             |
| Before injections             | $15 \pm 5$ (11 – 24)        |
| After injections              | $15 \pm 4$ (10 – 24)        |
|                               | <i>P</i> = not significant  |
| Exophthalmos (mm)*            |                             |
| Before injections             | $16 \pm 2$ (15 – 20)        |
| After injections              | $15 \pm 1.2$ (13 – 16)      |
|                               | <i>P</i> = .07              |
| Percentage regression*        | $50\% \pm 33\%$ (10% – 85%) |
| Followup examination (mo)*    | $19 \pm 6$ (12 – 24)        |

\*Data given as mean  $\pm$  SD (range).

total resolution of the anterior component of the lesion as documented photographically (Figures 2, 3, and 4). Two of the six patients had a score of 2+, with improvement of the lesion shown. These two patients had significant upper eyelid involvement of the tumor, and the last patient had a large amount of cicatrix in the upper eyelid that was the result of previous surgical excisions.

At the end of the follow-up period, visual acuity and intraocular pressure remained unchanged (Table); exophthalmos decreased an average of  $1.5 \pm 1.8$  mm, from  $16 \pm 2$  mm before the treatment to  $15 \pm 1.2$  mm after the injections. This difference was marginally significant (*P* = .07, Wilcoxon signed-rank test).

Patients with a longer duration of the orbital lesion had an average lower visual acuity before and after the injections ( $R^2 = 0.87$ ; *P* = .011) and underwent previous debulking surgeries before sodium morrhuate injections ( $R^2 = 0.8$ ; *P* = .037, Pearson bivariate correlation).

Complications included one case of intra-orbital hemorrhage that resolved spontaneously over a 1-week period. No sight-threatening hemorrhage occurred. All patients



**FIGURE 2.** A patient with left orbital lymphangiomas. (Top) Ten years after a remote surgical excision of orbital lymphangioma. (Bottom) Near complete resolution of anterior component of tumor after four treatments of intralesional injections of sodium morrhuate 5%.



**FIGURE 3.** A patient with right orbital lymphangiomas. (Top) Preoperative anterior orbital lymphangioma 6 years after remote surgical excision with regrowth shown above. (Middle) After one treatment that consisted of three intralesional 0.1-ml injections of sodium morrhuate 5%. (Bottom) After the second treatment of three injections.

with predominantly anterior lymphangioma who received transconjunctival injection showed evidence of mild keratopathy after anterior injection with resolution after 3 days on artificial tear therapy (Figure 5). All patients experienced pain immediately after the procedure for 2 to 4 hours. One of the six patients who was treated anteriorly had symblepharon in inferior fornix (Figure 6). No assessment of extraocular muscles was performed; however, none of the patients reported new onset diplopia.

The patient with the deep orbital lesion displayed no change in visual acuity or intraocular pressure, with 2 mm decrease in Hertel measurement on the affected side. She had a score of 3 for cosmetic outcome (Figure 7).

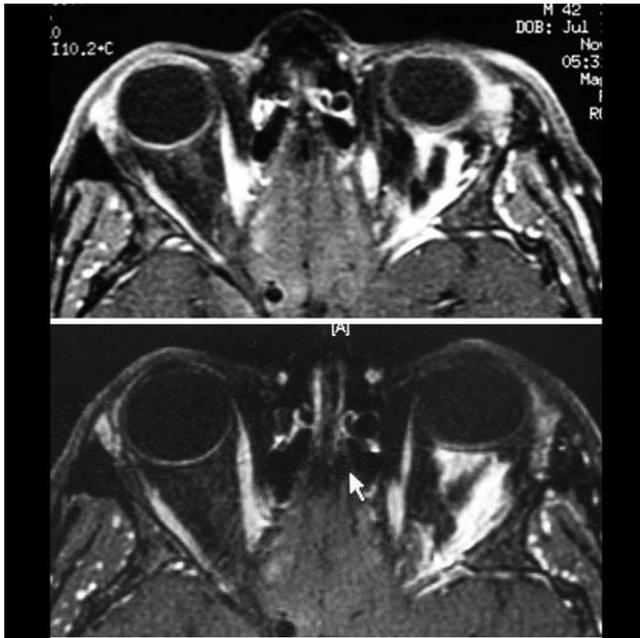
One patient, with orbital intraosseous cavernous hemangioma was treated with sodium morrhuate injections intraoperatively. Before the operation, her visual acuity was 20/80; after the operation, her visual acuity was 20/30; her Hertel measurements were decreased 4 mm on the affected side with a decrease in intraocular pressure, as measured with applanation tonometry of 5 (Figure 8).

