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Complications Following Injection of Soft-Tissue Fillers

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Abstract

Background: Soft-tissue filler injection is a very common procedure in the United States. Although the safety profile is favorable, adverse events (AE) can occur, ranging from mild to severe in intensity.

Objectives: The authors performed a literature search to identify the facial sites most prone to severe complications. They review the course of these complications and discuss preventive measures.

Methods: The National Library of Medicine, the Cochrane Library, and Ovid MEDLINE were searched, and relevant articles (published through August 2012) were retrieved based on prespecified inclusion criteria. The complications reviewed were limited to "severe" events, such as soft-tissue necrosis, filler embolization, visual impairment, and anaphylaxis. The filler materials included were those approved by the US Food and Drug Administration at the time of this study.

Results: Forty-one articles, representing 61 patients with severe complications, were identified. Data collected from these case reports included filler type, injection site, complication site, symptom interval, symptom of complication, time to therapy, modality of treatment, and outcome. The most common injection site for necrosis was the nose (33.3%), followed by the nasolabial fold (31.2%). Blindness was most often associated with injection of the glabella (50%). An estimated incidence of 0.0001% for developing a severe complication was calculated by reviewing society-based filler data and case reports within same time period.

Conclusions: Although soft-tissue fillers are a popular choice for minimally invasive rejuvenation of the face, physicians should be aware of the serious potential adverse effects, recognize their presentations, and have appropriate treatments readily available.

Keywords

filler, injectable, complication, blindness, necrosis, cosmetic medicine, literature review

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The use of soft-tissue fillers for cosmetic purposes has increased dramatically in recent years. According to the 2012 statistics published by the American Society for Aesthetic Plastic Surgery (ASAPS), fillers are now the second most common minimally invasive procedure performed among plastic surgeons, behind botulinum toxin injections.[1] The trend is similar in dermatology practice. Data from the American Society for Dermatologic Surgery (ASDS) demonstrate that injectables are also the second most common minimally invasive procedure performed by dermatologists (also following botulinum toxin).[2] The popularity of fillers is attributable to their ease of application, significant beneficial effect on appearance, and low rate of complications.

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Although soft-tissue fillers have a very favorable safety profile, adverse events (AE) can occur. Minimal and self-limited complications are relatively common and perhaps would be more appropriately termed *adverse sequelae* rather than true complications. Such events include ecchymosis, swelling, and erythema. More significant yet self-limited complications also have occurred, including overcorrection, irregularities, filler visibility, Tyndall effect, and granuloma formation. Complications of greater severity also have been reported, such as visual impairment, skin necrosis, and anaphylaxis. The goal of the present review is to highlight the more serious complications, identify the areas and techniques most prone to complications, suggest means for minimizing complications, and discuss effective methods of treatment.

METHODS

A literature search was performed to gather information on severe complications following injection of soft-tissue fillers from reports published through August 2012. The databases of the National Library of Medicine (PubMed), the Cochrane Library, and Ovid MEDLINE were searched using the following Boolean string: (anaphylaxis OR blindness OR necrosis OR embolization OR scar OR complication) AND (filler OR injectable). Additional searching was done using the phrases *soft-tissue filler complications, dermal filler complications*, and *injectable complications*. The references cited in selected articles also were reviewed to potentially identify additional reports that matched the criteria. The search was limited to the English-language literature and to the head and neck region.

Reports of "severe" complications following use of injectables were selected for this review; these included soft-tissue necrosis, filler embolization resulting in impending necrosis, blindness, partial loss of vision, transient loss of vision, and anaphylaxis. Cases of visual impairment with concomitant necrosis were counted only once, in the vision loss subgroup. The only filler materials included were those that had been approved by the US Food and Drug Administration (FDA) at the time of the review. These materials were collagen, hyaluronic acid (HA), polymethylmethacrylate (PMMA) suspended in collagen, calcium hydroxylapatite (CaHa), poly-L-lactic acid (PLLA), and injectable dermal matrix. Autologous fat, liquid silicone, and other non-FDA-approved substances were excluded.

RESULTS

A total of 41 reports representing 61 patients with severe complications were identified. A summary of the cases, therapies, and outcomes is presented in Table 1. The complications were classified into 3 groups: (1) soft-tissue necrosis or impending necrosis as a result of filler embolization, (2) visual impairment, and (3) anaphylaxis. Figure 1 shows the distribution of complications by injection site. Of the 61 cases, the injection site most commonly associated with complications was the nose (32.8%; n = 20), followed by the glabella (26.2%; n = 16) and the nasolabial fold (NLF) (26.2%; n = 16). In 4 cases, the injection site was not specified.[3,4] The distribution of complications according to filler type is shown in Figure 2. Hyaluronic acid was the most common filler implicated in necrotic complications, and collagen was the most common filler resulting in visual impairment. Filler type was not reported for 2 cases.[5,6] One case of anaphylactic shock occurred after the eighth injection session of PMMA.[7] However, neither the specific clinical presentation nor the outcome was described.

Soft-Tissue Necrosis and Impending Necrosis

There were 39 cases of significant soft-tissue loss and 9 cases of "impending necrosis" (Table 1). The responsible substances were HA, PMMA, collagen, and CaHa. Common injection sites for these complications were the nose (33.3%; n = 16),[3,4,8-15] NLF (31.2%; n = 15),[4,8,13,16-23] and glabella (20.8%; n = 10).[17,24-30] Other sites were the cheeks and lips (in 1 and 2 cases, respectively).[31-33] In 4 cases (8.3%), the site of injection was not reported.[3,4] Of the 16 nasal injections, 5 were in the nasal tip,[3,8-10,13] 1 was in the lateral nose,[4] 3 were in the dorsum,[10] and 2 were in the dorsum as well as the tip.[11,14] One patient had multiple injections to the nose, forehead, and glabella.[14] For the other 4 cases, the specific nasal location was not reported.[3,9,12,15] Details of injection technique and needle size were not described for any case of necrosis.

The symptom most often associated with intravascular injection was immediate pain upon administration of the product. Other acute symptoms included blanching, duskiness, and ecchymosis. In several cases, no signs were noted at the time of injection, and delayed compression of vessels by product was proposed as a possible mechanism of injury.[20,21,33]

The affected sites showed additional signs of vascular compromise within 1 to 2 days, including erythema, white or violaceous discoloration, edema, bruising, and ongoing pain. In patients with "impending necrosis," the symptoms and signs improved, sometimes associated with early intervention, and resolved without sequelae.

When soft-tissue loss occurred, slough, ulceration, and eschar developed within 3 to 7 days after injection. The tissue loss occurred directly at the injection site in 46.2% of cases (n = 18) and at the site nourished by the compromised vessel in 28.2% (n = 11). The latter included necrosis developing at the forehead and nose after glabellar injection[26,27,30] and necrosis developing at the nasal ala and lip after NLF injection.[4,8,13,16,18,23] In 10 cases (25.6%), the data were insufficient to make a correlation between treatment site and complication site.

