REVIEW ARTICLE

Avoiding and Treating Blindness From Fillers: A Review of the World Literature

Katie Beleznay, MD, FRCPC, FAAD,* Jean D. A. Carruthers, MD, FRCSC, FRC (OPHTH), FASOPRS,† Shannon Humphrey, MD, FRCPC, FAAD,* and Derek Jones, MD‡§

BACKGROUND As the popularity of soft tissue fillers increases, so do the reports of adverse events. The most serious complications are vascular in nature and include blindness.

OBJECTIVE To review the cases of blindness after filler injection, to highlight key aspects of the vascular anatomy, and to discuss prevention and management strategies.

METHODS A literature review was performed to identify all the cases of vision changes from filler in the world literature.

RESULTS Ninety-eight cases of vision changes from filler were identified. The sites that were high risk for complications were the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%), and forehead (12.2%). Autologous fat (47.9%) was the most common filler type to cause this complication, followed by hyaluronic acid (23.5%). The most common symptoms were immediate vision loss and pain. Most cases of vision loss did not recover. Central nervous system complications were seen in 23.5% of the cases. No treatments were found to be consistently successful in treating blindness.

CONCLUSION Although the risk of blindness from fillers is rare, it is critical for injecting physicians to have a firm knowledge of the vascular anatomy and to understand key prevention and management strategies.

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Fillers have become an important treatment for patients who seek noninvasive rejuvenation. However, as the field of soft tissue augmentation becomes increasingly popular, reports of adverse events have increased. The most serious complications are vascular in nature and can lead to blindness. To highlight the significance of this issue, the Food and Drug Administration recently issued a safety communication about the risk of intravascular injection with soft tissue fillers.[1]

Having a thorough understanding of the vascular anatomy before injecting is critical. In this article, the authors review 98 cases of ocular complications secondary to soft tissue fillers and discuss the vascular anatomy and prevention and management strategies. To the knowledge of the authors, this is the largest review of blindness secondary to fillers in the literature.

Methods

A literature search was performed to gather information on ocular complications after injection of soft tissue fillers from reports published up to January 2015. The databases of the National Library of Medicine, Ovid MEDLINE, and Cochrane Library were searched using the following Boolean string: (soft tissue augmentation OR filler OR injectable) AND

*Departments of *Dermatology and Skin Science, and †Ophthalmology and Visual Science, University of British Columbia, Vancouver, British Columbia, Canada; ‡Skin Care and Laser Physicians of Beverly Hills; §Division of Dermatology, University of California at Los Angeles, Los Angeles, California*

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(blindness OR ophthalmoplegia OR vision OR visual impairment OR retinal artery occlusion OR ophthalmic artery occlusion). The search was limited to the English language literature. In addition, the references cited in the identified articles were reviewed to identify any additional reports. The review was limited to injected fillers and ocular complications.

Results

A total of 98 reports of filler-induced vision changes were identified. The data reported from the different studies were not consistent. The amount of the filler injected, injection technique, and needle type were reported in a minority of cases, and as such, this information was not included. This is likely due to the fact that often the physicians managing the blindness reported the cases as opposed to the injecting physician. A description of the cases, therapy, and outcomes are highlighted in Table 1.

Virtually Every Anatomic Location Where Filler is Injected on the Face is at Risk for Blindness

The most common sites for this complication were the glabella (38.8%, $n = 38$), nasal region (25.5%, $n = 25$), nasolabial fold (NLF) (13.3%, $n = 13$), and forehead (12.2%, $n = 12$) (Figure 1). Of the 25 nasal injections, 18 were listed as the nasal dorsum or nose, 1 was in the nasal tip, 4 were documented as lateral nasal or perinasal, 1 was in the septum, and 1 was in the nasal root. Moderate risk sites included the periocular region (8.2%, $n = 6$), temple (6.8%, $n = 5$), and cheek (6.8%, $n = 5$). However, although the cheek seems to be at a moderate risk, only 1 case occurred with injection at the cheek alone. Uncommon sites were the eyelid (4 cases), lips (3 cases), and chin (1 case). The exact anatomic location of injection was not listed in 5 cases. Although complications occurred when injecting at the lip and chin, it is important to note that these sites were not injected in isolation at the time of complication. Other anatomic sites that are at a higher risk, such as the NLF and nose, were injected at the same session and were therefore more likely to be the location of complication.

The fillers that caused blindness included: autologous fat (47.9%, $n = 47$), hyaluronic acid (HA) (23.5%, $n = 23$), collagen (8.2%, $n = 7$), paraffin (4.1%, $n = 4$), polymethyl methacrylate (3.1%, $n = 3$), silicone oil (3.1%, $n = 3$), poly-L-lactic acid (3.1%, $n = 3$), and calcium hydroxylapatite (2.0%, $n = 2$). There was one case each (1.4%) with injections from polyacrylamide hydrogel and micronized dermal matrix (Figure 2). The filler type was not reported in 4 cases. There were 8 cases of visual complications reported in the United States and 1 case reported in Canada. Most cases ($n = 58$) were reported out of South Korea. This could represent a reporting bias as many of the large case series are from South Korea. Data were collected from the major retinal centers in the country. To the knowledge of the authors, no similar data collection from ophthalmologists has been done in North America. There are limited data to assess whether the injection technique, needle or syringe type, or location of injection contribute to the higher number of cases of blindness seen in Korea. However, volumization of the diamond-shaped central portion of the face has become culturally popular in Korea; this area includes the glabella, nose, medial cheek, and NLF, all of which are high-risk sites for vascular occlusion of distal branches of the ophthalmic artery.

In 65 cases, complete unilateral vision loss was reported as the initial symptom or sign. In 41 cases, ocular pain or headache was reported. Nausea and vomiting were reported in 10 cases. Lack of extraocular movement or ophthalmoplegia was reported in 40 cases, ptosis in 32 cases, and exotropia, in which the eyes are deviated outward, in 16 cases. Although most cases of vision loss did not improve, only 2 patients had ongoing ophthalmoplegia, and 1 patient had persistent ptosis that was reported. Significant skin changes such as necrosis or a violaceous reticulated pattern were reported in 15 cases. Although a thorough review of neurological complications secondary to the filler was not undertaken, there were 23 cases (23.5%) of symptoms or signs involving the central nervous system (CNS), including infarction and hemiplegia in association with the cases of blindness. There was 1 case[14] of death in association with blindness after 5 mL of autologous fat was injected into the glabella. One minute after the injection, the patient developed mental status change; after 12 hours, she developed deep coma; and after 2 days, the left eye became necrotized. The patient died after 4 days.

