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ORIGINAL ARTICLE
Cosmetic

Soft-tissue Filler–associated Blindness: A Systematic Review of Case Reports and Case Series

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Background: With the increase in the use of soft-tissue fillers worldwide, there has been a rise in the serious adverse events such as vascular compromise and blindness. This article aims to review the role of fillers in causing blindness and the association between hyaluronic acid (HA) filler and blindness.
Methods: The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to report this review.
Results: A total of 190 cases of blindness due to soft-tissue fillers were identified, of which 90 (47%) cases were attributed to autologous fat alone, and 53 (28%) cases were caused by HA. The rest of the cases were attributed to collagen, calcium hydroxylapatite, and other fillers.
Conclusions: Autologous fat was the most common filler associated with blindness despite HA fillers being the most commonly used across the globe. However, the blindness caused by other soft-tissue fillers like collagen and calcium hydroxylapatite was represented. It was also evident through the review that the treatment of HA-related blindness was likely to have better outcomes compared with other fillers due to hyaluronidase use. *(Plast Reconstr Surg Glob Open 2019;7:e2173; doi: 10.1097/GOX.0000000000002173; Published online 2 April 2019.)*

INTRODUCTION

"Beauty" is a universal phenomenon that transcends geographical boundaries and cultures. Its occurrence or attainment influences self-confidence, improves psychological standing, and elevates personal and professional capabilities.[1] Minimally invasive cosmetic procedures have increased relative to other aspects of cosmetic surgery due to its advantages of achieving a subtle natural appearance, restoring natural contour, reducing morbidity, requiring less downtime posttreatment, and the easy availability of these procedures.[2]

A plethora of soft-tissue fillers for facial aesthetic correction ranging from autologous fat, polymethylmethacrylate, calcium hydroxylapatite, poly-L-Lactic acid, polycaprolactone, and hyaluronic acid (HA) are available. Of these, HA is the most widely used filler (over 2 million) with the longevity of approximately 6–24 months depending on the molecular size, a method of cross-linking, and the region of injection.[3] Fillers have been traditionally associated with mild and transient adverse events such as bruising, swelling, infection, and surface irregularities. However, with the increased use of fillers worldwide, more serious and permanent adverse events such as vascular compromise and blindness are on the rise.[4] Vision loss is a rare adverse event but catastrophic to both patient and the physician.[5]

With the increase in the availability of the soft-tissue fillers, number of aesthetic practitioners, and demand for aesthetic procedures globally, the usage of fillers is expected to rise. It is imperative that aesthetic physicians have a firm knowledge of the vascular anatomy and understand potential complications, critical prevention, and management strategies.[6,7]

The present systematic review has been conducted to elucidate the occurrence of blindness with various soft-tissue fillers, the association between HA filler and blindness, and to review factors influencing the development of blindness. We aim to fill in the gap between the existing practice and knowledge about the adverse effect of blindness in relation to the use of soft-tissue fillers, so that clinicians can make evidence-based decisions.

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Received for publication October 22, 2018; accepted January 8, 2019.

DOI: 10.1097/GOX.0000000000002173

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

METHODS

A systematic review of the published literature was conducted to assess the association of blindness with the soft-tissue filler injections. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to report this review.[8]

Criteria for Considering Studies for the Review

Inclusion Criteria

The relevant articles that met the following criteria were selected.

1. Original articles and expert's opinions published between January 2000 and September 2018 that investigated or discussed the role of soft-tissue fillers (or HA fillers, autologous fat, calcium hydroxylapatite or collagen, and others) in causing blindness.
2. Articles published in English Language only.

Exclusion Criteria

We excluded the following articles:

1. in which patients underwent surgical correction,
2. where injections of nonfiller materials (corticosteroids) were given,
3. where vascular complications other than blindness were discussed, and
4. posters/abstracts and studies on animal models.

Literature Search

The goal was to analyze all the published literature comprising original research, clinical trials, case reports, retrospective and prospective case studies, systematic reviews and meta-analysis. A search of the computerized bibliographic database: Medline, Cochrane, PubMed, Google, and Google Scholar were performed. The MeSH terms used in the search were: tissues; blindness; injections; face; cosmetics; HA, including additional search terms like blindness; soft; filler; fat; hyaluronic; and autologous fat. The favorite key phrases used for search included cosmetic injections; facial aesthetics; soft-tissue fillers; hyaluronic acid; soft-tissue fillers; injectables; blindness; vision loss; acquired blindness; autologous fat; collagen; and calcium hydroxylapatite. In a backward chronological search, the bibliographies of all relevant articles were checked for citations that could not be identified in our primary search. The primary search strategy is outlined in Table 1.

Screening

Titles and abstracts from the electronic search were screened, and full-text manuscripts meeting the selection criteria were obtained. Crucial information from all the articles such as study design, number of cases, adverse effects, the filler used, mechanism, treatment, or any other pertinent data was extracted. Two investigators (V.C. and P.S.B.) independently extracted data from eligible studies, and any differences were resolved through discussion and consensus between the authors. When a consensus was not reached, arbitration was done by the third author (E.R.).

Table 1. Main Search Strategy for PubMed

Search Items
Primary
"blindness"[MeSH Terms] OR "blindness"[All Fields]
"tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields]
"cosmetics"[Pharmacological Action] OR "cosmetics"[MeSH Terms] OR "cosmetics"[All Fields] OR "cosmetic"[All Fields]
"face"[MeSH Terms] OR "face"[All Fields] OR "facial"[All Fields]
"injections"[MeSH Terms] OR "injections"[All Fields]
"durapatite"[MeSH Terms] OR "durapatite"[All Fields] OR "hydroxylapatite"[All Fields]
Extended
{("blindness"[MeSH Terms] OR "blindness"[All Fields]) AND SOFT [All Fields] AND ("tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields]) AND FILLERS [All Fields]) AND AUTOLOGOUS [All Fields] AND FAT [All Fields]}
{("blindness"[MeSH Terms] OR "blindness"[All Fields]) AND ("cosmetics"[Pharmacological Action] OR "cosmetics"[MeSH Terms] OR "cosmetics"[All Fields] OR "cosmetic"[All Fields]) AND ("face"[MeSH Terms] OR "face"[All Fields] OR "facial"[All Fields]) AND FILLER [All Fields] AND ("injections"[MeSH Terms] OR "injections"[All Fields])}
{("blindness"[MeSH Terms] OR "blindness"[All Fields]) AND ("durapatite"[MeSH Terms] OR "durapatite"[All Fields] OR "hydroxylapatite"[All Fields]) AND ("injections"[MeSH Terms] OR "injections"[All Fields] OR "injection"[All Fields])}
Boolean: 1 AND 2
Date limit: ("2000/01/01"[PDAT]: "2018/09/15"[PDAT])

The selected articles were then qualitatively and quantitatively analyzed by the investigators. The process of screening, selection, and the inclusion of eligible articles and reasons for exclusion were displayed in Figure 1.

