Iatrogenic Retinal Artery Occlusion Caused by Cosmetic Facial Filler Injections

SUNG WOOK PARK, SE JOON WOO, KYU HYUNG PARK, JANG WON HUH, CHEOLKYU JUNG, AND O-KI KWON

• PURPOSE: To investigate the clinical manifestations and visual prognosis of retinal artery occlusion resulting from cosmetic facial filler injections.
• DESIGN: Retrospective, noncomparative case series.
• RESULTS: Seven, 2, and 3 patients had ophthalmic, central retinal, and branch retinal artery occlusions, respectively. Injected materials included autologous fat (7 cases), hyaluronic acid (4 cases), and collagen (1 case), and injection sites were the glabellar region (7 cases), nasolabial fold (4 cases), or both (1 case). Injected autologous fat was associated with worse final best-corrected visual acuity than the other materials. All patients with ophthalmic artery occlusion had ocular pain and no improvement in best-corrected visual acuity. Optical coherence tomography revealed thinner and less vascular choroids in eyes with ophthalmic artery occlusion than in adjacent normal eyes. Concomitant brain infarction developed in 2 cases each of central retinal artery occlusion and ophthalmic artery occlusion. Phthisis developed in 1 case of ophthalmic artery occlusion.
• CONCLUSIONS: Cosmetic filler injections into the glabellar region or nasolabial fold can cause retinal artery occlusion. Iatrogenic ophthalmic artery occlusion is associated with painful blindness, a thin choroid, brain infarction, and poor visual outcomes, particularly when autologous fat is used. Ophthalmic examination and systematic brain magnetic resonance imaging should be performed in patients with ocular pain after such injections. (Am J Ophthalmol 2012;154:653–662. © 2012 by Elsevier Inc. All rights reserved.)

Aesthetic Soft-Tissue Augmentation of the Face by Filler Injections is Dramatically Increasing in Popularity. Although autologous fat injection for facial soft-tissue augmentation is considered safe, retinal artery occlusion in young, healthy patients has been reported after this procedure. In addition to autologous fat, the most popular fillers for cosmetic surgery are composed of partially cross-linked hyaluronic acid. Recently, I case of retinal artery occlusion as a complication of cosmetic injection of hyaluronic acid has been reported. Most cases of cosmetic facial filler injection-associated retinal artery occlusion result in blindness in the affected eye.

Despite the increasing number of cases of retinal artery occlusion resulting from cosmetic facial filler injections, the clinical features and visual outcomes of this condition and the causative surgical procedures are not well established. Adequate knowledge about this visually impairing iatrogenic complication is necessary to prevent the condition itself and subsequent blindness. Therefore, in this study, we aimed to investigate the clinical manifestations and visual prognosis of retinal artery occlusion resulting from cosmetic facial filler injections.

METHODS

The electronic medical records of consecutive patients treated from January 2003 through January 2012 who met the following criteria were reviewed retrospectively: (1) nonarteritic retinal artery occlusion newly diagnosed by fundus fluorescein angiography; (2) no history of intraocular surgery or vascular interventions for retinal artery occlusion before symptom development; and (3) history of cosmetic facial filler injection immediately before retinal artery occlusion.

The collected data included information on underlying diseases, demographics, injection sites, injected substances, initial and final best-corrected visual acuities (BCVAs), associated ocular symptoms and systemic problems, duration of follow-up, and type of treatment (intravitreal thrombolysis or conservative therapy). Findings of spectral-domain optical coherence tomography (SD OCT), fundus fluorescein angiography, and brain magnetic resonance imaging, including diffusion-weighted imaging, also were recorded. Choroidal thickness was measured in the...
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<th>Eye</th>
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<th>Substance</th>
<th>Site</th>
<th>Treatment</th>
<th>Time to Treatment or Visit</th>
<th>Associated Ocular Symptom</th>
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<td>(+)</td>
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<td>XT, ophthalmoplegia, RAPD</td>
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<td>ACP</td>
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<td>XT</td>
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<td>2 wks</td>
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<td>Massage, ACP</td>
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<td>R: inferotemporal VFD</td>
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- = absent; + = present; ACA = anterior cerebral artery; ACP = anterior chamber paracentesis; BCVA = best-corrected visual acuity; BRAO = branched retinal artery occlusion; CF = counting fingers; CRAO = central retinal artery occlusion; ET = esotropia; F = female; FU = follow-up; IAT = intra-arterial thrombolysis; L = left; LP = light perception; M = male; MCA = middle cerebral artery; NLP = no light perception; OAO = ophthalmic artery occlusion; R = right; RAPD = relative afferent pupillary defect; VFD = visual field defect; XT = exotropia; y = years.
fovea by SD OCT with an enhanced depth imaging protocol.12 Snellen visual acuities were converted to logarithm of the minimal angle of resolution measurements, and hand movements, light perception, and no light perception were designated as 4, 5, and 6, respectively.13