TABLE 1. Cases of Blindness in the World Literature

Case	*Type of Filler*	*Injection Site*	*Symptoms*	*Signs*	*Management*	*Outcome (Variable Time for Follow-up)*	*Country*
1	Autologous fat	Glabella	Immediate: RE vision loss, hemicranial pain	NR	NR	RE vision loss	United States[2]
2	Autologous fat	Glabella	Immediate: RE vision loss, periocular pain	Paralyzed left limbs, left lower face hemiplegia, anosognosia, left spatial neglect, ↓ sensation on left	NR	RE vision loss, left-sided hemiplegia	Spain[3]
3	Autologous fat	Glabella	Immediate: RE vision loss, pain, vomiting	NR	NR	RE vision loss	Brazil[4]
4	Autologous fat	Left bridge of the nose, NLFs, lips	10 minutes: LE vision loss, eye and head pain, disoriented	Right-sided hemiparesis	NR	LE vision loss, neurologically normal, necrosis on the nose	United States[5]
5	Autologous fat	NLF	Immediate: LE vision loss, headache, dyspnea, irritability, near unconscious state	NR	Ocular massage, CO_2 and O_2 intermittently	LE vision loss, recovered mental status	Korea[6]
6	Autologous fat	Temple	RE vision loss, headache	Ophthalmoplegia, ptosis	NR	RE vision loss	China[7]
7	Autologous fat	Forehead	LE vision loss	Ophthalmoplegia, ptosis	NR	LE vision loss	China[7]
8	Autologous fat	Glabella, forehead	LE vision loss	NR	NR	LE vision loss	China[7]
9	Autologous fat	Forehead, temple	RE vision loss	Ophthalmoplegia, ptosis	NR	RE vision loss	China[7]
10	Autologous fat	Periorbital, cheek, nose, and lip	LE vision loss	Ophthalmoplegia, ptosis	NR	LE vision loss	China[7]
11	Autologous fat	Forehead, temple	RE vision loss, dizziness, vomiting	Ophthalmoplegia, ptosis	NR	RE vision loss	China[7]
12	Autologous fat	Temple	RE vision loss	Ptosis	NR	RE vision loss	China[7]
13	Autologous fat	Glabella	Immediate: RE vision loss, pain, nausea	NR	Drip infusion of urokinase, hyperbaric O_2, corticosteroid	RE vision loss	Japan[8]

TABLE 1. (Continued)