One patient of the six with anterior orbital lymphangiomas experienced an intralesional hemorrhage that resolved spontaneously over 1 week. Six of six patients experienced a mild

keratopathy after anterior injection, with resolution after 3 days on artificial tear therapy (Figure 5). All patients experienced pain immediately after the procedure for 2 to 4 hours. One of the six patients who had been treated anteriorly had symblepharon in inferior fornix (Figure 6).

## DISCUSSION

SEVEN PATIENTS WITH LOW FLOW ORBITAL VASCULAR tumors were treated nonsurgically by intralesional injec-



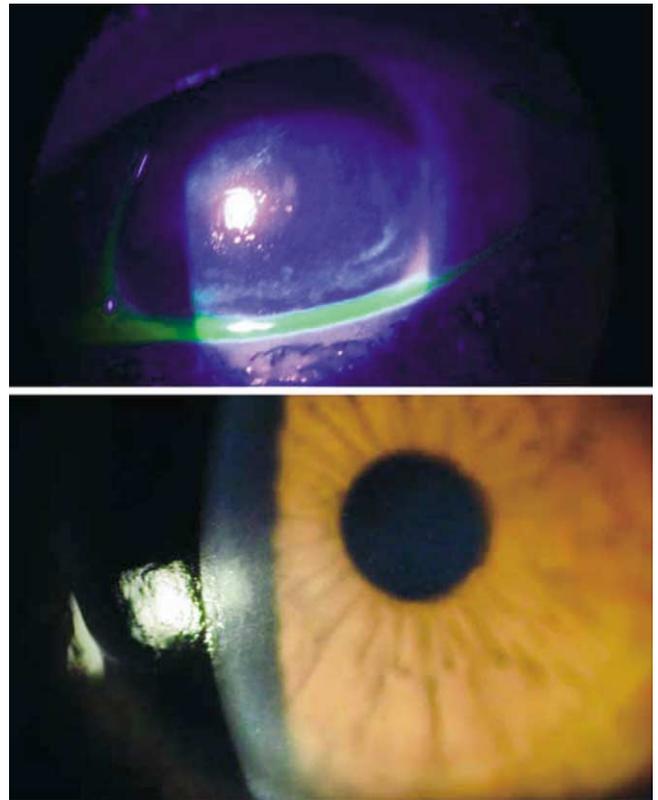
**FIGURE 4.** Magnetic resonance imaging scan of a patient with left orbital lymphangiomas who underwent surgical debulking. (Top) Regrowth after two remote surgical excisions of orbital lymphangiomas 4 years earlier. (Bottom) After four treatments of sodium morrhuate 5% injections over a 4-month period.

tions of sodium morrhuate 5%. The outcome displayed an obvious improvement of these tumors.

Low flow vascular tumors can be difficult to treat and often bleed excessively at the time of surgery, with a high recurrence rate. Often these lesions are cosmetically unpleasing and demonstrate destruction of adjacent tissues. Surgical debulking of these lesions may result in marked disfigurement. Issues of recurrence, vascularity, and invasiveness support the idea that a conservative approach should be sought when possible.

Orbital lymphangioma continues to challenge the orbital specialist. Surgery is almost never curative and often results in progressive loss of function with multiple surgical debulking attempts, thereby becoming a treatment of last resort. A conservative therapy should target the abnormal membranes that make up the lymphangioma, while sparing the adjacent normal tissue through which the lymphangioma infiltrates. This proposed therapy should work on a microscopic level to address the diaphanous, infiltrating characteristics of these benign tumors.

Sclerosing therapy has the potential to supply some of these benefits. Sclerosing agents may have specificity for the abnormal tissues if introduced intralesionally. A scattered small case series has suggested the efficacy and has shown an acceptable side-effect profile of sclerosing therapy for the lymphangioma. Two sclerosing agents that have been discussed in the literature, Picibanil (OK-432; an investigational drug and orbital lesions are not part of the current



**FIGURE 5.** (Top) Anterior segment image of a patient with anterior orbital lymphangiomas who received transconjunctival injection showed evidence of mild keratopathy after anterior injection (Bottom) with resolution after 3 days on artificial tear therapy.