Data Items, Extraction, and Synthesis

The data were retrieved by reading the entire article. Papers were reported in a table with the following fields: record number, the name of the author(s), publication year, article title, and journal. Relevant data from eligible full texts were extracted by 2 authors (V.C. and P.S.B.) using prestructured data abstraction sheets. Two data abstraction sheets were predesigned to extract available data on the author, year of case reporting with a number of cases, geographic region, type of soft-tissue filler used, the anatomical area of injection, and any ocular complication and recovery. The disagreements were resolved as detailed above.

Assessment of Methodological Quality

A validated tool for the determination of the methodological quality of the case reports and case series proposed by Murad et al[9] based on the previous criteria from Pierson, Bradford Hills, and Newcastle-Ottawa scale modifications was used. Each case study or series was evaluated under 4 domains (selection, ascertainment, causality, and reporting) that are summarized in Table 1. This resulted in 8 leading exploratory questions with a binary response (yes/no), whether the item was suggestive of bias or not. No disagreements were found between the reviewers.

Data Synthesis and Analysis

Due to the small number and evident heterogeneity among the included studies reporting on a wide variety of risk factors associated with ocular complication, the

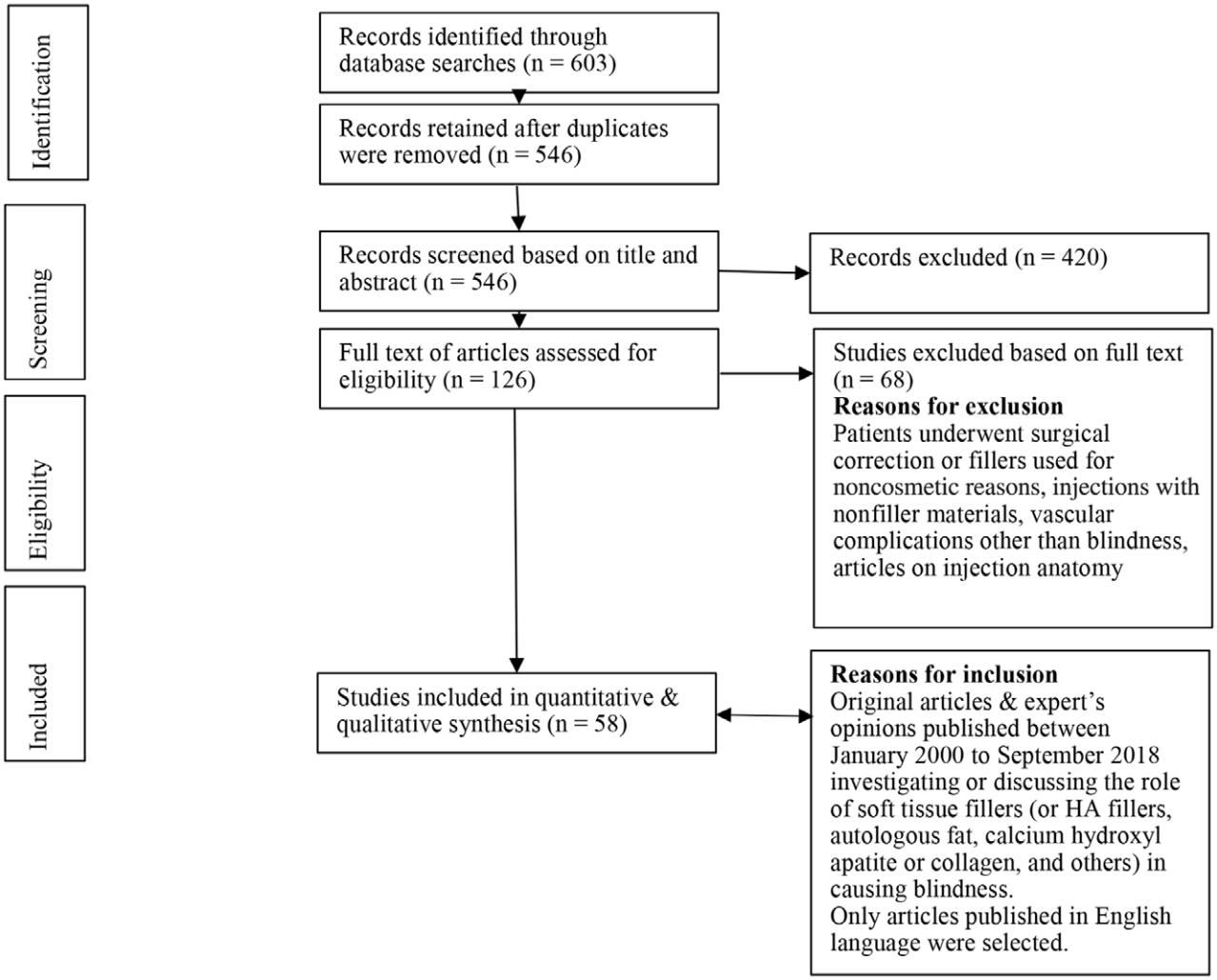

Fig. 1. Flow diagram for study screening, selection, and inclusion.

findings herein were presented using tables and narrative summaries.