Case	*Type of Filler*	*Injection Site*	*Symptoms*	*Signs*	*Management*	*Outcome (Variable Time for Follow-up)*	*Country*
14	Autologous fat	NLF, lip, chin	No vision change, but multiple fat emboli in right retinal and choroidal arterioles	7 hours: global aphasia, mild right sensorimotor hemiparesis	NR	Ocular emboli no longer visible, aphasia	Switzerland[9]
15	Autologous fat	Forehead	Injection day: swelling, unable to open eyelids. Day 1: LE vision loss	Day 1: decreased sensation forehead, scalp, paresthesias right leg. Day 3: ophthalmoplegia, ptosis	IV methylprednisone for 3 consecutive days	LE vision loss, recovery of ophthalmoplegia	Korea[10]
16	Autologous fat	Periorbital area (crow's feet)	Immediate: LE weak reaction to light, pain, headaches, stuporous, unresponsive	Right hemiplegia, global aphasia, deviation of the head and eye to the left	NR	LE vision loss, recovery of ability to walk, improved global aphasia	Switzerland[11]
17	Autologous fat	Nose (left side)	Immediate: LE vision loss, pain	Ophthalmoplegia	Microcatheter at proximal ophthalmic artery with mechanical thrombolysis by rotating microwire, 500,000 U of urokinase and 500 μg of tirofiban infused	LE vision loss, recovery of ophthalmoplegia	Korea[12]
18	Autologous fat	Cheek	Vision loss	5 days later: vesicular lesion on ipsilateral nose	NR	Vision loss	NR[13]
19	Autologous fat	Transverse scar and wrinkle in the forehead	Immediate: vision loss, hemicranial pain	4 days later: superficial skin eruption forehead	NR	NR	NR[13]
20	Autologous fat	Glabella	30 minutes: LE vision loss	1 minute: mental change, aphasia, right hemiplegia. 30 minutes: drowsy, global aphasia, right sensorimotor hemiplegia. 12 hours: deep coma, central hyperventilation, decorticate rigidity. 2 days: necrotized left eye	Artificial ventilation, IV dexamethasone and saline	4 days later: death	Korea[14]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
21	Autologous fat	Glabella	24 hours: RE vision loss, ocular pain	NR	IV corticosteroids and antiplatelet therapy	RE vision loss	France[15]
22	Autologous fat	NLF	10 minutes: RE vision: hand motion	Ptosis, petechiae right NLF	IV methylprednisolone 1 g per day for 3 days followed by oral methylprednisolone	RE vision: hand motion	Korea[16]
23	Autologous fat	Forehead	Immediate: RE vision loss	NR	NR	NR	United States[17]
24	Autologous fat	Glabella	Immediate: LE vision loss, pain	Ophthalmoplegia, ptosis	Intra-arterial thrombolysis	LE vision loss	Korea[18]
25	Autologous fat	NLF	Immediate: LE vision loss, pain	Ophthalmoplegia, exotropia	Intra-arterial thrombolysis	LE vision loss	Korea[18]
26	Autologous fat	NLF	Immediate: RE vision loss, pain	Ophthalmoplegia, ptosis, esotropia	Intra-arterial thrombolysis	RE vision loss	Korea[18]
27	Autologous fat	Glabella	1 week: LE vision loss, pain	Ophthalmoplegia, ptosis, exotropia, MCA infarction	NR	LE vision loss	Korea[18]
28	Autologous fat	Glabella	Immediate: RE vision loss, pain	Ophthalmoplegia, exotropia	Anterior chamber paracentesis	RE vision loss	Korea[18]
29	Autologous fat	Glabella	2 hour: LE vision loss, pain	Exotropia	Anterior chamber paracentesis	LE vision loss	Korea[18]
30	Autologous fat	Glabella	2 days: LE vision: light perception	2 days: ACA and MCA infarction	Anterior chamber paracentesis	LE vision: light perception	Korea[18]
31	Autologous fat	Periocular	After effect of anesthesia: LE vision loss	2 hours later: dysarthria, purple discoloration to nose, MCA infarction	Ocular massage, IV mannitol, O_2 and CO_2 therapy	LE vision loss	Korea[19]
32	Autologous fat	Face	13 hours: RE vision loss, left hemiplegia, right-sided facial palsy	Multiple brain infarctions	IV methylprednisolone (9 mg/kg) followed by prednisolone (30 mg/kg) taper	NR	Korea[20]
33	Autologous fat	Left face	10 minutes: LE vision loss, headache	Decreased cognition, multiple bilateral infarcts	NR	NR	Korea[21]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
34	Autologous fat	Glabella	RE vision loss, LE: 20/130 (0.15)	Right ophthalmoplegia, ptosis, red reticular pattern on the glabella and necrosis, infarction bilateral frontal lobes	NR	RE vision loss, exotropia, LE vision: 20/20, minimal scarring	Korea[22]
35	Autologous fat	NR	Within 1 day: RE vision: light perception, pain	Ophthalmoplegia, exotropia	Observation	RE vision loss	Korea[23]
36	Autologous fat	Glabella	Within 1 day: RE vision loss	Ophthalmoplegia, ptosis, exotropia, border-zone infarct in the brain	Intraocular pressure lowering	RE vision loss	Korea[23]
37	Autologous fat	Glabella, NLF	Within 6 hours: LE vision loss	Ophthalmoplegia, MCA infarct	Anterior chamber paracentesis	LE vision loss	Korea[23]
38	Autologous fat	NR	Within 1 day: LE vision loss, pain	Ophthalmoplegia, border-zone infarct in the brain	Observation	LE vision loss	Korea[23]
39	Autologous fat	NR	Within 8 hours: LE vision: counting fingers	NR	Anterior chamber paracentesis	LE vision loss	Korea[23]
40	Autologous fat	Glabella	Within 4 hours: LE vision loss, pain	Ophthalmoplegia, ptosis	Anterior chamber paracentesis	LE vision loss	Korea[23]
41	Autologous fat	Glabella	Within 1 day: RE vision loss	Multifocal brain infarcts	Anticoagulant	RE vision loss	Korea[23]
42	Autologous fat	Glabella	Within 30 hours: RE vision: light perception	Ophthalmoplegia, ptosis, MCA infarct	Anterior chamber paracentesis	RE vision loss	Korea[23]
43	Autologous fat	Glabella, NLF	Within 2 hours: LE vision loss, pain	NR	Observation	LE vision loss	Korea[23]
44	Autologous fat	NLF	Within 1 day: LE vision loss	Multifocal brain infarcts	Intraocular pressure lowering	LE vision loss	Korea[23]
45	Autologous fat	Nasal dorsum	Within 1 day: LE vision: 20/25	Ophthalmoplegia	Observation	LE vision: 20/50	Korea[23]
46	Autologous fat	Eyelid	Within 1 day: RE vision: 20/25	NR	Anticoagulant	RE vision: 20/40	Korea[23]
47	Autologous fat	Glabella	Within 1 day: LE vision loss	Ophthalmoplegia, exotropia	Observation	LE vision loss	Korea[23]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
48	HA	Glabella, cheeks	1 minute: vision loss in the inferior half of the RE	NR	Immediate: 500 mg acetazolamide	RE vision recovery, visual field defect improved	Germany[24]
49	HA	Nasal tip	Immediate: LE vision loss, pain in the left upper face	Day 2: violaceous, reticulated, ulcerative patches, ophthalmoplegia	Day 2: IV methylprednisolone ×3 days, then tapered oral prednisolone; aspirin 100 mg orally	LE vision loss; recovery from ophthalmoplegia and skin necrosis	Korea[25]
50	HA	Nose	LE vision: 20/400, headache	NR	NR	LE vision: 20/1,000	China[7]
51	HA	Periorbital	RE vision counting fingers 33 cm	NR	NR	RE vision counting fingers 33 cm	China[7]
52	HA	Forehead	LE vision hand movement	NR	NR	LE vision: 20/1,000	China[7]
53	HA	Upper eyelid	LE vision loss, dizziness, vomiting	Ophthalmoplegia, ptosis	NR	LE vision loss	China[7]
54	HA	Nose	RE vision loss, dizziness, vomiting	Ophthalmoplegia, ptosis	NR	RE vision loss	China[7]
55	HA	Nasal dorsum	Immediate: RE vision loss, periocular pain	Ophthalmoplegia, ptosis	High-dose IV corticosteroids	RE vision loss, ophthalmoplegia	Korea[26]
56	HA	Forehead	3 weeks: LE vision: 20/30, superior field vision loss	NR	NR	LE vision: 20/25	United States[17]
57	HA	NLF and glabella	Immediate: RE vision loss, pain	Ophthalmoplegia, ptosis, exotropia	Intra-arterial thrombolysis	RE vision loss	Korea[18]
58	HA	NLF	2 weeks: LE vision: 20/20 (1), inferior visual field defect	NR	NR	LE vision: 20/20 (1), no comment on visual field defect	Korea[18]
59	HA	Glabella	5 hours: LE vision: 20/30 (0.7), inferior visual field defect	NR	Massage, anterior chamber paracentesis	LE vision: 20/130 (0.15)	Korea[18]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
60	HA	NLF	3 weeks: RE vision: 20/20 (1), inferotemporal visual field defect	NR	NR	RE vision: 20/20 (1), no comment on visual field defect	Korea[18]
61	HA	Nose	Immediate: RE vision loss, pain, drowsiness	Paralysis of the right face and left limbs. MCA infarction with intracerebral hemorrhage, SAH	Thrombolysis, decompressive craniectomy	RE vision loss, motor weakness (walks with a cane), drowsiness	Korea[27]
62	HA	Nasal dorsum	Immediate: RE vision: 20/63 (0.3), pain, nausea, vomiting, headache. Few seconds: diplopia, dizziness	Ophthalmoplegia, ptosis, exotropia. Ecchymosis, reticulated discoloration, swelling forehead and nasal dorsum	Aspirin, "nicergorline," eye drops, systemic steroid pulse therapy for 3 days, then oral steroids. Hyaluronidase to skin lesions, topical antibiotic, IV antibiotics	RE vision: 20/32 (0.6), recovery of ptosis, strabismus, ophthalmoplegia, diplopia. Minimal skin blemish	Korea[28]
63	HA	Glabella	Few minutes: vision loss, pain, headache. Exam: RE vision loss, LE vision: 20/25 (0.8)	Erythematous violet reticular discolouration in the glabella. Infarction right frontal, occipital, parietal lobes	Topical timolol maleate, oral acetazolamide (500 mg), aspirin 100 mg daily	Vision loss RE, left hemianopia	Taiwan[29]
64	HA	Glabella	Within 1 hour: LE vision loss, pain	Ophthalmoplegia, ptosis, exotropia	Anterior chamber paracentesis	LE vision loss	Korea[23]
65	HA	Glabella	Within 7 hours: RE vision loss	NR	Intra-arterial thrombolysis	RE vision loss	Korea[23]
66	HA	NLF	Within 20 hours: RE vision: hand motion, pain	Ophthalmoplegia, ptosis, exotropia	Anterior chamber paracentesis	RE vision: 20/25	Korea[23]
67	HA	Glabella	Within 3 hours: LE vision: 20/32	Ophthalmoplegia, ptosis, exotropia	Anticoagulant	LE vision: 20/25	Korea[23]
68	HA	Glabella	Within 2 days: RE vision: 20/200	NR	Observation	RE vision: 20/63	Korea[23]
69	HA	Glabella	Within 5 hours: RE vision: 20/500	NR	Anterior chamber paracentesis	RE vision: 20/100	Korea[23]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
70	HA	Glabella, nasal dorsum	Within 4 hours: RE vision: light perception, pain	Ophthalmoplegia, ptosis, exotropia	Observation	RE vision: light perception	Korea[23]
71	Collagen (Zyderm)	Glabella and cheek (acne scars)	Within minutes: vision loss	NR	NR	Vision loss	NR[30]
72	Collagen	Glabella	NR	NR	NR	NR	United States[31]
73	Collagen	Glabella, cheeks	NR	NR	NR	Vision loss	NR[32]
74	Collagen	Left nasal septum	Immediate: LE vision loss, headache	Reticulated violaceous pattern nose, supraorbital area, forehead and philtrum, ptosis, ophthalmoplegia, acute cerebral infarction, and SAH	Antiplatelet agent, calcium channel blocker	LE vision loss	Korea[33]
75	Bone collagen	Nose	RE vision loss	Ophthalmoplegia, ptosis	NR	RE vision loss	China[7]
76	Collagen	Glabella	1 hour: LE vision: counting fingers	NR	Massage, mannitol	LE vision: 20/63 (0.3)	Korea[18]
77	Collagen	Nasal dorsum	Within 3 days: LE vision: 20/1,000	NR	Observation	LE vision: 20/200	Korea[23]
78	Paraffin	Nose	Immediate: vision loss	NR	NR	NR	United States[34]
79	Paraffin	Forehead	Immediate: RE vision loss	NR	NR	NR	Korea[15]
80	Paraffin	Nose	Immediate: vision loss, vomiting, collapse	NR	NR	NR	NR[34]
81	Paraffin	Nose	Immediate: LE vision loss, lacrimation, vertigo	NR	NR	NR	NR[34]
82	PMMA	Glabella	Immediate: RE vision loss, pain	Ophthalmoplegia	None	RE vision loss, ophthalmoplegia	Brazil[35]
83	MetaCrill (PMMA)	Nasal dorsum	15 minutes: RE vision: hand motion, pain	Ophthalmoplegia, ptosis	NR	RE vision loss, recovery from ophthalmoplegia and ptosis	Japan[36]