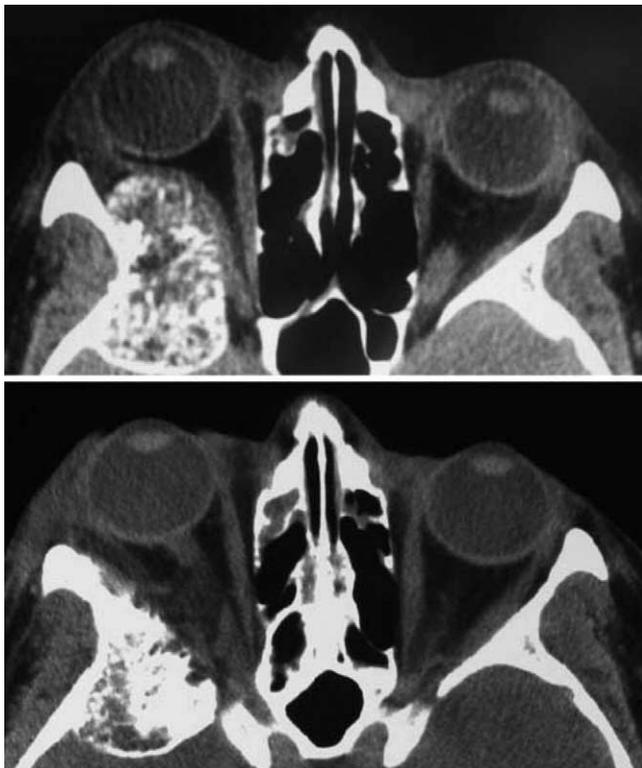
**FIGURE 6.** Symblepharon noted in the inferior fornix of a patient with orbital lymphangiomas after four treatments with sodium morrhuate injections.

protocol) and sodium tetradecyl sulfate (Sotradecol, which has been taken off the market).

Sodium morrhuate is available widely and has been used in the past for sclerosing therapy, commonly in the



**FIGURE 7.** A patient with left orbital lymphangiomas. Before (Top) and after (Bottom) four treatments of sodium morrhuate 5% injections. Postoperative photographs taken 10 months after last injection.



**FIGURE 8.** Computed tomography scan of a patient with right orbital intraosseous cavernous hemangioma. (Top) Before and (Bottom) after injection with sodium morrhuate. Direct intraoperative injection of sodium morrhuate 5%, with immediate involution of vascular component that allowed for a dry excision of bony component of tumor.

treatment of esophageal varices. Sodium morrhuate is a sclerotherapy agent that acts most likely in phlebosclerosis not necessarily through plasma coagulation, but by destroying endothelial and red cells, triggering platelets, and aggregating granulocytes at the level of the endothelial walls.<sup>27</sup>

We have used this modality on a small case series with success. No serious irreversible complications were noted, and all the patients in the series were satisfied with the results. Many of the low flow vascular tumors are made of ecstatic veins that eventually communicate with the cavernous sinus through the ophthalmic veins. Thus, a concern for accidental thrombosis is present, but the properties of sodium morrhuate are such that, when injected intralesionally, there is an almost immediate destruction of the endothelial cells locally. In the current study, most lesions were located in the anterior orbit and are accessible easily to local injections. For more posterior lesions, neuroimage-guided injection may be more appropriate; however, this may carry the risk of delivering the sclerosing agent into the cavernous sinus with severe thrombotic consequences. In these more posterior lesions, the imaging of radiographic contrast injection before the sclerosant injection may be indicated. Additional materials may be injected in vascular lesions of the orbits, and their benefit should be weighed against the possible risk of complications. Further studies are needed to compare various treatment options in orbital low flow and high flow vascular lesions.

Limitations of the current study are that it was a small clinical case series that was subjected to selection bias and in which no comparison to an alternate form of treatment was performed. However, our study analysis showed that tailored intralesional injections of sclerosing agent sodium morrhuate can be used in the manner described in the treatment of orbital lymphangiomas that otherwise are not resected easily. To our knowledge, this is the first study to analyze the effectiveness of sodium morrhuate in the treatment of these low flow orbital vascular lesions.

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