RESULTS

A total of 190 cases of filler-induced blindness were identified in the present study. The maximum cases of filler-induced blindness or other ocular disturbances were attributed to autologous fat injections (90 cases; 47%). The second most prominent cause of filler-induced blindness was due to HA (53 cases; 28%), whereas rest of the cases were attributed to collagen, calcium hydroxylapatite, and other fillers. However, it is interesting to note that 11 HA-related blindness cases had significant improvement in visual acuity and 6 cases of complete vision restoration when treated with hyaluronidase. The visual outcome was not good in any other filler-induced blindness. It is also notable that 8 cases of calcium hydroxylapatite (CaHA)–induced blindness were reported between 2014 and 2018. Figures 2 and 3 depict the number of blindness cases caused by various soft-tissue fillers and the percentage of reported blindness according to the injection site.

Characteristics of the studies included in the review (Table 3) and a summary of different cases of blindness between the January 2000 and September 2018 based on the type of filler used, ensuing adverse event, management, and its outcome is presented in Table 4.

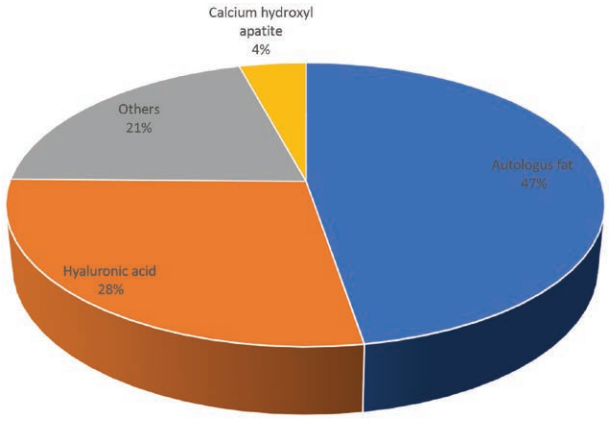

Fig. 2. Number of blindness cases due to various soft-tissue fillers.

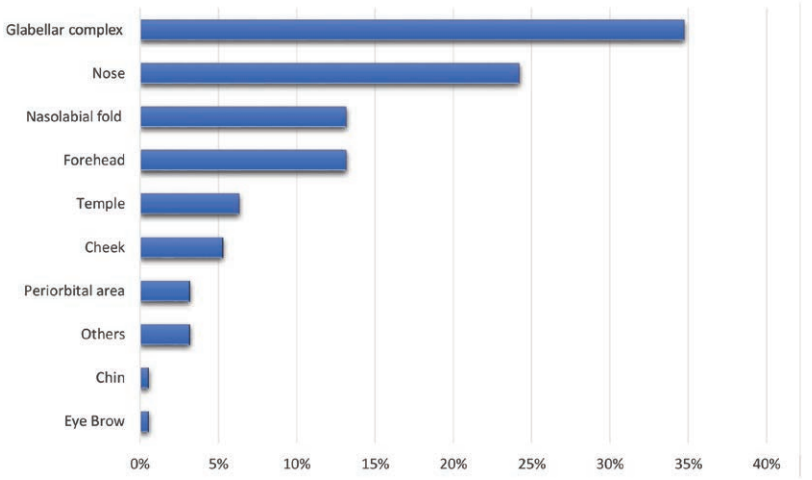

Fig. 3. Percentage of reported filler-associated blindness according to the injection site.

DISCUSSION

Blindness Associated with Soft-tissue Fillers

Vascular occlusion is a rare but severe and dreaded complication of soft-tissue fillers. It occurs because of inadvertent injection of the filler material in a blood vessel. This intravascular injection of fillers may lead to complications such as tissue ischemia and loss, blindness, pulmonary embolization,[46] and even stroke.[47] In a recent study published by Povolotskiy et al[48] investigating the adverse events arising with various aesthetic fillers, vascular complications were cited to be among some of the commonly occurring complications. This study comprised 5,024 cases, out of which vascular complications were observed in 590 cases. Even though blindness caused by soft-tissue fillers is an infrequent event, it is a matter of great concern owing to its distressing consequences.[49] The causative agents that may lead to blindness include autologous fat, HA, collagen, poly-L-Lactic acid, calcium hydroxylapatite, and even corticosteroid suspensions.[50] Vision loss manifests as an immediate complication of facial filler injection with other associated signs and symptoms depending on the location of vascular occlusion.[51]

Rzany and DeLorenzi[52] reported in a small retrospective study that vascular occlusions, such as of ophthalmic and/or retinal artery resulting in blindness, are apparently more common and more severe in non-HA fillers. A review by Beleznay et al[2] demonstrated that the incidence of vascular occlusion following an injection of a filler is estimated to be approximately 3–1,000 in case of calcium hydroxylapatite, whereas 3–9 per 10,000 for HA preparations. It was also suggested that vascular complications and sequelae were more severe with non-HA fillers such as calcium hydroxylapatite and polymethylmethacrylate.[52]

Beleznay et al[2] showed that almost 47.9% of cases of blindness were caused by autologous fat, whereas HA fillers were responsible for 23.5% of the cases which are consistent with the present finding. Autologous fat, the most viscous soft-tissue filler had the highest risk of diffuse occlusion in the ophthalmic artery and was also associated with poor prognosis.[50]

In a retrospective study conducted between January 1, 2008 and August 31, 2014, Kim et al[53] also observed that the prevalence of diffuse occlusion of ophthalmic artery and its branches is less in HA-injected patients compared with autologous fat–injected group. This could be attributed to the difference in the particle sizes of the 2 fillers. Autologous fat has a variable particle size, whereas HA particles are approximately 400 μm in size. Hyaluronic acid fillers are more likely to block the central retinal artery (approximately 160 μm in size) or its smaller branches and fat more likely the ophthalmic artery (2 mm in diameter) due to the particle size and the amount of filler injected per injection site.[53] Chen et al[22] while studying fundus artery occlusion also found that the prognosis was found to be much worser in autologous fat than in HA.