TABLE 1. (Continued)

Case	Type of Filler	Injection Site	Symptoms	Signs	Management	Outcome (Variable Time for Follow-up)	Country
84	Bovine collagen and PMMA (ArteFill)	Forehead	Immediate: RE vision loss	NR	Anterior chamber paracentesis, IV normal saline, ocular massage, hyperbaric O_2	RE vision: faint light perception	United States[17]
85	Silicone oil	Nasal root	Immediate: RE vision: counts fingers, pain	NR	Digital massage, vasodilators, acetazolamide	RE vision: counts fingers	Korea[37]
86	Silicone oil	Nose	1 day: LE vision loss	1 day: right hemiplegia	NR	NR	Korea[15]
87	Silicone oil	Temple	Immediate: RE vision loss, pain, headache	NR	Ocular massage, anterior chamber paracentesis, oral acetazolamide	RE vision loss	Thailand[15]
88	PLLA	Periorbital and lateral nasal area	Immediate: LE vision loss, pain. Day 2: nausea	Day 2: ophthalmoplegia, ptosis	NR	LE vision: decreased light perception and projection; recovery from ophthalmoplegia and ptosis	Canada[38]
89	PLLA	Eyelid	Within 3 hours: RE vision: light perception, pain	Ophthalmoplegia, exotropia	Observation	RE vision loss	Korea[23]
90	PLLA	Glabella	Within 1 day: LE vision: hand motion	NR	Steroid	LE vision: hand motion	Korea[23]
91	CaHA	Nasal dorsum	Immediate: RE pain. 8 hours: RE vision: hand movement	Ophthalmoplegia, ptosis, exotropia. Late: necrosis and reticulated erythematous-patterned glabella, nasal bridge and right eyelid	Immediate: aspiration. Later: topical and IV antibiotics, oral corticosteroids	RE vision recovery, fixed dilated pupil, minimal scarring	Korea[39]
92	CaHA	Nose	Vision loss bilateral	Bilateral ptosis, ophthalmoplegia, skin necrosis, red reticular pattern affecting the bridge of the nose and frontal area	NR	Vision loss bilateral	Korea[40]

TABLE 1. (Continued)

Case	*Type of Filler*	*Injection Site*	*Symptoms*	*Signs*	*Management*	*Outcome (Variable Time for Follow-up)*	*Country*
93	Polyacrylamide hydrogel (Aquamid), botulinum toxin Type A	NR, likely periocular	Immediate: nausea, vomiting. Left upper eye visual field defect for 3 days when reported. LE vision: 20/70	Ophthalmoplegia, ptosis, transient third nerve palsy. Edema, erythema, pustules, and cellulitis from glabella to nasojugal folds	Oral steroids, IV antibiotics, aspirin	LE vision: 20/30 with superior half visual field defect	Taiwan[41]
94	Cymetra (micronized dermal matrix)	Forehead (depressed scar)	10 minutes: nausea, diaphoresis. Subsequent: LE pain. 30 minutes later: LE vision: hand motion	Ptosis, exotropia	NR	LE vision: light perception, hypertropia, exotropia	United States[42]
95	NR	Glabella	Immediate: vision loss	Subsequent necrosis to the glabella	NR	NR	NR[43]
96	NR	Glabella, perinasal, periorbital	Immediate: LE vision loss	Erythema to injection sites	Acetazolamide (1 week), IV methylprednisolone (3 days)	Vision: 20/200	Korea[44]
97	NR	Nasal dorsum	Within 1 day: LE vision: 20/32	NR	Intraocular pressure lowering	LE vision: 20/20	Korea[23]
98	NR	Eyelid	Within 2 days: RE vision: 20/20	NR	Anticoagulant	RE vision: 20/20	Korea[23]

CaHA, calcium hydroxylapatite; CO_2, carbon dioxide; LE, left eye; MCA, middle cerebral artery; NR, not reported; O_2, oxygen; PLLA, poly-L-lactic acid; PMMA, polymethyl methacrylate; RE, right eye; SAH, subarachnoid hemorrhage.

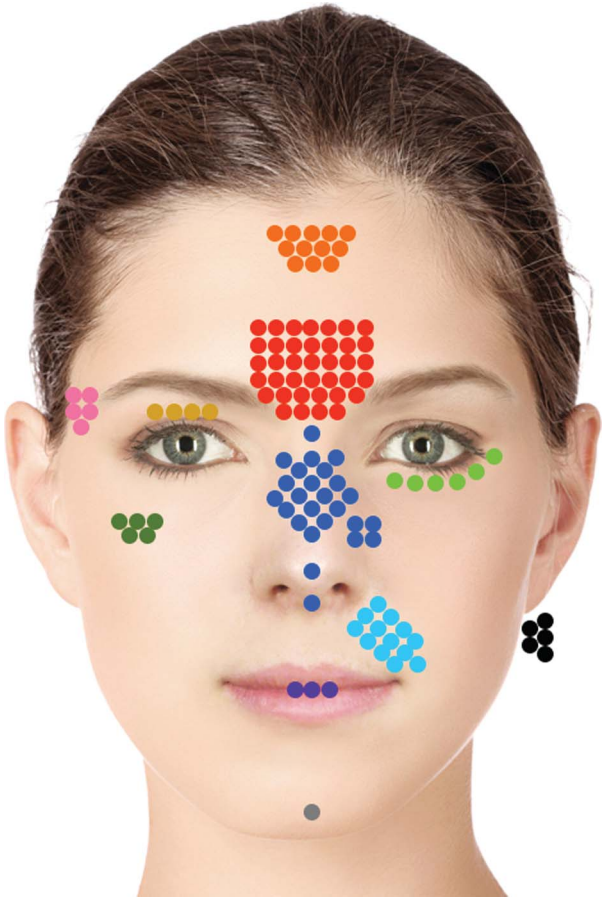

Figure 1. Location of injection for each case of blindness from filler. The 5 black dots represent cases in which the location was not specified and listed as "face."

The most serious complications were secondary to autologous fat. In this series, 38/47 or 80.9% of the cases of ocular complications from autologous fat resulted in complete vision loss, 4 cases did not report a final vision outcome, and 5 cases had some vision ranging from light perception to 20/40 at follow-up; 19/23 or 82.6% of the cases of CNS complications seen in association with blindness were secondary to autologous fat. Hyaluronic acid injections did not have such serious ocular outcomes. Vision loss was seen in 9/23 or 39.1% of the cases of ocular complications from HA. Some degree of vision ranging from counting fingers to full vision was seen in the remaining 14 cases. CNS complications in association with vision changes after HA injection were seen only in 2 cases.