A variety of treatments were used, including hyaluronidase, nitroglycerin paste, warm compresses, intravenous

(text continues on p. 7)

Table 1. Literature Summary: Reports of Severe Complications After Use of Injectable Fillers

Reference and No. of Cases	Complication	Type of Filler	Injection Site	Symptom Interval, Complaints, Location	Time to Therapy, Treatment Utilized	Outcome	Injecting Physician	Country
Hanke et al, 1991[29] 1 case	Necrosis	Collagen	Glabella	NR	NR	NR	Dermatologist	United States
Monheit, 1998[12] 1 case	Necrosis	Collagen	Nose	NR	NR	NR	NR	United States
Schanz et al, 2002[27] 1 case	Necrosis	HA	Glabella	Minutes: reticular pattern at injection site and nose; no pain 10 days: ulceration at injection site, glabella, and nose	Immediate: low-molecular-weight heparin 5000 IE daily (1 wk)	Complete recovery	Dermatologist	Germany
Friedman et al, 2002[24] 2 cases	Necrosis	HA	Glabella	NR	NR	NR	NR	NR
Lowe, 2003[33] 1 case	Impending necrosis	HA	Lip	Venous occlusion; persistent edema at injection site	NR	NR	Dermatologist	United Kingdom
Bellman, 2006[19] 1 case	Impending necrosis	HA	NLF	Immediate: bruising; edema at injection site 2 days: sensitivity; pustules; reticulated bruising; edema at injection site and nasal tip	2 days: dynacin 100 mg PO and prednisone 20 mg PO 4 days: hydrogen peroxide, mupirocin ointment, and warm compress	Complete recovery	Dermatologist	United States
Narins et al, 2006[32] 1 case	Necrosis	HA	Lip	Immediate: bleeding and bruising Later: necrosis of left lower lip	2 weeks: PO corticosteroid and antibiotics; secondary intention	Complete recovery	NR	United States
Steinsapir and Steinsapir, 2006[25] 1 case	Necrosis	HA	Glabella	NR	NR	Scarring	Ophthalmologist	United States
Gladstone and Cohen, 2007[26] 1 case	Necrosis	HA	Glabella	Necrosis at forehead	NR	NR	Dermatologist	United States
Hirsch et al, 2007[21] 1 case	Impending necrosis	HA	NLF	2 days: pain and erythema at injection site	2 days: aspirin 325 mg, nitroglycerin paste, and warm compress 3 days: hyaluronidase 30 U	Complete recovery	Dermatologist	United States
Hirsch et al, 2007[22] 1 case	Impending necrosis	HA	NLF	6 hours: erythema and discoloration at injection site	6 hours: aspirin 325 mg, nitroglycerin paste, warm compress, and hyaluronidase 30 U	Complete recovery	Dermatologist	United States
Salles et al, 2008[13] 3 cases	All 3 cases: necrosis	All 3 cases: PMMA	Case 1: nose (tip) Case 2: NLF and nose Case 3: NLF	Case 1: 7 days: hyperemia, swelling, and necrosis of ala Case 2: Immediate: pain Later: necrosis of ala and upper lip Case 3: necrosis of ala upper and lower lateral lip	All 3 cases: NR	All 3 cases: scarring	Case 1: plastic surgeon Case 2: dermatologist Case 3: plastic surgeon	Brazil

(continued)

Table 1. (continued)

Reference and No. of Cases	Complication	Type of Filler	Injection Site	Symptom Interval, Complaints, Location	Time to Therapy, Treatment Utilized	Outcome	Injecting Physician	Country
Inoue et al, 2008[16] 1 case	Necrosis	Collagen	NLF	Immediate: pain at left side of face First hours: reddish discoloration 6 days: necrosis of nasal ala	6 days: IV alprostadil 120 µg/d for 2 wk; surgical debridement	Scarring; reconstruction with skin graft	Plastic surgeon	Japan
Grunebaum et al, 2009[8] 3 cases	Case 1: necrosis Case 2: necrosis Case 3: impending necrosis	All 3 cases: HA	Case 1: NLF Case 2: NLF Case 3: nose (tip)	Case 1: 1 day: skin irritation; numbness 3 days: necrosis of nasal ala Case 2: First hours: pain; dusky erythema 12 hours: necrosis of nasal ala Case 3: Immediate: erythema of nose	Case 1: 3 days: Bacitracin; secondary intention Case 2: Immediate: hydrocolloid dressing; hyaluronidase 40 U Case 3: Immediate: nitropaste (for 1 wk) and hyaluronidase (3 times)	Case 1: complete recovery Case 2: scarring Case 3: complete recovery	NR	United States
Georgescu et al, 2009[17] 2 cases	Both cases: necrosis	Both cases: CaHa	Case 1: glabella Case 2: NLF	Case 1: Hours: pain and bruising at injection site 2 days: necrosis at glabella Case 2: Same day: pain and swelling over fold; necrosis; ecchymosis	Case 1: 2 days: PO corticosteroid; nitroglycerin paste (1 wk) 4 months: microdermabrasion Case 2: Same day: PO antibiotics and steroids Months: Microdermabrasion and hydrocortisone ointment	Both cases: complete recovery	NR	United States
Winslow, 2009[15] 1 case	Necrosis	CaHa	Nose	Immediate: blanching Days: bluish discoloration; ischemic purpura; edema; mild epidermolysis of nose	Nitroglycerin paste (timing not specified)	Complete recovery	Plastic surgeon	United States
Bachmann et al, 2009[28] 2 cases	Both cases: necrosis	Both cases: HA	Both cases: glabella	Case 1: 1 day: erythema; inflammation; abscess formation at injection site Case 2: Immediate: pain 1 day: erythema and edema 5 days: discoloration abscess 3 weeks: ulceration	NR	Both cases: recovery with scarring	NR	Germany
Humphrey et al, 2009[9] 2 cases	Both cases: impending necrosis	Both cases: HA	Both cases: nose (tip)	Case 1: 12 hours: blanching and discoloration at injection site Case 2: 1 week: discoloration and numbness at cold temperature	Case 1: 12 hours: nitroglycerin paste (1 wk), warm compress, and hyaluronidase (15 U; 3 times) Case 2: hyaluronidase (15 U)	Both cases: partial recovery	Otolaryngologist	United States
Burt et al, 2010[18] 1 case	Necrosis	HA	NLF	1 day: pain and poor perfusion 3 days: sloughing and ulceration of nasal ala	NR	Complete recovery	Plastic surgeon	United States

(continued)

Table 1. (continued)