Previous studies have also reported that injections with autologous fat are associated with a higher diffuse occlusion rate, resulting in a much worse visual prognosis and more frequent cerebral infarctions compared with HA.[24,53]

The Mechanism for HA-induced Blindness versus Blindness Induced by Other Fillers

Currently, it is thought that an accidental injection of fillers into the blood vessel can lead to the formation of tissue filler emboli. Various authors have suggested that the mechanism of this is most likely through initially retrograde flow against the prevailing blood pressure to a point at or past the retinal branches. Consequent release of the syringe pressure allows the usual blood pressure to reestablish the antegrade blood flow carrying forward these emboli allowing them to enter the ophthalmic artery circulation. This embolus is responsible for retinal ischemic necrosis. The ophthalmic artery branches with cutaneous innervation (supplying the glabella, nose periorbital zone, and forehead) probably carry the greatest risk, but anasto-

Table 2. Qualitative Assessment of the Included Studies

	Domains for Evaluating the Methodological Quality of Case Reports and Case Series*							
	Selection	Ascertainment		Causality				Reporting
	Leading Explanatory Questions							
References	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8
Danesh-Meyerr et al.[10]	Yes	Yes	Yes	Yes	No	No	Yes	No
Silva and Curi[11]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Mori et al.[12]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Park et al.[13]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Sung et al.[14]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Lee et al.[15]	Yes	Yes	Yes	Yes	No	No	Yes	No
Park and Kim[16]	Yes	Yes	Yes	Yes	No	No	Yes	No
Lee et al.[17]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Lazerri et al.[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Park et al.[19]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Ozturk et al.[20]	Yes	Yes	Yes	Yes	No	No	Yes	No
Kim et al.[21]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Chen et al.[22]	Yes	Yes	Yes	Yes	No	No	Yes	No
Carle et al.[23]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Park et al.[24]	Yes	Yes	Yes	Yes	No	No	Yes	No
Hong et al.[25]	Yes	Yes	Yes	Yes	No	No	Yes	No
Chang et al.[26]	Yes	Yes	Yes	Yes	No	No	Yes	No
Lee et al.[27]	Yes	Yes	Yes	Yes	No	No	No	No
Kim et al.[28]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hsieh et al.[29]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Chou et al.[30]	Yes	Yes	Yes	Yes	No	No	Yes	No
Zhu et al.[40]	Yes	Yes	Yes	Yes	No	No	No	No
Chen et al.[32]	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Hu et al.[33]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Cohen et al.[34]	Yes	Yes	Yes	Yes	No	No	No	Yes
Goodman and Clague[35]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Dagi et al.[36]	Yes	Yes	Yes	Yes	No	No	No	Yes
Lee et al.[37]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Myung et al.[39]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Szantyr et al.[38]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Marumo et al.[41]	Yes	Yes	Yes	Yes	No	No	No	Yes
Sharudin et al. [42]	Yes	Yes	Yes	Yes	Yes	No	No	No
Thnasarnaksorn et al.[43]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Chesnut[44]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Liu et al.[45]	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Selection: 1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment: 2. Was the exposure adequately ascertained? 3. Was the outcome adequately ascertained?
Causality: 4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/rechallenge phenomenon? 6. Was there a dose–response effect? 7. Was follow-up long enough for outcomes to occur?
Reporting: 8 Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?
*Adopted from Murad et al.[9]

moses between facial artery and branches of the ophthalmic artery have been shown in cadaveric studies.[49]

A cadaveric study published in June 2018 has suggested that retrograde HA filler emboli to the ophthalmic artery may be a result of the cannulation of the supratrochlear artery, primarily due to its superficial location surrounded by rich vasculature and a variable anatomy.[54] Sufan et al[55] published an article in 2017 which showed that in the glabellar region, the deep injection on the periosteum will be at a risk of entering the supratrochlear artery and supraorbital artery, whereas, in nasal dorsum and nasolabial folds, the subsuperficial musculoaponeurotic system layer injection has the possibility to enter the dorsal nasal artery, angular artery, and facial artery.

It has also been suggested that the volume of the filler injected, and the pressure of injection can impact the outcome of blindness by influencing the retrograde flow of the filler into the ophthalmic circulation. The amount of soft-tissue filler injected varies according to the type of filler used, for example, autologous fat is typically injected in larger volumes compared with HA fillers.[56]

Even though both fat and HA fillers may cause vision loss, the occlusion of the ophthalmic circulation vessels would vary due to the particle size and the amount of filler injected per injection site. This could explain why the case series by Park et al. showed that autologous fat was associated with a higher diffuse occlusion with worse visual prognosis and a higher incidence of concomitant cerebral infarction.[13,23]

The speed and pressure of injection have also been proposed to influence the flow of the filler after its inadvertent injection into the vessel. This has a direct impact on the speed and pressure of injection as the viscosity of the filler influences the extrusion force (injection pressure) used by the injector that will then determine the speed and pressure of injection finally affecting the flow of the filler within the vessel. A highly viscous filler (like