Treatment varied from observation to digital massage, intraocular pressure-lowering agents such as acetazolamide and mannitol, intravenous (IV) methylprednisolone oral corticosteroids, oxygen and carbon dioxide therapy, antibiotics, mechanical and chemical thrombolysis, anterior chamber paracentesis, or anticoagulants. Hyaluronidase was injected to the skin at signs where signs of vascular compromise were present in one case. In many cases, treatments were not reported. The authors suspect that in these cases no treatment was instituted in large part because there is little evidence for improvement with any one treatment. Given the lack of consistent reporting on treatment, it is difficult to make any correlation between treatment and symptom improvement or resolution. In this review, there were only 2 cases that had complete vision recovery. In 1 case[22] of bilateral ocular complications, there

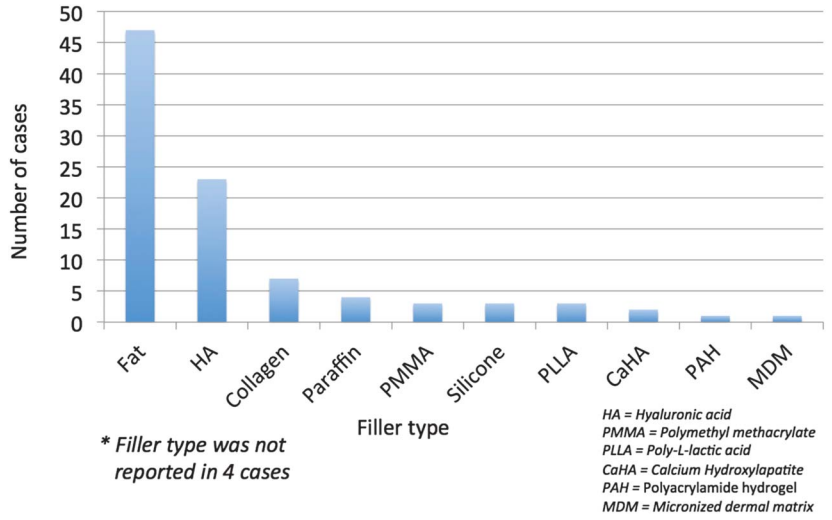

Figure 2. Number of cases of blindness from each filler type.

was resolution of the vision defects in the left eye, but vision loss in the right eye persisted.

Discussion

Background

The increasing demand for soft tissue fillers has been well documented. Similarly, the number of reported cases of vascular complications secondary to fillers is rising.[45] This could be secondary to a number of issues. First, there are increasing numbers of filler treatments being performed and risks would parallel this. Second, there has been a shift from 2-dimensional treatment of discrete wrinkles toward 3-dimensional panfacial volume restoration to achieve improved esthetic results. In such a scenario, larger volumes of filler are often placed in a deeper plane for revolumization. The combination of larger volumes and deeper placement increases the risk of blood vessel compromise. Last, there is a concern that nonexpert injectors are injecting fillers without a proper understanding of facial anatomy, thereby increasing the risk of complications. Between 1906 and 2015, 98 cases of blindness were documented in the literature with most cases being reported in the last 5 years. In 2014 alone, there were 5.5 million filler treatments performed worldwide, with that number forecasted to grow.[46] Thus, although blindness is a devastating complication, the risk is still exceedingly low.

Proposed Mechanism

With the rising reports of blindness secondary to soft tissue augmentation, the understanding of the mechanism of this complication has evolved. It has been suggested that vascular complications such as blindness can be attributed to intravascular injection and retrograde embolization of the filler.[47] Although it may seem logical that the material injected into an artery would flow in the direction of blood flow, in fact, the arteries branch and become smaller more distally, which increases resistance. A rapidly injected bolus may find less resistance proximally than distally. It has been shown that arterial pressure can be easily overcome when injecting and the material can travel in a retrograde fashion.[48] Multiple branches of the ophthalmic artery project outside the ocular area and onto the nose and forehead. Proximal branches include the supraorbital, supratrochlear, and dorsal nasal artery. Furthermore, there are anastomoses between many other arteries of the face and those branches of the ophthalmic artery. If the tip of the needle or cannula penetrates the vessel and enough pressure is applied to the plunger when injecting even small volumes of filler, the arterial pressure can be overcome and the filler can reach the ocular vessels. When the injector stops the pressure of injection, the arterial pressure can carry the embolus from the proximal vessels such as the ophthalmic artery to the more distal retinal arteries. Because these are small arteries, a large volume of filler is not required to cause occlusion. Indeed, many of the reported cases have involved injections of 0.5 mL or less.[48] If the injector applies greater pressure for longer, there is a chance that the filler may travel retrograde into the internal carotid artery and from there may advance into the cerebral circulation, causing a stroke.[47]

Anatomy

A firm understanding of anatomy is critical to minimize the risks of vascular complications. Most of the blood supply to the face is through the external carotid artery with the exception of a region of the central face that encompasses the eye, upper nose, and central forehead. The ophthalmic artery of the internal carotid provides blood supply to this area.[49] The ophthalmic artery arises behind the eye and branches into vessels including the supraorbital, supratrochlear, dorsal nasal, and lacrimal artery. These arteries are the most likely implicated in cases of vascular complications when injecting the glabella, nose, and forehead. The internal carotid system also anastomoses with branches of the external carotid system.[50]

The facial artery branches off the external carotid artery. It passes over the face anterior to the masseter muscle and proceeds with a tortuous course in a superior and diagonal direction. It gives rise to the inferior and superior labial arteries. The lateral nasal artery (LNA) branches off the facial artery to supply the lateral nose. The exact course of the facial artery as it courses superiorly is variable. Traditionally, the

facial artery becomes known as the angular artery (AA) in the region of the NLF. As the AA continues superiorly, it anastomoses with the dorsal nasal artery connecting the external and internal carotid systems. This anastomosis is the reason that injections in the NLF, medial cheek, or periorbital area can lead to blindness. The facial artery also anastomoses with the infraorbital artery and the transverse facial artery, a branch of the superficial temporal artery.[50] In this section, the cutaneous vascular anatomy of at high-risk anatomic sites of injection is reviewed (Figure 3).

Glabella and Forehead

The most likely arteries to cause complications secondary to soft tissue augmentation in the glabellar and forehead regions are the supratrochlear and supraorbital artery. Both these arteries are branches of the ophthalmic artery. As such, filler placed intravascular into one of these arteries with enough pressure can travel retrograde and lead to ocular complications. The supratrochlear artery is found to be relatively constant along the medial canthal vertical line. It rarely deviates more than 5 mm lateral or medial from this vertical line. It starts its course deep at the superomedial orbit and then becomes subcutaneous from 15 to 25 mm above the supraorbital rim as it travels superiorly. The supraorbital artery appears over the supraorbital rim on a vertical line corresponding to the medial limbus of the cornea. It also starts its course deep and becomes more superficial approximately 15 to 20 mm above the supraorbital rim and remains subcutaneous as it travels superiorly up the forehead. As such, injections at the glabella or inferior forehead at the level of the supraorbital rim or within 2 cm of that location should be superficial. However, injections more superiorly on the forehead should be deep in a supraperiosteal plane to avoid intravascular injection.[51]