In some patients, superselective intra-arterial thrombolysis with urokinase or mechanical disruption was attempted, after obtaining informed consent, within 24 hours from the symptom onset; the techniques were performed as described previously.14 Otherwise, the patients were managed by various conservative therapies including observation, anterior chamber paracentesis, ocular digital massage, and mannitol infusion.

The cases of iatrogenic retinal artery occlusion were divided according to the affected arteries, as follows: (1) ophthalmic artery occlusion, (2) central retinal artery occlusion, and (3) branch retinal artery occlusion. Ophthalmic artery occlusion was defined as central retinal artery occlusion with evidence of choroidal ischemia and definite embolic occlusion of the ophthalmic artery on cerebral angiography. Central retinal artery occlusion applied to cases without evidence of choroidal ischemia and definite embolic occlusion of the ophthalmic artery on cerebral angiography.

Statistical analyses were performed by using SPSS software version 18.0 (IBM Inc, Chicago, Illinois, USA). The Mann–Whitney U test was used to compare nonparametric variables and BCVAs among the groups. The Wilcoxon signed-rank test was used to compare the initial and final BCVAs. A P value less than .05 was considered significant.

RESULTS
TWELVE CONSECUTIVE PATIENTS WITH COSMETIC FACIAL filler injection-associated retinal artery occlusion were included in the study. Of these, 7, 2, and 3 patients had ophthalmic artery occlusion, central retina artery occlusion, and branch retina artery occlusion, respectively. All the patients had a history of sudden visual loss immediately after the injections. Further, all were women, and their mean age was 30.8 ± 12.8 years (range, 18 to 66 years). The mean follow-up duration was 17.1 ± 25.0 weeks.
Almost all the patients were healthy, without underlying diseases; patient 1 had hypertension.

The clinical characteristics of the 12 patients with iatrogenic retinal artery occlusion are described in Table 1. With respect to the injected substances, autologous fat was injected in 7 cases (6 cases of ophthalmic artery occlusion and 1 case of central retinal artery occlusion), hyaluronic acid was injected in 4 cases (1 case of ophthalmic artery occlusion and 3 cases of branch retinal artery occlusion), and collagen was injected in 1 case of central retinal artery occlusion. The injection sites included the glabellar region (7 cases, 58.3%), the nasolabial fold (4 cases, 33%), or both regions (1 case, 8.3%).

Visual decline was the most severe in the patients with iatrogenic ophthalmic artery occlusion, followed by iatrogenic central retinal artery occlusion and iatrogenic branch retinal artery occlusion. The injection sites included the glabellar region (7 cases, 58.3%), the nasolabial fold (4 cases, 33%), or both regions (1 case, 8.3%).

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perfusion, but intact choroidal perfusion, in both the patients. No associated initial ocular problems were detected, except for a relative afferent pupillary defect. The initial and final BCVAs of these patients were 3.50 ± 2.12 logMAR units and 2.76 ± 3.17 logMAR units, respectively. One patient (Patient 9) experienced combined brain infarction by fat embolism after autologous fat injection.

**BRANCH RETINAL ARTERY OCCLUSION (N = 3):** The initial presentation of iatrogenic branch retinal artery occlusion was also decreased vision without ocular pain. All patients had occluded superior branch arteries (2 cases of supero-temporal branch retinal artery occlusion and 1 case of supero-nasal branch retinal artery occlusion) and reported an inferior visual field defect in the affected eye (Figure 4). Fundus fluorescein angiography showed filling defects in the branch retinal arteries and retrograde retinal artery filling (Figure 4). The initial and final BCVAs of these patients were 2.05 ± 3.42 logMAR units and 2.23 ± 3.28 logMAR units, respectively.

**DISCUSSION**

HEREIN WE PRESENT THE CLINICAL MANIFESTATIONS AND visual prognosis of 12 cases of cosmetic facial filler injection-associated retinal artery occlusion, which may be the largest case series of this condition. We also reviewed 11 case reports of facial filler injection-associated retinal artery occlusion (Table 2). Our data indicate that predominantly women are affected by iatrogenic retinal artery occlusion, because cosmetic facial filler injections are usually performed in female patients.