Table 3. Characteristics of Studies Included

References	Region	Type of Study (No. Cases)	Type of Soft-tissue Filler	Location of Injection
Danesh-Meyerr et al.[10]	United States	Case report (1)	Autologous fat	The left side of the bridge of the nose
Silva and Curi[11]	Brazil	Case report (1)	PMMA	Glabellar region
Mori et al.[12]	Japan	Case report (1)	Autologous fat	Glabellar region and nose
Park et al.[13]	Korea	Case report (1)	Autologous fat	Right nasolabial fold
Sung et al.[14]	Korea	Case report (1)	Calcium hydroxylapatite	Nose
Lee et al.[15]	Korea	Case report (1)	Autologous fat	Forehead
Park and Kim[16]	South Korea	Case report (1)	Autologous fat	Forehead
Lee et al.[17]	Korea	Case report (1)	Autologous fat	Periocular area
Lazerri et al.[18]		Case review (32)	Autologous fat injection (15); nonfat filler injection (corticosteroids, paraffin, silicone oil, bovine collagen, PMMA, HA, calcium hydroxylapatite) (n = 17)	Lower third of the face (n = 3), upper third of the face (n = 7), mid third of the face (n = 3), nonfat fillers: nose (n = 7), scalp (n = 3), and remaining n = 7 involved the forehead, glabella, glabella and cheek, and temple area
Park et al.[19]		Retrospective, noncomparative case series (12)	Autologous fat (n = 7), HA (n = 4), and collagen (n = 1)	Glabellar region (n = 7), nasolabial fold (n = 4), and both (n = 1)
Ozturk et al.[20]	United States, Brazil, Japan, and Korea	Review of case reports (12)	Collagen (n = 3), injectable soft-tissue matrix (n = 1), PMMA (n = 2), HA (2), CaHa (n = 1), PLLA (n = 1), and NR (n = 2)	Glabella, cheek (n = 2), forehead (n = 1), glabella (n = 4), nose dorsum (n = 2), nose septum (n = 1), nose tip (n = 1), and periorbital region (n = 1)
Kim et al.[21]	South Korea	Case report (1)	HA	Nose dorsum
Chen et al.[22]	China	Case review (13)	Autologous fat (n = 7), HA (n = 5), and bone collagen (n = 1)	Frontal area (n = 5), periocular area (n = 2), temple area (n = 2), and nose area and nasal area (n = 4)
Carle et al.[23]	United States	Case reports (3)	HA (n = 1), autologous fat (n = 1), and PMMA microspheres (n = 1)	Forehead
Park et al.[24]	Korea	National survey, case reports (44)	Autologous fat injection (n = 22), HA (n = 13), collagen n = 4), and others (n = 5)	Glabella (n = 26), nasolabial fold (n = 11), and nasal dorsum, rhinoplasty (n = 10)
Hong et al.[25]	Korea	Case report (1)	Autologous fat	Glabella
Chang et al.[26]	Taiwan	Case report (1)	Calcium hydroxylapatite	Nose
Lee et al.[27]	Korea	Case report (1)	HA	Glabella
Kim et al.[28]	Korea	Case report (1)	HA	The anterior chamber of the eye
Hsieh et al.[29]	Taiwan	Case reports (2)	Calcium hydroxylapatite	Glabellar area (n = 1) and nose (n = 1)
Chou et al.[30]	Taiwan	Case report (1)	Calcium hydroxylapatite	Nose
Qi et al.[31]	China	Retrospective noncomparative case series (27)	Autologous fat	Glabellar area (n = 3), nasolabial area (n = 5), forehead area (n = 4), periocular area (n = 2), nose area and nasal area (n = 2), multiple places (n = 2), and other areas (n = 3)
Chen et al.[32]	China	Case report (1)	HA	Nasal dorsum
Hu et al.[33]	China	Case report (1)	HA	Forehead
Cohen et al.[34]	Israel	Case report (1)	Calcium hydroxylapatite	Nose bridge
Goodman and Clague[35]	Australia	Case report (1)	HA	Temple and brow
Dagi et al.[36]	United States	Case report (1)	Calcium hydroxylapatite	Both temples, both cheeks, forehead, and the chin
Lee et al.[37]	Korea	Case report (1)	HA	
Szantyr et al.[38]	Poland	Case report (1)	Autologous fat	Left supraorbital and right forehead area
Myung et al.[39]	Korea	Retrospective case review (9)	HA	Glabella (n = 5), nasolabial fold (n = 3), nasal dorsum (n = 3), and glabella and nasal dorsum (n = 2)
Zhu et al.[40]	China	Case series (4)	HA	Nose (n = 3) and forehead (n = 1)
Marumo et al.[41]	Japan	Case report (1)	Calcium hydroxylapatite	Glabella
Sharudin et al.[42]	China	Case report (1)	HA	Nose dorsum
Thnasarnaksorn et al.[43]	Thailand	Case series (6)	HA	Nose (n = 4), forehead (n = 1), and temple (n = 1)
Chesnut[44]	United States	Case reports (1)	HA	Right-sided midface
Liu et al.[45]	China	Case reports (3)	Autologous fat	Forehead

fat) will require a higher extrusion force compared with a filler that is less viscous.

Another factor influencing the extrusion force is the size of the syringe and gauge of the needle/cannula which is determined by choice of the soft-tissue filler used. Typically, autologous fat is injected using large gauge needles and an increased force used to inject it would be easier to produce[57] increasing the likelihood of a large bolus if intravascular penetration occurs.

Interestingly, the propensity of soft-tissue fillers in activating clotting mechanism also influences their effect. The noninflammatory fillers may purely cause a mechanical obstruction when placed within the blood vessel. However, others can activate an intravascular inflammatory

Table 4. Brief Description of the Ocular Adverse Event, Management, and Outcome Associated with Soft-Tissue Fillers