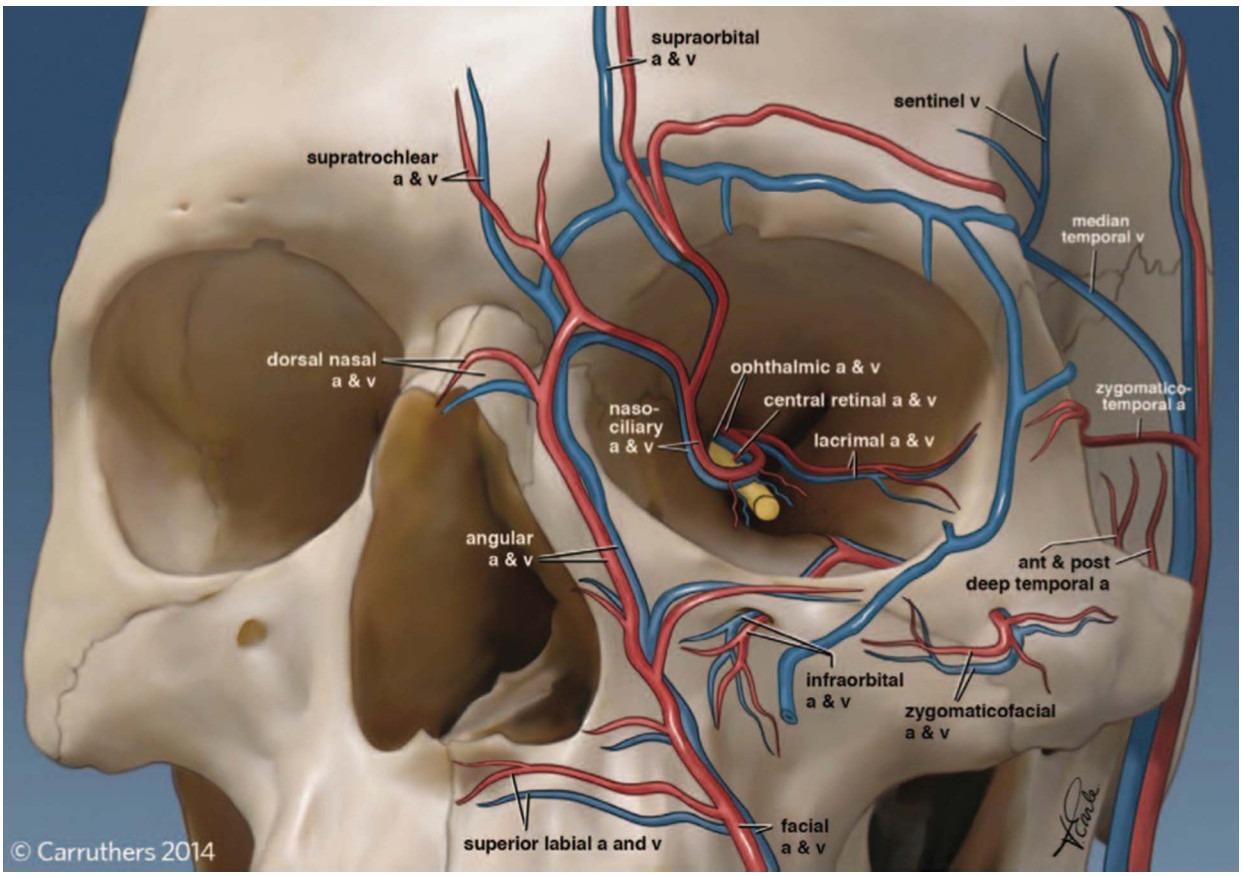

Figure 3. Vascular anatomy of the upper face (Copyright Jean D. Carruthers, MD, 2014).[47] a, artery; v, vein. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Nose

The major nasal arteries at risk for complications are the LNA and dorsal nasal artery. However, there are many small arteries and several anastomoses in the nasal region. In most cases, the LNA provides the main blood supply to the tip, and the dorsal nasal artery is the main supplier to the upper portion of the nose. The dorsal nasal artery can be identified usually 5 mm above the medial canthal horizontal line.[51] The main arteries anastomose connecting the external and internal carotid systems at the level of the superficial musculoaponeurotic system (SMAS) plane and above. The presence of so many anastomotic vessels in the nasal area, whose blood flow can be easily reversed with injections, creates risk of embolism when injecting fillers. When injecting filler in the nose, the filler is most safely placed in the avascular deep supraperiosteal plane below the nasal SMAS. If the patient has had previous surgical treatments on the nose, filler injections are not advised or should be performed with extreme caution with the risks extensively reviewed with the patient.[52]

Nasolabial Fold/Medial Cheek/Periorbital Region

The most likely blood vessel at risk for compromise in the medial cheek, NLF, and medial periorbital area is the AA. A recent study by Kim and colleagues describes 4 patterns of the AA (Figure 4). In Type I (19.3%), the AA originates from the branching point of the LNA adjacent to the ala of the nose and continues superiorly to the forehead. In Type II (31.6%), the AA originates from the facial artery near the mouth corner, proceeds to the infraorbital area, and then courses medially along the nasojugal and medial canthal areas. In Type III (22.8%), the AA originates from the ophthalmic artery at the medial canthal area. In Type IV (26.3%), the facial artery terminates as the LNA without producing an AA branch. Given the variable pattern, care must be taken when injecting the medial cheek, tear trough, or NLF as the AA can be present at these sites.[53]

The depth of the facial artery and its branches varies. Lee and colleagues[54] studied 54 cadavers to examine the relationship between the facial artery and facial muscles. They found 3 different branching patterns of the facial artery, which parallel the findings of the study by Kim and colleagues; however, the proportions varied. In the study by Lee and colleagues, the Type I pattern or nasolabial pattern was the most common with 51.8% of cadavers having the facial artery ascend along the lateral side of the nose. This pattern reflects the typical description in anatomy textbooks.[54] Lee and colleagues went further and described the depth of the facial artery and its branches. In the region of the NLF between the mouth corner and nasal ala, the facial artery branches were located in the subcutaneous layer on the surface of the facial muscles in 85.2% of cases. Therefore, injection in the NLF is best placed in a more superficial plane, that is, dermal or immediately subdermal. In addition to the NLF, the vessels are commonly located in a subcutaneous plane lateral to the mouth corner at the modiolar region and lateral to the nasal ala. If present, the infraorbital branch seen in Type II is also commonly seen in a subcutaneous plane.[54] The key message from both of these studies is that the AA may be located in the medial cheek/infraorbital area and that the facial artery and its branches may be in the subcutaneous plane, making intravascular injection a risk factor when injecting in this plane.

There are other important cutaneous arteries in the cheek region. The infraorbital artery is a branch of the maxillary artery and is located in the region of the medial cheek. It anastomoses with the facial artery and the dorsal nasal branch of the ophthalmic artery.[55] The lacrimal artery branches into the zygomaticofacial artery and zygomaticotemporal artery. The zygomaticofacial artery passes through the lateral wall of the orbit and emerges to supply the skin overlying the cheek prominence. Both the zygomaticofacial and infraorbital arteries connect with the ophthalmic artery either directly or through anastomoses. The zygomaticotemporal artery also passes through the lateral wall of the orbit and contributes to the blood supply of the temple in addition to the arteries highlighted in the next section.[56]

Temple

The lateral face, scalp, and forehead are primarily supplied by the superficial temporal artery and its branches. This artery begins in the superficial lobe of the parotid gland as the terminal branch of the external