Reference and No. of Cases	Complication	Type of Filler	Injection Site	Symptom Interval, Complaints, Location	Time to Therapy, Treatment Utilized	Outcome	Injecting Physician	Country
Kassir et al, 2011[31] 1 case	Necrosis	HA	Cheek	First hours: pain; bluish discoloration 5 days: slough and eschar of right cheek	5 days: massage; IM, topical, and PO antibiotics; Valtrex; silicone gel	Scarring	Plastic surgeon	United States
Kim et al, 2011[10] 4 cases	All 4 cases: necrosis	All 4 cases: HA	Case 1: nose (tip) Cases 2, 3, and 4: nose (dorsum)	All 4 cases: Immediate: pain Later: reticular skin discoloration and necrosis of nasal dorsum and tip	Case 1: 1 day: hyaluronidase Case 2: 1 day: hyaluronidase	All 4 cases: scarring	Plastic surgeon	Korea
Park et al, 2011[4] 3 cases	All 3 cases: necrosis	All 3 cases: HA	Case 1: nose (sidewall) Case 2: NR Case 3: NLF	Case 1: NR Case 2: necrosis of mentum Case 3: necrosis of ala	Case 1: 3 months: PO antibiotics Case 2: 2 months: surgical excision Case 3: 1 week: oral antibiotics	NR	NR	Korea
Kim et al, 2011[11] 1 case	Necrosis	HA	Nose (dorsum and tip)	Hours: swelling and discoloration at injection site Days: dark brown and purple discoloration at nasal tip	1 day: filler removal (puncture) Days: IV alprostadil and topical antibiotics	Recovery with minimal scarring	Plastic surgeon	Korea
Dayan et al, 2011[20] 3 cases	Cases 1 and 2: impending necrosis Case 3: necrosis	All 3 cases: CaHa	Case 1: NLF, infra-orbital region Case 2: NLF Case 3: NLF	Case 1: Immediate: blanching over left cheek, NLF, and left upper lip 2 days: edema and erythema of left lower face; reticulated vascular congestion of upper lip and left buccal mucosa Case 2: 1 day: tenderness; erythema; drainage at fold Case 3: 1 day: edema; erythema; bruising at fold and malar region Later: ulceration at fold	Case 1: Immediate: nitroglycerin paste (for 5 days) 2 days: hyaluronidase 150 U; methylprednisone PO; aspirin 325 mg/d (2 wk); topical oxygen infusion cream Case 2: 1 day: Nitroglycerin paste; antibiotic ointment; hyaluronidase 20 U; aspirin 325 mg/d; PO antibiotics 4 days: Hyaluronidase 15 U; topical oxygen infusion cream Case 3: Days: IV and PO antibiotics; PO valacylclovir; topical steroid 4 weeks: hyaluronidase 40 U; nitroglycerin paste; aspirin 325 mg/d, antacids; topical oxygen infusion cream	Cases 1 and 2: complete recovery Case 3: NR	NR	United States
Park et al, 2011[23] 1 case	Necrosis	HA	NLF	1 hour: erythema on central face 2 days: Necrosis at nasal tip with pain and tenderness	1 day: hyaluronidase 20 U (once) and warm compress 2 days: Bacitracin ointment	Complete recovery	Dermatologist	Korea

(continued)

Table 1. (continued)

Reference and No. of Cases	Complication	Type of Filler	Injection Site	Symptom Interval, Complaints, Location	Time to Therapy, Treatment Utilized	Outcome	Injecting Physician	Country
Sung et al, 2011[14] 2 cases	Both cases: necrosis	Both cases: HA	Case 1: nose, forehead, glabella Case 2: nose (tip and dorsum)	Case 1: 1 day: tenderness and erythema 5 days: necrosis of nasal tip Case 2: 1 day: erythema and pain 5 days: necrosis of nasal tip and dorsum	Case 1: Immediate: IV antibiotics; hydrocolloid dressing 3 days: adipose-derived stem cells Case 2: Immediate: hyaluronidase 1000 U; steroid injection 5 days: IV antibiotics; debridement 11 days: adipose-derived stem cells	Both cases: recovery with scarring	NR	Korea
Nettar and Maas, 2012[30] 1 case	Necrosis	HA	Glabella	Immediate: blanching 1 day: discoloration; bruising at injection site 1 week: necrosis of forehead	1 day: arnica cream and ice compress 1 week: surgical debridement	NR	Plastic surgeon	United States
de Melo Carpaneda and Carpaneda, 2012[3] 5 cases	All 5 cases: necrosis	All 5 cases: PMMA	Case 1: nose (tip) Case 2: nose Cases 3, 4, and 5: NR	All 5 cases: Immediate: intense pain 1-2 days: white to violet discoloration Later: necrosis Case 1: necrosis of nasal tip Case 2: necrosis of nasal ala and dorsum Case 3: necrosis of nasal ala and tip and lips	NR	Cases 1, 3, 4, and 5: NR Case 2: scarring	NR	Brazil
Castillo, 1989[34] 1 case	Blindness	Collagen	Glabella, cheek	NR	NR	NR	NR	United States
Hanke, 1998[43] 1 case	Blindness	Collagen	Glabella	NR	NR	NR	Dermatologist	United States
Apte et al, 2003[36] 1 case	Visual impairment	Injectable dermal matrix	Forehead	10 minutes: nausea; diaphoresis; pain in left eye; blurred vision	NR	Vision loss with light perception	NR	United States
Silva and Curi, 2004[40] 1 case	Blindness	PMMA	Glabella	Immediate: severe pain and visual loss in right eye	NR	Blindness and total ophthalmoplegia	NR	Brazil
Kubota and Hirose, 2005[38] 1 case	Blindness	PMMA	Nose (dorsum)	15 minutes: pain and visual loss in right eye	NR	Blindness	Plastic surgeon	Japan
Peter and Mennel, 2006[35] 1 case	Visual impairment	HA	Glabella, cheeks	1 minute: partial loss of vision in inferior right visual field	Immediate: acetazolamide	Complete recovery	NR	United States
Kang et al, 2007[6] 1 case	Visual loss and necrosis	NR	Glabella	Immediate visual loss; necrosis of glabellar region	NR	NR	NR	Korea

(continued)

Table 1. (continued)

Reference and No. of Cases	Complication	Type of Filler	Injection Site	Symptom Interval, Complaints, Location	Time to Therapy, Treatment Utilized	Outcome	Injecting Physician	Country
Hwang et al, 2008[5] 1 case	Visual loss	NR	Glabella, nose, periorbita	Immediate: visual loss in left eye; erythematous color change at site of injection	Acetazolamide (1 wk) and methylprednisolone (3 d)	Partial recovery with 20/200 visual acuity	NR	Korea
Kwon et al, 2010[42] 1 case	Blindness, necrosis, stroke lesion	Collagen	Nose (septum)	Immediate: visual loss in left eye; headache Later: reticular violet discoloration	Antiplatelet agent and calcium channel blocker	Blindness	NR	Korea
Sung et al, 2010[41] 1 case	Visual loss, necrosis	CaHa	Nose (dorsum)	Immediate: pain in right eye; ptosis; ophthalmoplegia Later: reddish reticular pattern in right eyelid	8 hours: IV antibiotics, topical steroids, and PO corticosteroids	Complete recovery with fixed dilated pupil; minimal scarring	Dermatologist	Korea
Kim et al, 2011[37] 1 case	Blindness, necrosis	HA	Nose (tip)	Immediate: visual loss in left eye; pain in left upper face; ophthalmoplegia 2 days: violaceous, ulcerative patches	2 days: IV methylprednisolone; aspirin 100 mg PO	Blindness; recovery from ophthalmoplegia	Plastic surgeon	Korea
Roberts and Arthurs, 2012[39] 1 case	Blindness	PLLA	Periorbital region	Immediate: visual loss and pain in left eye 1 day: nausea; ophthalmoplegia; ptosis	NR	Blindness; recovery from ophthalmoplegia	NR	Canada
Lemperle et al, 2003[7] 1 case	Anaphylactic shock	PMMA	NLF	NR	NR	NR	NR	Italy

Abbreviations: CaHa, calcium hydroxylapatite; HA, hyaluronic acid; IM, intramuscular; IV, intravenous; NLF, nasolabial fold; NR, not reported; PLLA, poly-L-lactic acid; PMMA, polymethylmethacrylate; PO, per oral.