References	Filler Used	Ocular Adverse Event	Management	Outcome
Danesh-Meyerr et al.[10]	Autologous fat	Ocular pain with vision loss, aphasic with right-sided hemiparesis, no light perception in left eye, and the left pupil amaurotic	Not reported (NR)	The left eye remained blind
Silva and Curi[11]	Polymethylmethacrylate (PMMA)	Severe right ocular pain and visual loss after the injection	NR	She remains blind with total right ophthalmoplegia 10 mo after the procedure
Mori et al.[12]	Autologous fat	Pain, visual loss in the right eye, widespread retinal whitening	Drip infusion of urokinase and hyperbaric oxygen therapy; corticosteroids were also given at a later stage	No vision with complete obstruction of the tight ophthalmic artery
Park et al.[13]	Autologous fat	Sudden visual loss of her right eye	High-dose steroid therapy—methylprednisolone	No improvement in visual acuity
Sung et al.[14]	Calcium hydroxylapatite	Blepharoptosis and orbital pain on the right side, associated with progressive visual disturbance of the right eye	The material was attempted to remove by aspiration, topical antibiotics, and steroids	After 3 mo, visual acuity, all intraocular inflammation, oculomotor nerve palsy resolved completely except for a dilated pupil
Lee et al.[15]	Autologous fat	Ipsilateral ophthalmic artery occlusion with infarction of the optic nerve and retina	NR	Blindness in the left eye
Park and Kim[16]	Autologous fat	Sudden, severe periocular pain, complete vision loss in left eye	NR	Vision not improved at the 2-mo follow-up
Lee et al.[17]	Autologous fat	Loss of vision in the left eye, ophthalmic artery obstruction, and left middle cerebral artery infarction	Ocular massage, intravenous mannitolization, and oxygen and carbon dioxide therapy	At 2 mo after the injection, the patient had no perception of light in the left eye, and the left fundus showed optic atrophy, multiple retinal hemorrhages and a fibrous change on its posterior pole
Lazerri et al.[18]	Autologous fat injection (15); nonfat filler injection (corticosteroids, paraffin, silicone oil, bovine collagen, PMMA, HA, calcium hydroxylapatite) (n = 17)	Complaint of excruciating pain and a sudden blackout of the involved eye. Nonfat filler injection: blindness following the injection	Fat filler: no information about the treatment (n = 9), ocular massage, carbon dioxide rebreathing, hyperbaric oxygen therapy, oral and intravenous corticosteroids, antiplatelet drugs, fibrinolytic agents or mechanical thrombolysis (n = 6); nonfiller injection: systemic corticosteroids (n = 2), diuretic agents carbonic anhydrase inhibitors (n = 3), antiaggregant drugs antiplatelet agents, aspirin (n = 1 each), ocular massage (n = 3), surgical treatment-anterior chamber paracentesis (n = 1)	Fat filler injection: Neither the treated nor the untreated patients had any return of vision. Nonfiller injection: Only 3 patients recovered their site (1 patient recovered sight 5 min after injection of corticosteroids for alopecia areata; in another case, vision recovered completely and the visual field defect improved after prompt administration of acetazolamide; a healthy 25-y-old man had complete recovery of visual acuity, oculomotor nerve palsy, and skin necrosis after treatment with oral and topical corticosteroid tapers, although his dilated pupil did not improve), permanent visual loss without light perception persisted in all the remaining patients regardless of the type of the treatment
Park et al.[19]	Autologous fat (n = 7), HA (n = 4), and collagen (n = 1)	Ophthalmic artery occlusion (n = 7), central retinal artery occlusion (n = 2), and branch retinal occlusion (n = 3)	Intra-arterial thrombolysis (n = 4), ACP (n = 3), Massage + Anterior chamber paracentesis (ACP) (n = 1), and Massage + Mannitol (n = 1)	All patients with ophthalmic artery occlusion had ocular pain and no improvement in best-corrected visual acuity
Ozturk et al.[20]	Collagen (n = 3), injectable soft-tissue matrix (n = 1), PMMA (n = 2), HA (2), CaHa (n = 1), poly-L-lactic acid (PLLA) (n = 1), and NR (n = 2)	10 min: pain in the left eye, blurred vision (n = 1); immediate: severe pain and visual loss in the right eye (n = 1); 15 min: pain and visual loss in the right eye (n = 1); 1 min: partial loss of vision in inferior right visual field (n = 1); Immediate visual loss, necrosis of glabellar region (n = 1); Immediate: visual loss in the left eye (n = 4); Immediate: pain in the right eye, ptosis, ophthalmoplegia (n = 1)	Acetazolamide and methylprednisolone (n = 1); Antiplatelet agent and calcium channel blocker (n = 1); intravenous antibiotics, topical steroids, oral corticosteroids (n = 1); IV methylprednisolone, aspirin 100 mg orally (n = 1); Immediate acetazolamide (n = 1) NR (n = 7)	Vision loss with light perception (n = 1); Blindness and total ophthalmoplegia (n = 1); Blindness (n = 2); Complete recovery (n = 1); Partial recovery with 20/200 visual acuity (n = 1); Complete recovery with fixed dilated pupil (n = 1); blindness, recovery from ophthalmoplegia (n = 2); NR (n = 3)

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Table 4. (*Continued*)

References	Filler Used	Ocular Adverse Event	Management	Outcome
Kim et al.[21]	HA	Ptosis, ophthalmoplegia, and vision loss	High doses intravenous corticosteroids	At 6-mo follow-up, visual acuity and ophthalmoplegia in the right eye had not improved
Chen et al.[22]	Autologous fat (n = 7), HA (n = 5), and bone collagen (n = 1)	Ophthalmic artery occlusion (n = 11), central retinal artery occlusion (n = 1), and anterior ischemic optic neuropathy (n = 1)	Treatment for fundus artery occlusion included nitro-glycerin, digital massage, eye drops to lower intraocular pressure, aspirin, ad prednisone. Laser treatment was panned retinal photocoagulation for the patients 1 wk later if the patients were not convenient for close observation there were widespread vascular nonperfusion	Injected autologous fat was associated with worse final best corrected visual acuity (BCVA) than HA. The BCVA of 7 patients with autologous fat injection in the frontal area and temple area was no light perception. Most of the patients with ophthalmic artery occlusion (OAO) had ocular pain, headache, ptosis, ophthalmoplegia, and no improvement in final BCVA
Carle et al.[23]	HA (n = 1), autologous fat (n = 1), and PMMA microspheres (n = 1)	Superior field visual loss in the left eye, blockage of inferior branches of the retinal circulation in the left eye (n = 1); immediate severe loss of vision (n = 1); immediate vision loss in the right eye, visual acuity was no light perception in right eye and 20/20 in left eye (n = 1)	Anterior chamber paracentesis, removal of aqueous to rapidly lower intraocular pressure, ocular massage, reactive hyperbaric oxygen therapy (n = 1) NR (n = 2)	Right pupil minimally reactive to light and her visual acuity was a faint light perception in treatment case (n = 1); NR (n = 2)
Park et al.[24]	Autologous fat injection (n = 22), HA (n = 13), collagen (n = 4), and others (n = 5)	Diffuse retinal and choroidal artery occlusions (ophthalmic artery occlusion, generalized posterior ciliary artery occlusion and central retinal artery occlusion) (n = 28); localized occlusions (localized posterior ciliary artery occlusi branch retinal artery occlusion, and posterior ischemic optic neuropathy) (n = 16)	NR	
Hong et al.[25]	Autologous fat	Retinal artery occlusion with multiple cerebral infarctions	Ocular massage, anterior chamber paracentesis, volume expansion	After 5 mo, no light perception, the fundus of the right eye had a thick fibrous membrane on the posterior pole and optic atrophy
Chang et al.[26]	Calcium hydroxylapatite	Acute onset left eye pain followed within a few hours by the progressive blurring of the vision of both eyes	Daily oral aspirin (100 mg) and acetazolamide (250 mg), a topical steroid 4 times per day, topical levofloxacin, and brimonidine 2 times per day, 95% oxygen therapy, and hydration with normal saline	No improvement on her visual acuity over 8 mo of follow-up
Lee et al.[27]	HA	Visual loss in the left eye; central retinal artery occlusion	NR	After 3 mo of follow up, the visual acuity in the left eye was no light perception
Kim et al.[28]	HA	Retrograde intravascular embolization into the small ocular arteries	Filler was removed	Complete recovery
Hsieh et al.[29]	Calcium hydroxylapatite	Sudden left eye blindness, no light perception in her left eye, with retinal cherry-red spots, moderate ptosis, limited eye movements (n = 1); sudden eye pain and visual impairment in the left eye, bilateral lower visual field defects (n = 1)	Anterior chamber paracentesis, timolol and acetazolamide (n = 1); hyperbaric oxygen therapy, systemic low dose steroids, antiaggregant, and topical and oral antiglaucomatous agents (n = 1)	No light perception in her left eye during follow-up (n = 1) altitudinal visual field defects in both eyes and generalized depression in the visual field of the left eye (n = 1)
Chou et al.[30]	Calcium hydroxylapatite	Ptosis, left periorbital pain, headache, after 30 min progressively blurring vision in the eye	Alprostadil and dextran + 10 sessions of hyperbaric oxygen therapy	Visual acuity in her left eye improved to 6/60 after 1 mo
Qi et al.[31]	Autologous fat	Sudden visual loss immediately after the injections. Ophthalmic artery occlusion (n = 13); central retinal artery occlusion (n = 6); branch retinal artery (n = 3)	Ocular massage, oxygen, and carbon dioxide therapy, hyperbaric oxygen therapy, steroid therapy, topical antibiotics, and anticoagulant	No light perception

