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ORIGINAL ARTICLE NON-SURGICAL AESTHETIC

Retrobulbar Injection for Hyaluronic Acid Gel Filler-Induced Blindness: A Review of Efficacy and Technique

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Abstract While blindness after hyaluronic acid gel filler injection occurs only very rarely, it represents a devastating complication for the patient and the surgeon. Retrobulbar injection with hyaluronidase is the only known potential means of reversing this adverse event. However, positive outcomes remain anecdotal. We have attempted to review the current literature regarding possible efficacy and detail the indications and technique to be utilized, if hyaluronidase retrobulbar injection is to be attempted.

Level of Evidence V This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Fillers · Filler-induced blindness · Retrobulbar injection · Retrobulbar hyaluronidase · Hyaluronidase · Hyaluronic acid

Introduction

Blindness following hyaluronic acid gel filler injection represents a devastating complication that is almost certainly underreported [1]. Even when promptly recognized and treated, a successful outcome is not assured [2, 3]. According to the International Society of Aesthetic Plastic Surgery (ISAPS) international survey, approximately, 3,298,266 hyaluronic acid filler injections were performed in 2017 [4]. This represents a 40% increase over the past 5 years. Given this dramatic increase in injection numbers, it is reasonable to assume that the incidence of this complication will in all likelihood increase as well. Proper management of this complication is therefore critical. While the proposed pathophysiology of injection-related visual compromise (IRVC) has been well described, [5–9] evidence of successful reversal remains sparse and anecdotal [10, 11].

Therefore, we seek to further examine the arguments for and against the efficacy of retrobulbar hyaluronidase injection for the treatment of IRVC. In addition, we will review the recommended clinical management of IRVC and retrobulbar injection technique in order to provide the plastic surgeon with a reference guide should the procedure need to be performed.

What the Literature Tells Us

A total of 98 articles were found related to this general topic by searching the PubMed/Medline database.

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Keywords and subjects used included "filler blindness pathophysiology," "injection-related visual compromise," "filler blindness treatment," "retrobulbar injection for filler-induced visual loss," or "hyaluronidase treatment of blindness." Thirty-two articles specifically addressed IRVC pathophysiology, treatment and overall efficacy of retrobulbar hyaluronidase injection.

The reports of blindness from filler injection date back to the early 1900s, and many of the first descriptions resulted from non-degradable fillers (i.e., fat, silicone) [1, 12]. The introduction of degradable hyaluronic acid (HA) fillers has resulted in an exponential increase in filler injection procedures being performed annually. This growth has led to a concomitant increase in publications related to complication prevention, recognition and treatment [1, 5, 6, 13–19]. The biodegradable characteristics of HA afford a potential opportunity for vision rescue following IRVC. As the variation in the composition of various HA fillers expands, certain HA fillers may be more or less susceptible to enzymatic degradation [19–21].

IRVC is the result of occlusion of the central retinal artery (CRA), and the most likely pathophysiologic description suggests retrograde flow resulting from the initiation and subsequent release of high-pressure injection [1, 11, 22]. Recent studies suggest that it is not just a mere embolus but rather a cascade of occlusive events resulting in thrombus formation and the initiation of an inflammatory response behind the HA plug [6, 20, 23].

Unlike other arteries of the face, the CRA lacks collateral support, and therefore, end-arterial occlusion can result in immediate retinal compromise and vision loss. It has been well demonstrated that the supraorbital, supratrochlear, zygomaticofacial, dorsal nasal, infraorbital and superficial temporal arteries all communicate with the ophthalmic artery systems. The generally accepted pathophysiology is as follows: High-pressure inadvertent injection of a systemic artery (supratrochlear or other centrally located vessels) overcomes systolic pressure leading to reverse of blood and filler flow back to the internal carotid system. The release of the pressure then allows for the anterograde flow of the blood and the filler embolus to enter the ophthalmic system [1, 7, 11, 22]. Paradoxical emboli can also occur. Reports have documented right-sided blindness following left side nasolabial fold filler injection [21]. It is hypothesized that the embolus crosses the midline through nasal collateral vessels demonstrating a connection between "perioral" external carotid and "periorbital" internal carotid artery systems [21].