(IV) prostaglandins, topical and oral antibiotics, topical and oral corticosteroids, low-molecular-weight heparin, topical oxygen, massage, hydrocolloid dressings, and eventual surgical treatment.* Adipose-derived stem cells were used in 2 cases of nasal tip necrosis.[14] The treatment choice varied according to when the patient was examined by the reporting physician. Because the case reports provided too little detail and the number of cases was small, it was not possible to establish a correlation between treatment initiation and outcome. Of the 39 cases of soft-tissue loss, 11 (28.2%) reportedly healed completely, with no or minimal scarring.[8,11,15-18,20,23,27,32] Fifteen patients (38.5%) had visible scars after complete healing.[8,10,13,25,28,31] For the remaining 13 cases (33.3%), outcomes were not reported.

Visual Impairment

There were 12 cases of visual impairment resulting from filler embolism to the ophthalmic vasculature (Table 1).

*References 4, 8, 9, 11, 12, 15-17, 20, 23, 27, 31, 32.

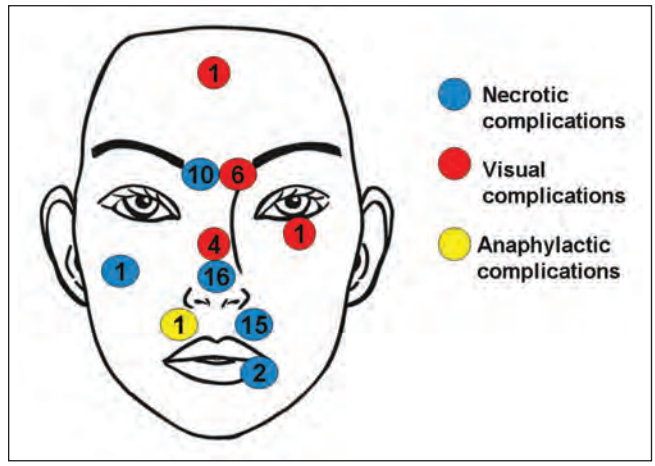

Figure 1. Distribution of complications according to injection site and type (necrotic, visual, anaphylactic). Numbers in blue, red, and yellow circles represent the number of cases who had necrotic, visual, and anaphylactic complications, respectively.

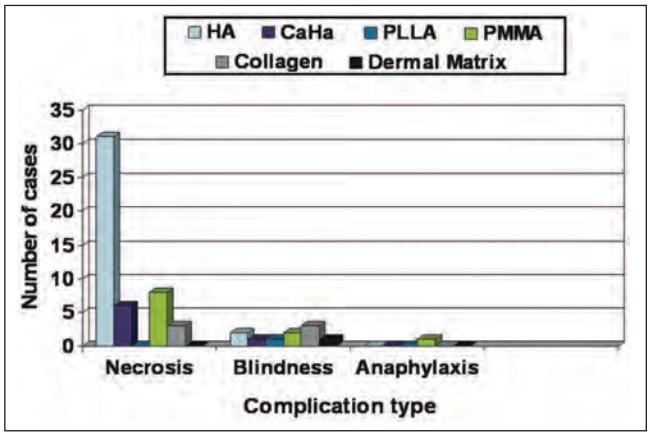

Figure 2. Distribution of severe complications according to type of filler. CaHa, calcium hydroxylapatite; HA, hyaluronic acid; PLLA, poly-L-lactic acid; PMMA, polymethylmethacrylate.

The injected substances were HA, PMMA, injectable dermal matrix, collagen, PLLA, and CaHa. Specific details regarding injection technique and needle type were not described in any of these reports. The glabella was the most common site yielding visual complications (50%; n = 6), followed by the nose (33.3%; n = 4), forehead (8.3%; n = 1), and periorbital region (8.3%; n = 1). In 3 patients who had injection of the glabella, injections also were made in the nose, cheeks, and periorbital area.[5,34,35]

In all 12 cases, the signs and symptoms of visual loss developed within minutes of the filler injection. Visual impairment was almost always accompanied by pain in the affected eye.[36-41] Other immediate symptoms included diaphoresis, nausea, headache, ophthalmoplegia, and ptosis.[36,37,39,41,42] In 4 cases, a violaceous reticular discoloration was evident several days after the injection, which was followed shortly by soft-tissue necrosis in the glabella and nose.[6,37,41,42] One patient experienced ischemic stroke in addition to vision loss.[42] Various treatment attempts were used, including diuretic agents, antiplatelet agents, systemic steroids, and aspirin.[5,35,37,41,42] In 7 cases, no information on treatment was provided.[6,34,36,38-40,43] Only 2 of the 12 patients (16.7%) had complete recovery of vision,[35,41] and 1 (8.3%) had partial recovery.[5] Six of the 12 cases (50%) resulted in permanent complete blindness.[36-40,42] In 3 cases (25%), the outcome was not clear.[6,34,43]

DISCUSSION

The increasing demand for soft-tissue augmentation, using a wide variety of fillers, has been documented repeatedly. Since the introduction of collagen as a standard injectable material in the 1980s, a number of filler materials have been manufactured and approved by the FDA. All FDA efficacy testing of newer fillers has been based on the collagen prototype, using split-face studies.[44-48] In other words, new fillers merely had to meet or exceed the safety and efficacy standards of collagen products when collagen was injected into 1 NLF and the filler tested in the contralateral fold. Direct comparisons were then made between the duration of soft-tissue correction and the complications that occurred. Since 2010, collagen filler products have not been available in the United States, with the exception of bovine collagen, used as a carrier for PMMA microspheres.

The FDA has approved a variety of different filler materials, each with a distinct composition, injection profile, and duration of effect. Many of them are in use off-label at the discretion of the physician. Currently, HA is the most commonly used injectable, followed by CaHa and PLLA.[1] Therefore, it is not surprising that HA products are implicated most frequently in severe complications. These fillers also have different mechanisms of action and different periods of persistence in tissue. Among the temporary materials, HA remains in the tissue for 4 to 12 months, whereas collagen typically lasts only 2 to 4 months. Recent studies have shown that reinjection 4 to 5 months following initial treatment significantly increases the efficacy of HA products.[49-51] CaHa and PLLA are considered semipermanent fillers and may last 1 to 2 years in tissue. The only FDA-approved permanent filler is PMMA. Although the collagen carrier of this filler resorbs over time, the microspheres do not degrade, resorb, or dissolve, yielding permanent correction of wrinkles.