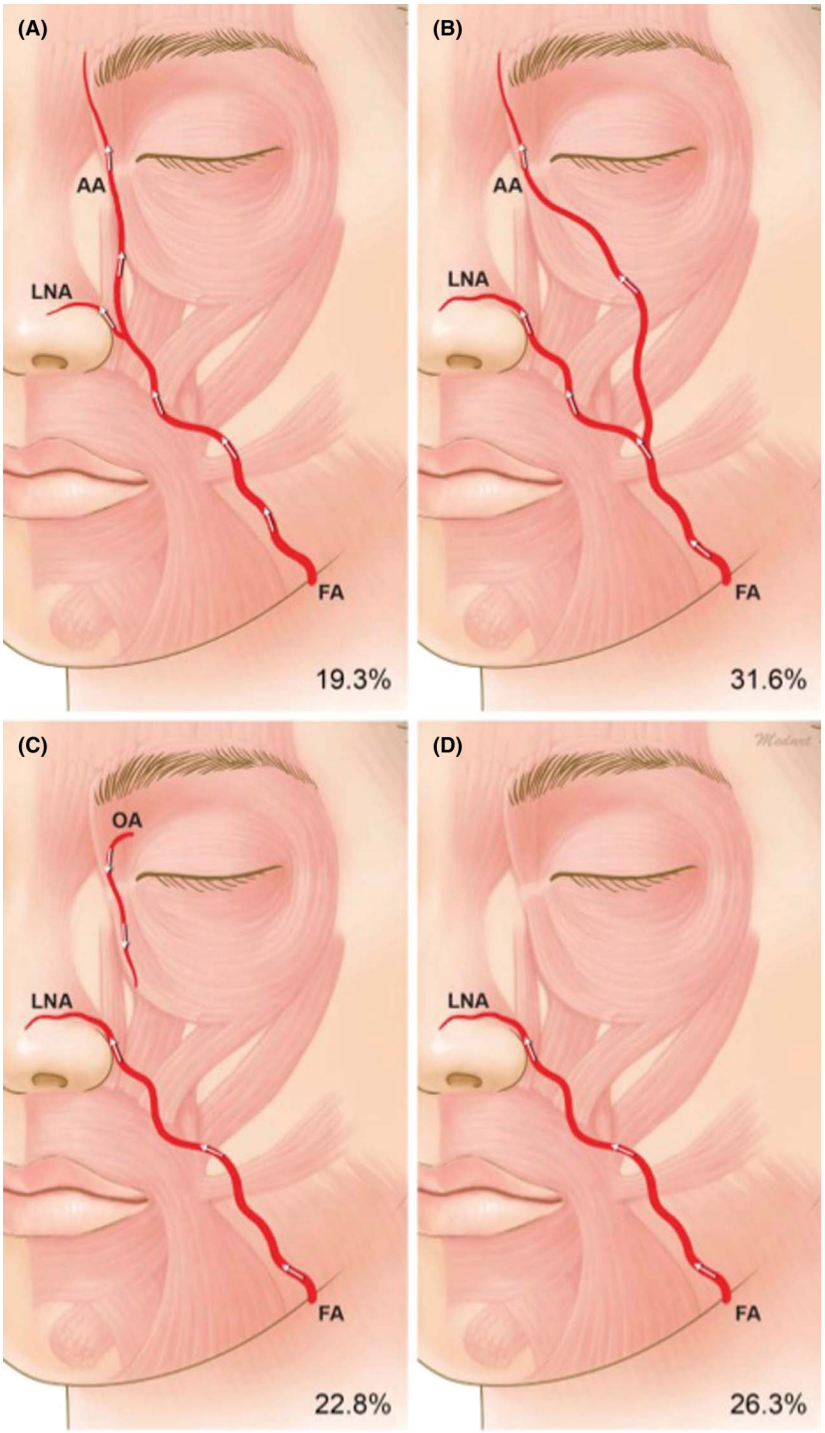

Figure 4. Schematic illustrations showing the 4 patterns of the AA. (A) Type I, the persistent pattern in which the AA originates from the branching point of the LNA from the facial artery (FA) adjacent to the ala of the nose. (B) Type II, the detouring pattern in which the AA traverses continuously from the detouring branch of the FA and ascends vertically to the nasojugal and medial canthal areas. (C) Type III, the alternative pattern in which the AA originates only from the ophthalmic artery. (D) Type IV, the latent pattern in which the FA terminates around the nasolabial area without giving off an AA branch. The arrows indicate the blood flow route in the arteries (Copyright Hee-Jin Kim, DDS, PhD, 2014).[53] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

carotid artery. It gives off the transverse facial artery, which runs parallel to and 2 cm below the zygomatic arch. This branch anastomoses with the facial artery. At the superior border of the zygomatic arch, the superficial temporal artery gives off a second branch, the middle temporal artery. From there, the superficial temporal artery continues superiorly and branches into the anterior or frontal branch and parietal branch just above the level of the ear. As the frontal branches of the superficial temporal artery move medially, they become more superficial up to a subdermal level.[51] There are many anastomoses on the scalp between the bilateral superficial temporal arteries and the supraorbital and supratrochlear arteries, which could contribute to vascular complications.[49] However, ocular complications when injecting in the temple may result from injection into the middle temporal vein (MTV). The MTV is connected to the cavernous sinus through the periorbital veins, and it has been hypothesized that it may be easier for filler to be inadvertently injected into the MTV, which is much larger than similar arteries in that area, leading to cavernous sinus embolization. The authors suggested that the safest area to inject filler in the temple is 1 fingerbreadth above the zygomatic arch as the MTV was not found in that area. In addition, it is recommended that filler be placed in a supraperiosteal plane rather than subcutaneously as the MTV is located more superficially.[57]

Eyelid

The vascular supply of the eyelids is complex and is derived from anastomoses between the internal and external carotid arteries. The medial and lateral palpebral arteries directly supply the lid with contributions from many different vessels including the ophthalmic, facial, superficial temporal, and infraorbital arteries. The rich anastomoses between the vessels can lead to embolic material reaching the ophthalmic artery, and as such, caution must be taken when injecting in the thin skin of the eyelid.[49]

Clinical Features

Most commonly, ocular symptoms occurred immediately after injection. Vision loss, ocular pain, and headache were the most common symptoms. Nausea and vomiting, secondary to increased intraocular pressure, were reported in 10 cases. Variable ocular signs were reported. Paralysis of the eye muscle resulting in ophthalmoplegia occurred in 40 cases, and ptosis was seen in 32 cases. Obstruction of the blood supply to the extraocular muscles or innervating nerves causes ophthalmoplegia. Ptosis results from the lack of blood supply to the levator palpebral muscle or its innervating nerves.[18] Although vision recovery was rare, ophthalmoplegia and ptosis recovered in the majority. This is likely because nerves and muscles regenerate after vascular compromise, whereas the retinal damage is irreversible after 90 minutes.[15] Skin changes along the path of the vessel where the vascular occlusion occurred were seen in 15 cases. Typically, this presented as a violaceous reticulated pattern, and occasionally necrosis.

Autologous fat was the filler type most likely to cause visual complications. This could reflect use of larger volumes, larger syringes, and higher extrusion pressures. A review of the 47 cases of blindness resulting from injection of fat found that only a few articles reported procedural details. In these cases containing more detailed information, a range of syringe sizes were used from 10 to 20 mL, the needle or cannula size ranged from 0.3 to 2 mm in diameter or 23 to 12 gauge, and the injection volume of fat ranged from 2 to 20 mL. The lack of consensus with regard to the technique and regional differences may have also contributed to safety outcomes. Autologous fat had a higher risk of permanent vision loss as the ultimate ocular outcome at 80.9% compared with HA at 39.1%. Autologous fat injections were much more likely to cause CNS complications in association with ocular adverse events, making up 82.6% of the cases compared with 8.7% from HA injections. The variable particle size of autologous fat means that it can block various sized arteries including larger ones such as the ophthalmic artery.[18] This could lead to more diffuse downstream effects, which may explain why the ocular complications were more serious from autologous fat injection.

Prevention

It is important to have a keen understanding of prevention strategies to avoid blindness from filler,

because if this adverse event occurs, there are no well-documented successful treatments. Key prevention strategies are highlighted in Box 1.