Most consider IRVC to be an underreported phenomenon [20, 22]. A recent review of the literature found 61 reported cases of filler-induced blindness or skin necrosis [13]. Ozturk et al. as well as others noted that the majority of injections resulting in these complications were in the central face [6, 13, 23]. Parks et al. examined locations of iatrogenic retinal artery occlusion and found the glabella (50%), nose and nasolabial fold (33%), forehead (8%) and periorbital (8%) to be the primary locations of injection leading to this complication [14]. A subsequent study found 98 reported cases with IRVC. In this study, injection location was isolated to the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%) and forehead (12.2%) [24]. Because of the rich vascular network of the face, intravascular injections can perhaps be minimized but not prevented.

In reviewing the literature, we have identified 107 cases of IRVC reported after various types of filler injection [2, 10, 14, 24–29]. Many treatment modalities were reported, and the majority of which were futile to reverse IRVC. Figure 1 depicts the severity of the IRVC and their management. Figure 2 describes the outcome of these cases.

Retrobulbar Injection Controversy: Does it Work?

The verdict remains unclear with regard to the ability of retrobulbar injection of hyaluronidase to reverse retinal artery occlusion. Factors such as time to treatment, technique, amount injected and type of HA filler causing the embolus may all play a role in the success of this intervention [2, 20, 30]. To date, several authors have described guidelines for recognition and treatment of IRVC. The retrobulbar injection was introduced as a treatment of

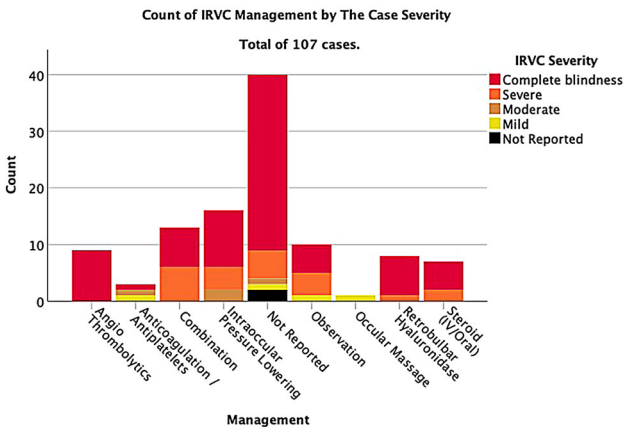

Fig. 1 The severity of the filler-induced visual compromise and their management. The majority of the reported cases have shown a complete visual loss as a result of filler injection and less commonly severe visual impairment which is limited to hand motion or light perception. The combination management involved more than one treatment modality such as anticoagulation, steroid, intraocular pressure lowering, or subcutaneous hyaluronidase. Intraocular pressure lowering involved anterior chamber paracentesis, acetazolamide, or mannitol. Although most cases report the severity of the visual compromise, not all have reported their management approach [2, 10, 14, 24–29]

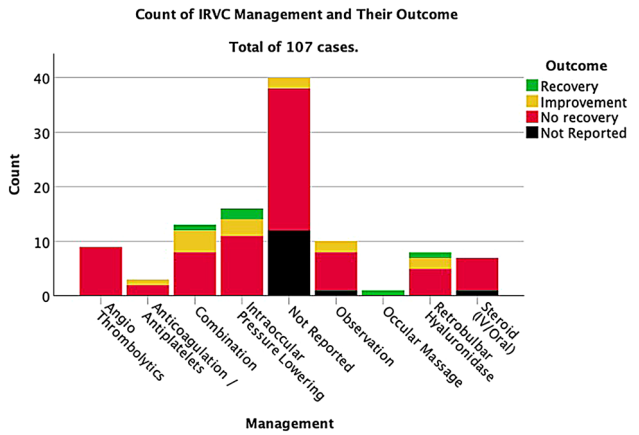

Fig. 2 The management outcome of filler-induced visual compromise. The combination management involved more than one treatment modality such as anticoagulation, steroid, intraocular pressure lowering, or subcutaneous hyaluronidase. Intraocular pressure lowering involved anterior chamber paracentesis, acetazolamide, or mannitol. Some cases reported only the outcome without discussing the management approach. Out of 75 cases with complete blindness, only one case reported complete restoration of vision which was after retrobulbar hyaluronidase injection, and only four cases have shown some degree of visual improvement (one case improved after intraocular pressure lowering, two cases after retrobulbar hyaluronidase, and one reported improvement, but management was not reported) [2, 10, 14, 24–29]

IRVC during an international coalition committee in 2013 [22]. This meeting was in response to a large number of cases from the Asian literature reporting filler-induced blindness resulting from injections to the nasal dorsum and glabella. The majority of cases reported abrupt development of symptoms within the first hour after injection if not immediately, with the median at 0 h (interquartile range of 11 h). To date, these cases continue to surface [3, 5, 10, 14–17, 24–29, 31–34].