Even though soft-tissue fillers are generally safe, undesirable effects can occur with any type of filler. Adverse effects may result from injection techniques (eg, overcorrection, irregularities, Tyndall effect, intravascular injection) or can be host-initiated local events. Some of these effects may resolve with time, but others will require intervention based on severity and/or the type of filler used. Visual impairment, soft-tissue necrosis, permanent scarring, and anaphylaxis are rare but severe events.

Determining the Incidence of Complications

The lack of an organized database, combined with the fact that the injections generally are not performed in hospitals or outpatient facilities, makes it very difficult to obtain accurate data on complications, although several attempts have been made to estimate the number. Hanke et al[29] published data pertaining to a 7-year period (1982-1989) and reported an average annual incidence of 0.09% for necrosis and abscess after collagen treatments. In 2002, based on a review of manufacturer-supplied data, Friedman et al[24] examined the safety profile of HA injections performed outside the United States. The overall incidence of AE was reportedly 0.15% in 1999 and 0.06% in 2000. Narins et al[32] used information from spontaneous drug AE reporting (SAER) systems to identify the more severe HA-related complications and reviewed the published cases in the United States in 2004. They estimated the incidence to be less than 0.001%.[32] Current statistics on fillers and associated complications can be gathered readily from company-based data as well as national societies.

Considering the widespread use of fillers by many specialties, the large variety of brands worldwide, and unreliable methods of data collection, determining an accurate incidence of complications is a challenging task. When combining procedural data from ASAPS and ASDS statistics from 2010 to 2011, the number of filler treatments performed by plastic surgeons and dermatologists totaled approximately 4 658 982 for the 2-year period.[1,2] In the same timeframe, the number of cases of severe complications in the United States reported by the same specialties was only 5,[18,20,31] yielding an estimated incidence of 0.0001 %. Until a database is established by our professional societies, which allows for prospective data entry, the true incidence of complications will remain unknown.

Treatment of Mild, Moderate, and Self-Limited Complications

A review of the Manufacturer and User Facility Device Experience (MAUDE) database from 2003 to 2008 demonstrated that the most common AE associated with fillers were swelling, erythema, and inflammatory reactions such as granulomas and nodules.[52] Other mild to moderate complications included hypersensitivity, infection, bruising, Tyndall effect, pain, blisters, beading of filler under skin, numbness, and migration.

Swelling and ecchymosis may develop at the time of injection and usually resolve spontaneously.[32,53-55] Erythema also is commonly transient but, on occasion, permanent telangiectasias may occur at the injection site. If this happens, treatment with intense pulsed light therapy or pulsed dye laser can be initiated.[56,57] Nodules and erythema that persist beyond the first few days of treatment may be signs of inflammation.[53,57,58] In these cases, massage and administration of hyaluronidase for HA products have proven helpful.[58] After infection is ruled out, intralesional or topical corticosteroids also may be used.[53,57]

Lumps or beading usually appear shortly after treatment in the form of well-confined palpable lesions, which can result from injection in areas of thin soft-tissue coverage (eg, eyelids, nasojugal region, lips), injection of too much material, clumping of filler, or dislocation by movement of muscles.[56,57,59,60] Common sites for irregularities and lumps include the lips and the perioral area. The lips are an area of high mobility and thin mucosa. Once irregularities in the mucosa of the lips occur, they are difficult to correct if semipermanent fillers have been injected. Therefore, the use of semipermanent fillers in this area is discouraged[61,62] (Figure 3). The tear trough and periorbital regions also are considered high risk and are prone to display irregularities if injected superficially.[54,63,64] Measures to avoid visibility of the implanted material include firm massage and meticulous placement of filler in the deep supraperiosteal plane.[58,65] Relatively short-term fillers such as HA products are preferable for these high-risk regions. An additional benefit of using HA in these areas is that irregularities can be reversed with hyaluronidase (15-300 U). Semipermanent fillers such as CaHa and PLLA have the advantage of being longer lasting than HA; however, with this benefit comes a disadvantage. If overcorrection occurs, irregularity and nodule formation can develop; these problems are more persistent and difficult to treat. To prevent technique-related complications, injection should be in the subdermal plane, bolus injection should be avoided, and injection sites should be massaged after injection.[66,67] Treatments for semipermanent fillers include direct excision of the filler, needle disruption and unroofing of lumps, and waiting for the product to absorb.[66-70] Lumps caused by PLLA or PMMA respond well to intralesional steroid injections, but steroids are less effective for CaHa.[56]

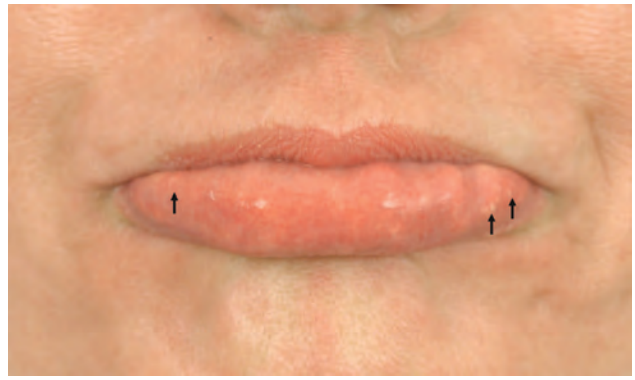

Figure 3. This 47-year-old woman, who had been injected with calcium hydroxylapatite at another clinic, presented 4 months later with white nodules along the lower lip. The granules were palpable and visible (arrows) just under the mucosa of the lower lip. The patient refused surgical excision.

True granulomas appear late, after weeks or months, and respond well to intralesional steroids[55-57,60,65] or incision and drainage. The reported rate of granuloma is 0.01 % to 1 %.[48,56] Recently, there has been discussion on the role of biofilms in causing delayed nodule formation.[32,55,71-75] Biofilms are accumulations of microorganisms within a self-developed matrix, which are irreversibly adherent to one another and to a variety of surfaces.[75,76] All fillers, especially longer-lasting products, are potential surfaces for biofilm formation. Because their growth rate is slow, biofilms usually are not identifiable by culture. They may present as sterile abscesses or cause a chronic inflammatory response.[55,75,77-79] Infections resulting from biofilms are notoriously difficult to treat because of their slow bacterial metabolism and their secretion of a protective matrix.[77] Hyaluronidase has been shown to help break down the matrix, thereby decreasing the biofilm mass.[80] Dayan et al[75] reported successful treatment of resistant inflammatory reactions with hyaluronidase regardless of the filler used. Other treatment options for biofilms are prolonged use of antibiotics, administration of intralesional 5-fluorouracil,