(*Continued*)

Table 4. (*Continued*)

References	Filler Used	Ocular Adverse Event	Management	Outcome
Chen et al.[32]	HA	Visual acuity impairment and ischemic oculomotor nerve palsy after injection of HA into the nasal dorsum	Cefuroxime and dexamethasone are given immediately without benefit; topical timolol maleate, tobramycin-dexamethasone ophthalmic eye drops, ocular massage. Additional treatments included intravenous injection of prostaglandin, periocular injection of anisodamine to dilate arteries, iv injection of dextran 40, iv injection of ozagrel, and oxygen inhalation. Intramuscular injection of methyl cobalamin was given, systemic steroid dexamethasone is given for 3 d, and a topical antibacterial agent was applied to the affected skin for 10 d	Visual acuity, extraocular movement, and visual field defects improved within 14 d
Hu et al.[33]	HA	Sudden visual loss of the right eye	Hyaluronidase was injected into the forehead, glabella, nose, and retrobulbar region; 2 h of daily hyperbaric oxygen therapy, oral aspirin, oral acetazolamide, and iv dexamethasone	At 2-wk follow-up, patiently showed improved visual acuity of the right eye to hand movements
Cohen et al.[34]	Calcium hydroxylapatite	Right eye periocular pain and blurred vision	Immediate management: injected material tried to be withdrawn by aspiration, hot water compress, topical massage. Treatment: Enoxaparin, acetylsalicylic acid, amoxicillin/clavulanate, prednisone, topical antibiotics-ofloxacin, and mupirocin ointment	At two-mo follow-up, best corrected visual acuity was 20/32 in the right eye and 20/20 in the left eye. At 18-mo follow up; visual acuity declined to 20/60, visual field showed severe progressive deterioration with a central and superonasal field remnant and the optic disc became pallor.
Goodman and Clague[35]	HA	Immediate and partial loss of vision	Hyaluronidase, 375 IU/mL Approximately, 0.8 mL of hyaluronidase twice in short succession into the area of the supratrochlear and supraorbital notches	Second injection resulted in instant relief of visual symptoms and return of eyesight
Dagi et al.[36]	Calcium hydroxylapatite	Horizontal diplopia and right upper eyelid ptosis	A short course of oral steroids	Moderate clinical improvement with interval resolution of the inflammation and enhancement of the right temporalis, lacrimal gland, and lateral rectus muscle was noted on computerised tomography (CT)
Lee et al.[37]	HA	Severe pain, blepharoptosis, and decreased visual acuity immediately after injection	Hyaluronidase injection, systemic steroid injections for 2 wk, broad spectrum antibiotics for 1 wk	1 wk later recovered from blepharoptosis and limited extraocular movement had improved. By 6 mo, persistent diplopia progressively resolved
Szantyr et al.[38]	Autologous fat	Ocular pain, complete visual loss, with no light perception in the right eye	Prolonged circular digital and contact lens-induced ocular massage, ocular drops (timolol, brimonidine, and dorzolamide), IV dexamethasone, mannitol, glycerol; acetazolamide per os	In the 2-y follow-up, visual acuity remained stable, no visual deficits in the visual field and Optical coherence tomography (OCT) have shown no further decrease in ganglion cell activity (GCC).

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Table 4. (*Continued*)