The clinical manifestations depend on the site of arterial obstruction. In all 12 patients, we detected several large clumps in the retinal vessels, including the central retinal arteries and multiple branches of the ophthalmic arteries, by fundus photography, fundus fluorescein angiography, transmural cerebral angiography, and SD OCT. The clinical images suggested near-total occlusion of the ophthalmic arteries and absence of the foveal cherry-red spot. The choroidal filling defect detected by fundus fluorescein angiography suggested occlusion of the short posterior...
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<td>Extinguished VEP, ptosis, RAPD</td>
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- = absent; + = present; ACP = anterior chamber paracentesis; BCVA = best-corrected visual acuity; BRAO = branch retinal artery occlusion; CF = counting fingers; CRAO = central retinal artery occlusion; ET = esotropia; F = female; HM = hand movements; IAT = intra-arterial thrombolyis; ICA = internal carotid artery; L = left; LP = light perception; M = male; mos = months; MCA = middle cerebral artery; NA = not available; NLP = no light perception; OAO = ophthalmic artery occlusion; PMMA = polymethylmethacrylate; R = right; RAO = retinal artery occlusion; RAPD = relative afferent papillary defect; Tx = treatment; VFD = visual field defect; XT = exotropia; y = years.
ciliary arteries. Further, the persistence of semidentlossis unresponsive to illumination of the contralateral iris suggested occlusion of the long posterior ciliary arteries. Obstruction of the blood supply to the extraocular muscles or innervating nerves, causing ophthalmoplegia, also was present. Moreover, ptosis implied ischemia of the levator palpebrae muscle or its innervations. The acute ischemia of the anterior segment and levator palpebrae muscle could explain the ocular pain, which usually does not accompany noniatrogenic retinal artery occlusion. In the present study, although BCVA did not improve, other ocular deficits resulting from iatrogenic ophthalmic artery occlusion improved at the final follow-up examination, including strabismus, ophthalmoplegia, ptosis, and corneal edema. However, ptosis bulbi, which occurred as a result of decreased production of aqueous humor in the ciliary body, was intractable and eventually caused enophthalmos.

Interestingly, all of the 7 patients with iatrogenic ophthalmic artery occlusion in our series experienced painful blindness and no light perception at the initial and final examinations. Taken together with the literature, 14 (73.7%) of 19 cases of iatrogenic central retinal artery or ophthalmic artery occlusion had ocular pain (10 cases of ophthalmic artery occlusion and 4 cases of central retinal artery occlusion). Among the 4 cases of iatrogenic central retinal artery occlusion, 3 patients (Patients 1, 2, and 3 in Table 2) were highly suggestive of ophthalmic artery occlusion on the basis of the associated ocular symptoms, although they were not confirmed by cerebral angiography. Moreover, Patient 7 in Table 2 had painful blindness at presentation, but was not evaluated for any associated ocular symptoms or the possibility of ophthalmic artery occlusion. Among the 11 patients with iatrogenic ophthalmic artery occlusion, 10 (90.9%) showed initial ocular pain; Patient 11 in Table 2 was not evaluated. Therefore, we hypothesize that ocular pain in patients with sudden blindness immediately after cosmetic facial filler injections indicates ophthalmic artery occlusion and poor visual prognosis.

Moreover, we observed that lack of choroidal perfusion resulting from iatrogenic ophthalmic artery occlusion can lead to profoundly attenuated choroidal vascularity and decreased choroidal thickness. This is the first visualization of the choroidal vasculature in iatrogenic ophthalmic artery occlusion both quantitatively and qualitatively by SD OCT. Such choroidal images may help in the diagnosis and prediction of visual outcomes.

In some cases, retrograde arterial embolism also caused brain infarction. We noted 1 case of middle cerebral artery infarction and 1 case of middle and anterior cerebral artery infarctions after autologous fat injection in the glabellar region. According to Table 2, 5 cases of brain infarction after filler-associated retinal artery occlusion have been reported. Taken together with our findings, 7 cases (30.4%) of brain infarction, especially middle cerebral artery infarction, among 23 cases of iatrogenic retinal artery occlusion were caused by autologous fat injection. None of the 7 patients with central retinal artery or ophthalmic artery occlusion caused by other fillers had brain infarction.

The clinical features of cosmetic facial filler injection-associated retinal artery occlusion are quite different, depending on the injected substances. Along with our findings, the literature on iatrogenic retinal artery occlusion includes 16 cases caused by autologous fat injection (10 cases of ophthalmic artery occlusion, 5 cases of central retinal artery occlusion, and 1 undetermined case), 5 cases caused by hyaluronic acid injection (1 case of ophthalmic artery occlusion and 4 cases of branch retinal artery occlusion), 1 case caused by collagen injection (central retinal artery occlusion), and 1 case caused by polymethyl methacrylate injection (central retinal artery occlusion).