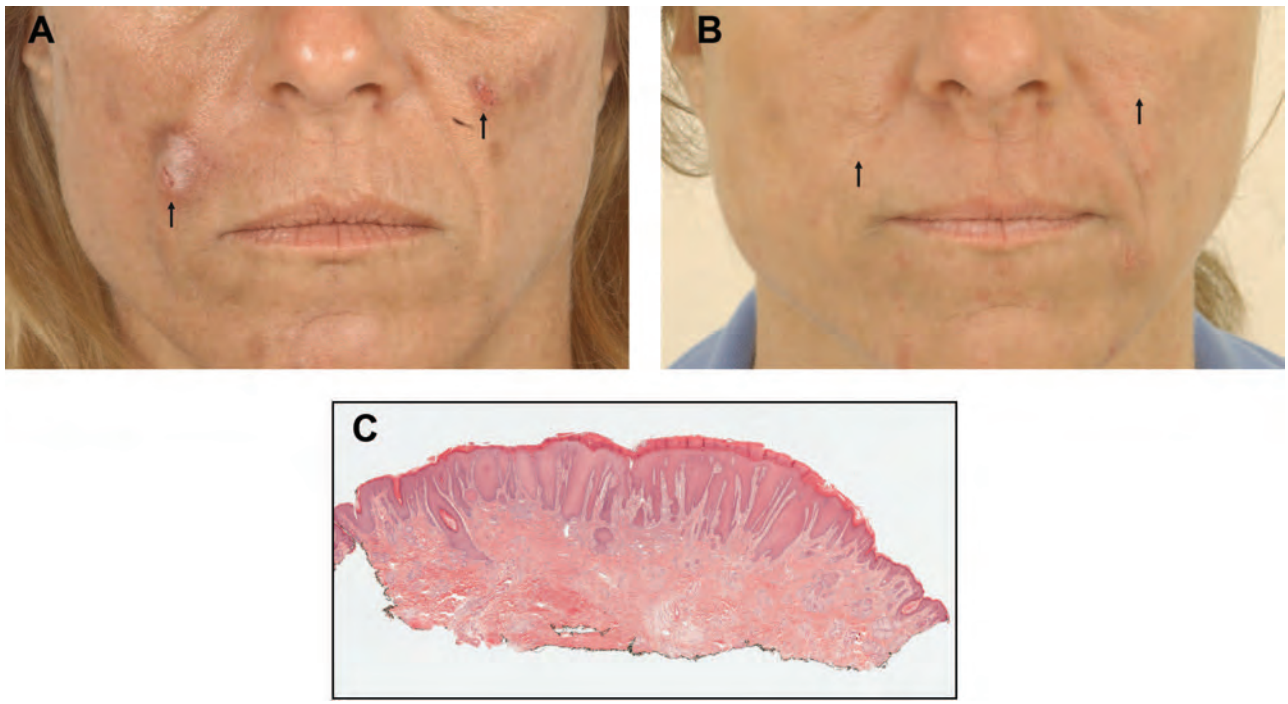

Figure 4. (A) Two weeks after injection of collagen to the nasolabial folds, this 42-year-old woman complained of nodules and ulceration, which persisted for another 2 weeks. She had multiple erythematous and partially ulcerated lesions (arrows) on other areas of the face, which suggested factitious disorder. She was treated with oral antibiotics and steroids. (B) Ten months after excision of the ulcerated lesion and granuloma on the right nasolabial fold (left arrow). The rest of the lesions healed by secondary intention (right arrow). (C) Pathologic findings of the excised area were consistent with prurigo nodularis (Picker nodule).

and intralesional laser therapy with a 532-nm or 808-nm laser.[77,81-83] With respect to antimicrobials, 2-drug therapy with a quinolone and third-generation macrolide has been recommended.[55,77] To prevent biofilm formation or other soft-tissue infections, care should be taken to avoid any contamination during implantation. A sterile technique should be used when reconstituting or diluting the product, the injection site should be prepared with topical antiseptics, injection to infected areas should be avoided, and makeup and other potential contaminants on the skin should be removed before injection.[67,74,84] Moreover, the following should be avoided: injection of high-volume bolus material, breaching of mucosa, and injection through previous filler.[75,76] However, it is important to note that cases of recurrent, unexplained infections can be the result of other pathology. Factitious ulceration also should be considered in this setting (Figure 4).

Hypersensitivity to fillers may trigger angioedema or anaphylactic reactions.[56,63,74,85] Delayed hypersensitivity reactions are usually self-limited systemic events that resolve without any sequelae but, depending on the presentation, oral steroid treatment may be required. Although collagen itself is no longer available, other collagen-containing products (such as PMMA in collagen suspension) require skin testing prior to administration.

Mild to moderate complications are usually self-limited. Consensus treatments for complications that fail to resolve within several weeks include hyaluronidase injection, intralesional steroids, and light-based therapies. Systemic steroids, systemic antibiotics, and/or surgical excision may be required depending on the extent of the problem. An algorithm for the treatment of mild to moderate complications is presented in Figure 5.

Treatment and Prevention of Severe Complications

Vascular-related events are the complications most likely to result in permanent sequelae. They can occur from intravascular embolism of injected material, direct needle injury to vessels, or external compression of vessels by surrounding filler[†] (Figure 6). Inadvertent injections of the angular, dorsal nasal, or supratrochlear artery are most likely to lead to an ischemic response that results in necrosis.[31,54,65]

Appropriate treatment should be started immediately upon suspicion of vascular compromise. Injection should

[†]References 10, 16, 18, 26, 27, 31, 53, 56.