Hamasaki et al. first demonstrated occlusion of the retinal artery in squirrel monkeys using rapid B-wave depression on electroretinogram and optic nerve discharges. Their study showed that return of blood supply to the retina in < 2 h resulted in complete recovery of the signal from the retina to the optic tract [35]. Decades later, Hayreh et al. induced transient CRA occlusion in 38 monkeys. Using a variety of measuring instruments, they reported that ischemia up to 97 min resulted in no permanent damage [36, 37]. This suggests that if IRVC is reversed in < 90 min, there may be an increased chance of vision recovery in the setting of filler-induced blindness. However, some question the validity of these studies. While the time of central artery ischemia is thought to be critical if IRVC is to be reversed, how much time remains unclear.

In 2014, DeLorenzi demonstrated in a cadaver model that cross-linked HA inside intact vessels is susceptible to hyaluronidase injected around the vessel in a cadaver model. This implies that passive diffusion occurs and may be effective in the degradation of intravascular filler emboli [21, 23]. DeLorenzi further expanded on this concept, suggesting that flooding an effected aesthetic subunit with hyaluronidase will also increase hydrostatic pressure and may assist in diffusion of the enzymatic degrader into the vessel. While preliminary clinical and anecdotal evidence may support this, there is some question as to whether this physiologic method holds with retrobulbar injection [20, 38].

Fathi et al. highlighted certain challenges with retrobulbar hyaluronidase injection. They noted that the central retinal artery is covered with three layers of meninges. The artery itself is located very posteriorly in the retrobulbar space. Therefore, they suggested that it may be difficult to generate enough pressure to induce retrograde flow from diffusion alone [39]. Theoretically, injection of a subtherapeutic amount of hyaluronidase may simply dissolve or dislodge the filler into small clots which may then travel to distal arterioles exacerbating the problem. In support of this concept, it is known that the degradation of smaller more distal clots may also occur [20]. Finally, an anti-hyaluronidase mechanism has been postulated to exist in the periorbital area, which might then lead to the need for large doses of hyaluronidase in the orbital structures [20].

Clinically, Chesnut reported successful improvement of filler-induced blindness after the use of retrobulbar hyaluronidase injection [10]. This patient had no other signs of ischemia that often accompany IRVC, and no formal visual acuity or pupillary function evaluation was performed at presentation. A case report from Australia reported the return of eyesight after two injections of 300 units of hyaluronidase in quick succession in the supratrochlear and supraorbital notches [11]. This patient claimed a "flashing sensation and partial loss of vision," but again, neither visual acuity nor pupillary function was tested.

On the other hand, Zhu et al. reported four cases of filler-induced blindness unsuccessfully treated with retrobulbar hyaluronidase [2]. However, all cases were seen 4 h or later following injection (4, 12, 32 and 34 h). Delay in treatment may have been the reason for the failure of re-cannulation of the CRA in these cases [2].

Although the overall efficacy of retrobulbar hyaluronidase injection in the reversal of IRVC is still uncertain, few other options exist to treat this devastating complication. Unlike intravascular-induced soft tissue ischemia where reversal can be successful hours or days later, IRVC requires emergent attention. The plastic surgeon injector may need to react as a "first responder" to initiate the treatment process by performing retrobulbar injection in hopes of preventing irreversible ischemia [8, 20, 22].

Therefore, it is a technique that should be familiar to all injectors.

Pre-injection Exam

Prior to performing facial filler injections, the surgeon should consider performing a brief ophthalmologic history screening for vision correction, cataracts, macular degeneration and glaucoma. Intraocular surgery (glaucoma and cataract) can predispose patients to pupillary defects or asymmetry which should be noted prior to injection. In the event that post-injection visual changes are suspected, it is helpful to know the specifics of the pre-injection exam. Visual acuity, pupillary response and any other notable findings should be documented [5].