The hyaluronic acid product used in the present study was Restylane (Medicis, Scottsdale, Arizona, USA), which contains stabilized hyaluronic acid produced from the fermentation of equine streptococci with 1% cross-linking. The hyaluronic acid concentration of Restylane is 20 mg/mL, and its gel particle size is 400 μm. Therefore, hyaluronic acid particles can block the central retinal artery, which is approximately 160 μm in diameter, or smaller branch retinal arteries more easily than the ophthalmic artery, which is approximately 2 mm in diameter. This may explain why hyaluronic acid injection caused 3 cases of branch retinal artery occlusion, but only 1 case of ophthalmic artery occlusion in our study. Schanz and associates reported arterial embolization caused by the injection of hyaluronic acid (Restylane) without visual loss. They suggested the dorsal nasal artery as a possible route of arterial embolization after hyaluronic acid injection in the glabellar region. Previously, branch retinal artery occlusion resulting from the injection of hyaluronic acid (Restylane) in the glabellar region was the only report on ophthalmic complications.

However, autologous fat has a variable particle size and can block various sized arteries. According to the reports listed in Table 2, autologous fat injection is highly associated with central retinal artery occlusion. Moreover, 2 cases of cerebral fat embolism leading to brain infarction after autologous fat injection in the glabellar region have been described. The anastomosis between the angular and the ophthalmic arteries could be a route for cerebral embolism.

The patients with iatrogenic ophthalmic artery occlusion showed no BCVA improvement after intra-arterial thrombolysis. A possible explanation is that this condition affects a more proximal artery than the central retinal artery, causing more severe vision loss and diverse ocular symptoms. Another explanation is that the embolic source in iatrogenic retinal artery occlusion is completely different from that in noniatrogenic retinal artery occlusion: in the former condition, hyaluronic acid and autologous fat
emboli may not be resolved by intra-arterial thrombolysis with urokinase.

With respect to the mechanism of retinal artery occlusion after cosmetic facial filler injection, we propose a retrograde embolic mechanism. Iatrogenic retinal artery occlusion can be caused by anterograde or retrograde embolism. Anterograde thromboembolism, as a cause of iatrogenic retinal artery occlusion, is related to major vascular procedures such as carotid artery stenting or cerebral aneurysm coil embolization. It seems to have no more additional risk than the known thromboembolic risk for retinal artery occlusion. Further, a substance accidentally injected into arterioles during cosmetic procedures can migrate to the proximal site of the arterial system against the arterial flow resulting from the great injecting force and subsequently can move distally to obstruct the ophthalmic or retinal artery, or any cerebral artery branching from the internal carotid artery. Preconditions, including local increase in pressure and well-vascularized tissue, have been proposed for the intravasation of subcutaneously injected fat materials, resulting in fat embolism. Excessive force and velocity of injection may cause an increase in local pressure. Potential anastomoses between the external and the internal carotid arteries may become active, and crossover of injected materials into the ophthalmic artery may occur. The possible inlet of retrograde flow differs depending on the injection site: in the glabellar region, the supratrochlear artery is the most likely entry point, followed by the supraorbital artery; in the nasolabial fold, any injection in the anastomosis of the dorsal nasal artery from the ophthalmic artery, angular artery, and lateral nasal artery from the facial artery can cause retrograde embolism (Figure 5). From the present study and previous case reports, we consider that cosmetic facial filler injections in the glabellar region and nasolabial fold are associated with similar risk of retinal artery occlusion.
In conclusion, retinal artery occlusion can occur after cosmetic facial filler injections. Ocular pain and attenuated choroidal vascularity on SD OCT may be good indicators of iatrogenic ophthalmic artery occlusion, which has poor visual prognosis. The glabellar region and nasolabial folds are high-risk sites for cosmetic facial filler injection-associated retinal artery occlusion. Such injections can cause severe clinical manifestations, including not only iatrogenic retinal artery occlusion and the associated ocular symptoms, but also brain infarction and phthisis bulbi. Therefore, patients should be informed about the risk of irreversible blindness from retinal artery occlusion, and the injections should be performed carefully. Moreover, ophthalmic examinations and systematic brain magnetic resonance imaging are recommended in patients who have ocular pain after these injections.


REFERENCES

Biosketch

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