Box 1. Key Prevention Strategies

(1) Know the location and depth of facial vessels and the common variations. Injectors should understand the appropriate depth and plane of injection at different sites.
(2) Inject slowly and with minimal pressure.
(3) Inject in small increments so that any filler injected into the artery can be flushed peripherally before the next incremental injection. This prevents a column of filler traveling retrograde. No more than 0.1 mL of filler should be injected with each increment.[15,58]
(4) Move the needle tip while injecting, so as not to deliver a large deposit in one location.
(5) Aspirate before injection. This recommendation is controversial as it may not be possible to get flashback into a syringe through fine needles with thick gels.[58] In addition, the small size and collapsibility of facial vessels limit the efficacy.[15]
(6) Use a small-diameter needle.*A smaller needle necessitates slower injection and is less likely to occlude the vessel.[15]
(7) Smaller syringes are preferred to larger ones as a large syringe may make it more challenging to control the volume and increases the probability of injecting a larger bolus.[13]
(8) Consider using a cannula, as they are less likely to pierce a blood vessel. Some authors recommend use of the cannula in the medial cheek, tear trough, and NLF in particular.
(9) Use extreme caution when injecting a patient who has undergone a previous surgical procedure in the area.
(10) Consider mixing the filler with epinephrine to promote vasoconstriction as cannulating a vasoconstricted artery is more difficult.[15]

*For injection of autologous fat, expert recommendations include limiting the syringe size to 1 mL and using larger blunter cannulas in the range of 16 to 18 gauge as smaller sharp needles/cannulas are more likely to perforate blood vessels. The volume placed with each pass of the cannula should be less than 0.1 mL.[59] In addition, many dermatologic surgeons recommend avoiding injecting fat into the glabella given the high risk of complications.

Management

Given the lack of successful outcomes and variable treatments reported, it is challenging to provide any evidence-based treatment recommendations. The goal of treatment is rapid restoration of perfusion to the eye. After 90 minutes, the damage secondary to retinal ischemia becomes irreversible.[15] Key management strategies are highlighted in Box 2.

Box 2. Key Management Strategies

(1) If a patient complains of ocular pain or vision changes, stop the injection at once. Immediately contact an ophthalmologist or oculoplastics colleague and urgently transfer the patient directly there.
(2) Consider treating the injected area and surrounding location with hyaluronidase if HA filler is used.
(3) Consider retrobulbar injection of 300 to 600 units (2–4 mL) of hyaluronidase if HA filler is used.[47]
(4) Reduction of intraocular pressure should be considered. Mechanisms to achieve this include ocular massage, anterior chamber paracentesis, IV mannitol, and acetazolamide.[15]
(5) Given the relatively high prevalence of CNS complications that accompany blindness, it is important to monitor the patient's neurologic status and consider ordering imaging studies of the brain if visual complications occur.[19]

As HA fillers become increasingly popular and diverse, it is important to recognize the related complications. Having a firm understanding of how to use hyaluronidase is critical. Hyaluronidase is an enzyme that catalyzes HA hydrolysis.[58] The authors recommend having a ready supply on hand. Ideally, it should not

be manufactured with thimerosal and should not be a compounded formula as this can increase allergenicity.[47] In the case of blindness, time is of the essence, making a skin test to evaluate for an allergic response impractical. An in vitro, dose–response study indicated that Juvederm (Allergan, Irvine, CA) is more resistant to hyaluronidase compared with Restylane (Galderma, Fort Worth, TX) perhaps because of the greater degree of cross-linking.[60] Therefore, higher doses of hyaluronidase may be needed with Juvederm products. The injector should consider injecting large volumes of hyaluronidase at the site of injection and surrounding areas if an HA filler was used. It has been shown that hyaluronidase can diffuse through the blood vessel walls without needing to be injected into the vessel directly.[58] Therefore, retrobulbar injection of hyaluronidase is a potential vision-saving treatment. To the best of the authors' knowledge, this strategy has not been attempted; however, they propose an injection of 300 to 600 units (2–4 mL) of hyaluronidase to the retrobulbar space. The technique involves placing a small amount of local anesthetic in the lower eyelid over the inferotemporal orbit. A 25-gauge needle is then advanced in that plane until it is at least 1 inch in depth. Then, 2 to 4 mL of hyaluronidase is injected into the inferolateral orbit.[47] One could also consider IV hyaluronidase or injection of the ophthalmic artery by a neuroradiologist with hyaluronidase.[47] However, these are hypothetical treatment strategies and have not been documented to date.

Other treatments that have been tried include mechanisms to decrease intraocular pressure including anterior chamber decompression, mannitol, and acetazolamide. Ocular massage may lower intraocular pressure and potentially increase blood flow or dislodge the embolus.[15] Retinal arterial dilation may be stimulated through carbon dioxide and oxygen inhalation. Hyperbaric oxygen has been recommended, but the concern with this is the time required to reach a location.[15] Systemic and local intra-arterial fibrinolysis has been attempted. This management strategy reflects studies showing improvement in central retinal artery occlusion secondary to thromboembolism when fibrinolysis was used.[61] However, fibrinolysis has not proven to be a successful treatment in the case of blindness from filler. Systemic corticosteroids to decrease the inflammatory component of the injury have also been recommended.

If any signs of cutaneous vascular compromise occur, it is important to treat that simultaneously. The authors previously reported on treatment strategies for vascular compromise in the skin, which included warm compresses, vigorous massage, and hyaluronidase if HA filler was used. Other treatments to consider include topical 2% nitroglycerin paste, aspirin, prednisone, and hyperbaric oxygen.[62]

The most important first step in the case of blindness is emergent assessment and management by an appropriate specialist. Injectors should know the ophthalmologists in their area to facilitate immediate transfer of the patient to that location. Whenever possible, the injecting physician or a staff member should accompany the patient to provide information about the filler used, location of injection, time of injection, and treatments instituted thus far. Furthermore, the injecting physician can review reported treatments and emphasize the timeline with the treating physician, as this may not be a complication he or she is familiar with. It is important to consider the possibility of CNS complications, and in such a scenario, the stroke service or a neurologist should be involved. Although many treatment strategies have been tried, none have definitive evidence. If any treatments are to be started, there is a 90-minute window to do this before the vision loss is permanent.[47]

Conclusion

With the increased use of soft tissue augmentation for revolumization, it is imperative to be aware of potential devastating ocular complications. Although the risk is very low, the authors believe that prevention begins with education and the ability to recognize potentially grave adverse events. Injectors should have a firm understanding of the vascular anatomy of high-risk sites and understand the depth and plane of injection. Key prevention strategies such as injecting small amounts under low pressure, using smaller needles or cannulas, and injecting slowly should be implemented. Despite proper technique, the possibility of embolization of filler into the ophthalmic artery

remains. As such, it is important that injectors have a management strategy in place, which should include immediate transfer to an ophthalmologist, and consideration of injection of high doses of hyaluronidase at the injection site and into the retrobulbar space in the case of HA filler. Further discussion among experts, relating their experiences with ocular complications from filler, is essential to build consensus that will improve patient safety and optimize outcomes.

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Address correspondence and reprint requests to: Katie Beleznay, MD, FRCPC, FAAD, Carruthers and Humphrey Cosmetic Medicine, Suite 820-943 West Broadway, Vancouver, BC V5Z 4E1, Canada, or e-mail: kbeleznay@gmail.com