References	Filler Used	Ocular Adverse Event	Management	Outcome
Myung et al.[39]	HA	Blindness without ptosis. Ophthalmoplegia (n = 2); blindness and ptosis without ophthalmoplegia (n = 2); blindness and ophthalmoplegia without ptosis (n = 2); blindness with ptosis and ophthalmoplegia (n = 3)	NR	Type I: During the 6-mo follow-up period, there were no signs of ptosis, ophthalmoplegia or enophthalmos. Type II: Levator function showed dramatic improvement 6 mo after injury, and eyeball movement remained normal during the follow-up period; Type III: Enophthalmos assessed 6 mo after injury indicated an average 1-mm posterior displacement, compared to symmetric eyeball position immediately after initial occlusion injury; Type IV: 6 mos after the initial injury, levator function, and dextraocular muscle tone were recovered to normal levels, but enophthalmos of 2-mm posterior displacement was present in the injured left eye
Zhu et al.[40]	HA	Immediate vision loss (n = 3), vision loss after 1 h (n = 1) 3 patients presented with retinal artery occlusion with retinal opacity and edema; 1 patient presented with no light perception in her left eye	Hyaluronidase (n = 4) and corticosteroids (n = 3)	No light perception (n = 3) and visual acuity 20/60 (n = 1)
Marumo et al.[41]	Calcium hydroxylapatite	Diplopia, visual loss in the left eye, and impaired consciousness	Subconjunctival injection and systemic administration corticosteroids	At 2 mo, diplopia and visual loss issues were mostly resolved
Sharudin et al.[42]	HA	Sudden onset of right monocular visual impairment associated with diplopia	Subcutaneous hyaluronidase injection	Complete visual recovery within 2 wk
Thnasarnaksorn et al.[43]	HA	Vision loss secondary to HA embolization in retinal or ophthalmic arteries; with complications including periorbital pain, ptosis, impairment of extraocular muscle functionality	Patient 1: Hyaluronidase, hyperbaric oxygen therapy and low-level laser therapy, anterior chamber paracentesis, methylprednisolone and antiplatelet drugs given along with oral antibiotics. Patient 2: Carbogen, right ocular massage, hyaluronidase injection, hyperbaric oxygen, oral cetazolamide, eye drop consisting of dorzolamide combined with timolol, and oral aspirin. Patient 3: hyaluronidase injection, nitroglycerin transsoft tissue pad on the chest, ocular massage, breathed into a plastic bag. Patient 4: Hyperbaric oxygen, hyaluronidase injection, retrobulbar hyaluronidase injection. Patient 5: Intralesional hyaluronidase injection and retrobulbar hyaluronidase injection, nitro-glycerin transsoft tissue pad, ocular massage and rebreathing in plastic bag. Patient 6: Hyaluronidase injection, ocular massage, hyperbaric oxygen	Patient 1: Received artificial eye, 6 mo later; Patient 2: After 21 d, ptosis completely resolved until full recovery 30 d after the incident; Patient 3: After 5 d, normal extraocular muscle function, visual field test normal; Patient 4: Extraocular muscles (EOM) function and ptosis continued to improve until full recovery 6 d later gradually; Patient 5: Ptosis and EOM function partially improved 20 d after initial injury, ophthalmoplegia almost fully recovered at 30 d; however, visual acuity of the left eye was still limited to light perception; Patient 6: Full recovery of vision
Chesnut[44]	HA	Visual changes in the ipsilateral eye that progressed toward full visual loss	Injection discontinued, hyaluronidase, and aspirin	Full recovery of vision
Liu et al.[45]	Autologous fat	Ophthalmic artery occlusion and/or hemiplegia		Unilateral permanent blindness

reaction over and above the mechanical blockage accentuating the obstruction and consequently cause ischemia and blindness. In fact, it has been shown that HA may have heparin-like activity as opposed to collagens clot promoting action.[58]

Can Blindness due to HA Injection Be Prevented or Treated?

It has been seen that hyaluronidase, an enzyme that degrades HA, may improve outcomes following an accidental intravascular HA filler injection. A review conducted by Carruthers et al[59] showed that when hyaluronidase was injected next to a blood vessel clogged with HA, it catabolized the HA without needing to canalize the affected artery. It is also suggested that in the case of retinal artery embolization with the HA product, retrobulbar injection of a large volume of hyaluronidase might well be the single most effective option to dissolve the intraorbital intravascular hyaluronan in a time-sensitive manner.[59]

In 2018, a case reported by Sharudin et al[42] showed a complete visual recovery of posterior ischemic optic neuropathy with ophthalmoplegia caused by HA filler injection. It has been suggested that in the case of embolism caused by HA, hyaluronidase given within the window period of 60–90 min has a strong chance of dissolving HA embolism.[42] Another series of 6 cases of vision loss caused by HA filler injection showed improved visual acuity or complete reversal in 4 of the cases. The authors suggested that early supratrochlear/supraorbital hyaluronidase injection, ocular massage, and rebreathing into a plastic bag can be safe, uncomplicated and effective methods to enable restoration of the retinal circulation, and reverse vision loss.[43] Chesnut[44] also reported a case of recovery of HA filler visual loss after using retrobulbar hyaluronidase injection, although Zhu et al[40] reported no recovery of vision loss in all 4 reported cases despite the use of retrobulbar hyaluronidase; albeit, these cases were all injected after 4 hours of occlusion and did not fall in the window of 60–90 min of perceived best opportunity for visual slavage.

Although consensus recommendations for the avoidance and management of complications from HA fillers including blindness are available[60] there is no evidence that following the currently available guidelines would reverse the vision loss necessitating a need for a specific protocol that can be followed to universally reverse all cases of blindness secondary to HA fillers. However, it is worthy to note that this possibility of reversal of iatrogenic blindness is likely to be possible with HA fillers and not others like autologous fat, collagen, or calcium hydroxylapatite.

Inconsistencies in recommendations for safer injection technique and lack of evidence to correlate the impact of injection technique on the occurrence of blindness necessitate the need for exploratory research. Better reporting of cases of blindness through a registry with details of the injection technique provided, including type of filler, use of needle or cannula (with size), use of local anesthesia, etc., can help to better understand the mechanism for the causation of blindness retrospectively so that preventive measures can be put in place. Additionally, the effect of different fillers (including the various brands of HA fillers available worldwide) on the vessel wall can be studied in vitro to establish the safety profile of the differently available fillers.

LIMITATIONS

This systematic review has many limitations. First, there was no uniformity in presenting the cases, and many important parameters or variables were not reported. Second, as with any case reports, the information regarding the rate, ratios, incidences, or prevalence cannot be generated because they are not representative of the population. Last, as with descriptive studies, one cannot deduce the cause–effect relationship; hence, the findings cannot be generalized.

CONCLUSIONS

Even though rare, vision loss due to HA injection is a disastrous event. When vision loss occurs, with limited time for restoration, early recognition and prompt treatment are crucial. There is no gold standard for the treatment of vision loss, and even though there have been consensus recommendations, no specific guidelines are available which have been universally successful in reversing this complication.

HA-based fillers appear to be relatively safer soft-tissue fillers, although it will be prudent to say that profound medical, anatomical, and product knowledge are required to minimize the occurrence of grave adverse reactions such as blindness associated with their use.

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