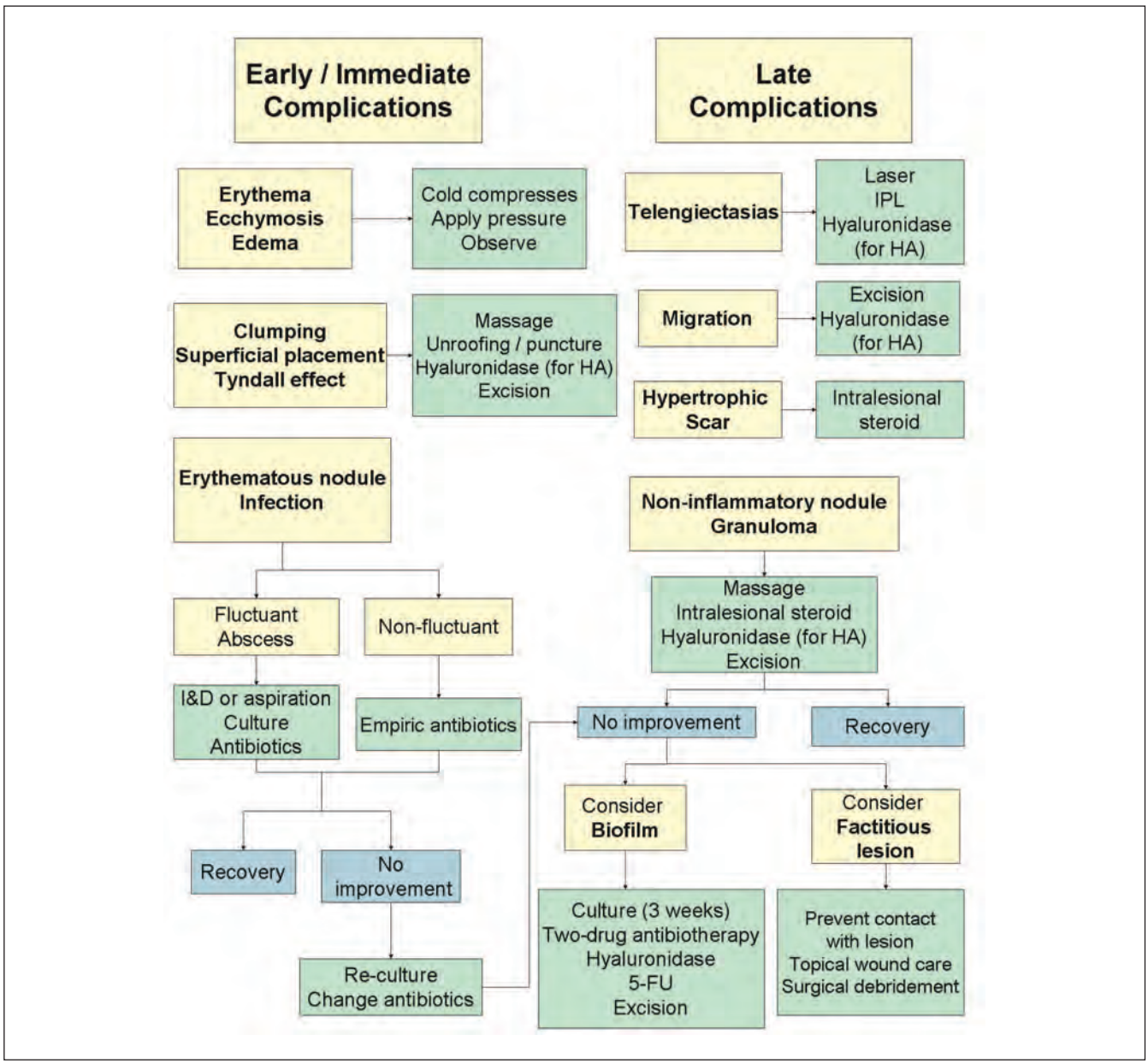

Figure 5. Algorithm for treatment of mild to moderate complications following filler injections. 5-FU, 5-fluorouracil; HA, hyaluronic acid; IPL, intense pulsed light; I&D, incision and drainage.

be stopped, and the area should be massaged and warm compresses applied to increase vasodilatation.[53,58] Utilization of nitroglycerine paste and hyaluronidase also is advocated for early presenting cases. Other treatments include systemic or topical steroids to reduce associated inflammation, thereby mitigating the degree of injury.[20,32,53,65] Although aspirin and IV prostaglandins have been suggested, their efficacy has not been proven.[11,16,21,22] Other options with unproven efficacy are filler removal via puncture and low-molecular-weight heparin.[11,20,27] Of course, patients with any vascular complication should remain under extremely close care. The treatment measures are aimed at dissolving the product, facilitating blood flow, and promoting vasodilation. Dayan et al[20] have suggested the use of hyaluronidase in all cases of vascular compromise, independent of the filler type, due to its edema-reducing benefits and theoretical advantage in reducing occluding vessel pressure.

Although we were not able to correlate the time of therapy initiation with outcomes due to the insufficient data of case reports, it is well known that prompt intervention is crucial. In an experimental study, Kim et al[10] found that the use of hyaluronidase within 4 hours of injection proved to be a successful salvage procedure for HA fillers.

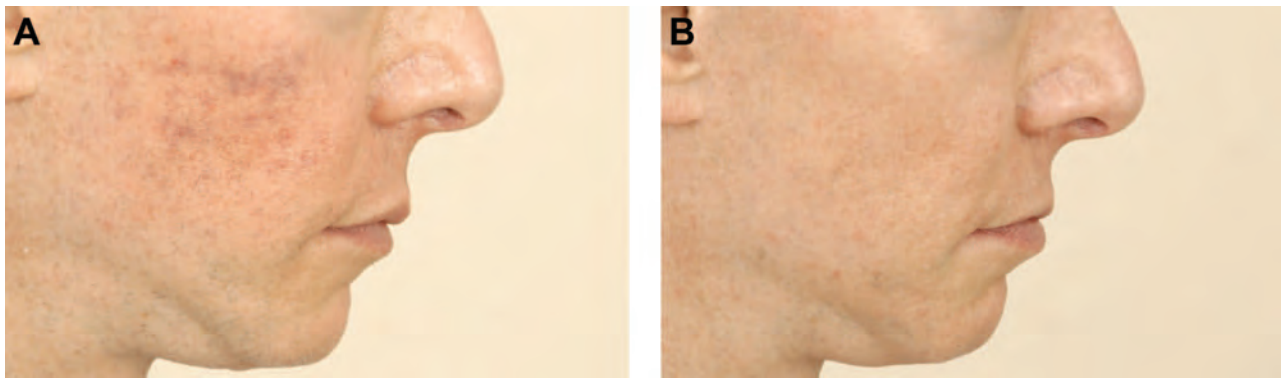

Figure 6. (A) This 62-year-old man had inadvertent intravascular injection of poly-L-lactic acid during treatment of the cheeks. Warm compresses were applied immediately. (B) Three months after injection. The patient recovered without any sequelae.

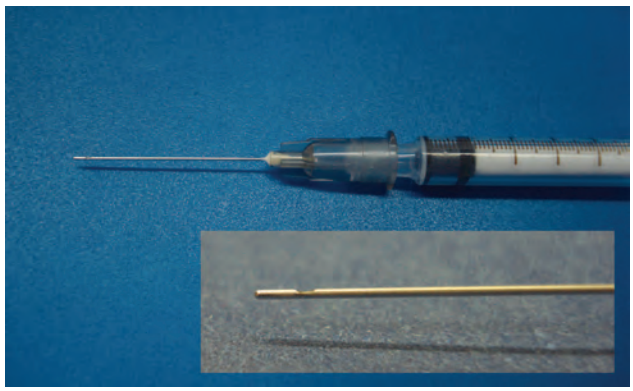

Figure 7. The use of a blunt-tip cannula during filler injection reduces the risk of intravascular penetration.

Once necrosis has occurred, debridement and wound care are required to minimize scarring. Typically, an eschar develops, which heals over several weeks by granulation and reepithelialization. The means of surgical reconstruction are site specific.

Vascular complications are best avoided with appropriate training and injection techniques. The most important controllable factor for practitioners is the speed of injection. Filler should be injected slowly and the needle withdrawn using the least amount of pressure.[86] Other precautions include aspiration before injection, delivery of material at different points, and injection of small volumes per pass.[58,67,74,86,87] The use of small-caliber needles has been advocated by some since they slow the speed of injection.[58,86] The use of blunt needles in high-risk regions such as the glabella, nose, and NLF is another means of reducing injury to vessels[88-90] (Figure 7). The injection technique differs with blunt tips: there is less movement and less subcision and consequently less trauma.[90] However, these cannulae are prone to bend with multiple passes, and some planes may be difficult to breach with the blunt tip, resulting in excess accumulation of the product. Use of an epinephrine-containing product has inherent risks and benefits. Although it may mask a complication because of its blanching effect, it also may decrease the chance of bruising by constricting the blood vessels.[26,31]

Consensus treatment of suspected intravascular injection includes immediate cessation of the injection, massage, warm compresses, topical nitroglycerine paste, and hyaluronidase (regardless of filler type). Other suggestions (but without proven efficacy) include removal of filler via puncture, systemic or topical steroids, aspirin, low-molecular-weight heparin, and IV prostaglandins. An algorithm for the treatment of suspected intravascular injection is presented in Figure 8.

The underlying mechanism for visual impairment after facial injection is related to retrograde embolization from peripheral vessels into the ophthalmic arterial system.[5,37-42,86,91] Intra-arterially injected material is displaced via a high injection pressure past the origin of the retinal artery, and when the plunger is released, it is propelled into this system. Even a very small amount of material can cause embolization of the retinal artery because it is an end artery with no physiologic anastomoses.[86,92] The retina is also very sensitive to ischemia.[86,92] Factors contributing to this phenomenon are high injection pressures, the distance between injection site and retinal circulation, and the amount of injected material.[37,86]

If symptoms of visual impairment occur, the goal is to reduce intraocular pressure and dislodge the embolus to improve perfusion of the retina and optic nerve. There is no single reliable treatment for iatrogenic retinal artery embolism.[86] Recommended measures include immediate ophthalmologic consultation, ocular massage, timolol eye drops, diuretics, hemodilution (with hydroxyethyl starch), corticosteroids, calcium channel blockers, anticoagulation, and needle decompression of the anterior chamber.[42,86,93] Other modalities that have been used after fat embolism to the retinal artery include carbon dioxide and oxygen therapy,[94] thrombolysis with urokinase,[95] and vasodilation.[96] However, attempts to reverse retinal artery occlusion are often unsuccessful. It is unclear whether the recovery is due to timely initiation of therapy, transient embolism, or favorable location of infarct in the retina. Unfortunately, in cases of vision loss, the outcome is grave regardless of the treatment rendered.

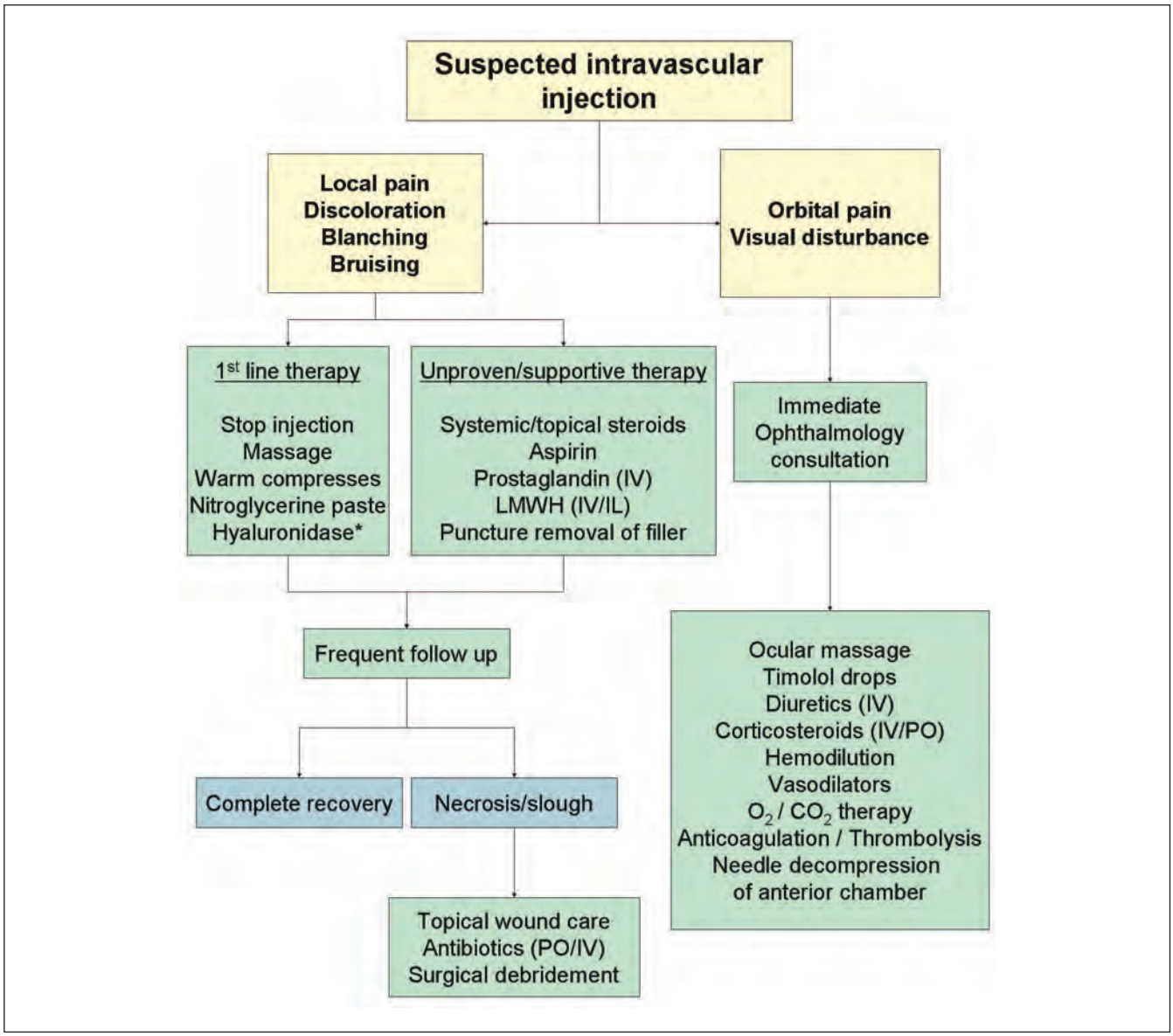

Figure 8. Algorithm for treatment of severe complications following filler injections. *Hyaluronidase is recommended independent of filler type. IL, intralesional; IV, intravenous; LMWH, low-molecular-weight heparin; PO, per oral.

CONCLUSIONS

The soft-tissue fillers approved for use in the United States have an excellent safety profile, which is reflected by their increasing use. Although serious complications are rare, they can occur. Whenever fillers are placed, the products needed to treat complications should be readily available. These should include, but not be limited to, hyaluronidase, nitroglycerine paste, and warm compresses. Physicians also should be aware of the high-risk regions of the midface, as identified in the present review. Injections to the nose, NLF, and glabella require additional caution. Familiarity with the prevention, presentation, and immediate treatment of these rare events is essential for attaining the best possible outcome.

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