Ocular Anatomy

The bony orbit is 42–54 mm deep in adults. The globe has an axial length of 20–25 mm and is located in the anterior half of the orbit. The retrobulbar space is approximately 25 mm posterior to the anterior orbital margin and sits immediately posterior to the globe. The optic nerve travels within a muscular cone from the optic foramen to the posterior aspect of the globe. Traveling within the dural sheath of the optic nerve is the ophthalmic and central retinal arteries. The central retinal artery is an end-arterial branch of the ophthalmic artery. The least vascular quadrant of the orbit is the inferotemporal quadrant which is why many consider it to be the safest location for retrobulbar hyaluronidase injection [22] (Figs. 3, 4).

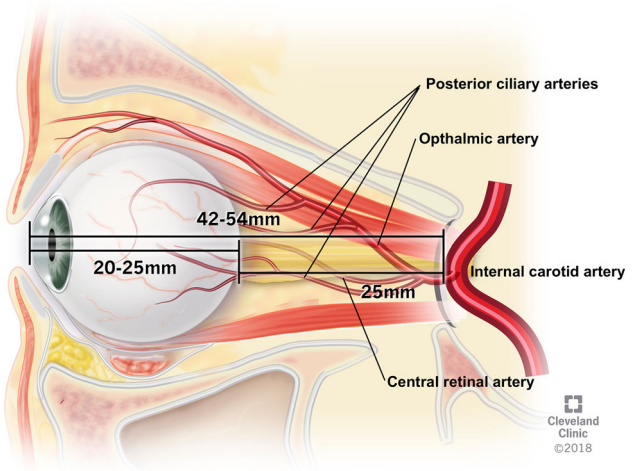

Fig. 3 Illustration of the cross-sectional plane of the orbital cone showing its depth and the anatomic relation to vital structures

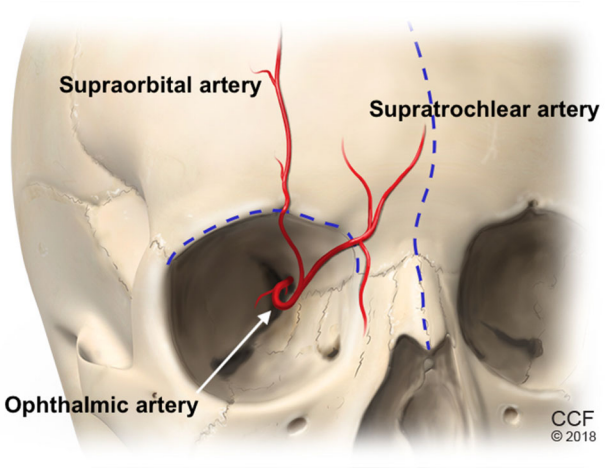

Fig. 4 Illustration of the anatomic relation of the supratrochlear and supraorbital arteries to the ophthalmic artery

Retrobulbar Injection Preparation

Before retrobulbar injection is attempted, the plastic surgeon should be trained in the technique. Prior to injection, the eye should be in primary gaze, not looking up. Topical anesthetic with 0.5% tetracaine is applied. A small wheel of 0.1–0.2 mL of 1% lidocaine can be injected in the lower eyelid skin at a point midway between the central and the lateral eyelid. Many practitioners recommend at least 500 units of hyaluronidase should be loaded in a syringe. The inferior orbital rim is palpated while mildly pushing up on the globe. A 25-gauge 1.5-in.-long needle is inserted just above the rim in the lateral third of the eyelid and is advanced with the needle bevel up, and the needle is parallel to the orbital floor with an inclination of approximately 15°. The needle should not be wiggled in the orbit. One should feel a "pop" at the orbital septum at 1 cm from the skin when advancing the needle in the orbit. Once the needle has passed the "equator" of the globe, the needle should be redirected 30° supranasally and advanced another 2.5 cm. One should feel another "pop" upon entering the intraconal space. If a second "pop" is not appreciated, the needle may be outside the muscle cone. Injecting outside the cone may allow for adequate diffusion in any case and may be safer for the novice injector to perform this peribulbar injection. Injection should not proceed if resistance is encountered as the needle may be inside the globe. The syringe should be aspirated, 3–4 mL of solution is injected, and the needle removed. With the eye closed, mild pressure is applied for several minutes to prevent hemorrhage. The algorithm for the steps of retrobulbar hyaluronidase injection is detailed in Fig. 5.

Although commonly performed by ophthalmologists to administer regional anesthesia, risks of retrobulbar

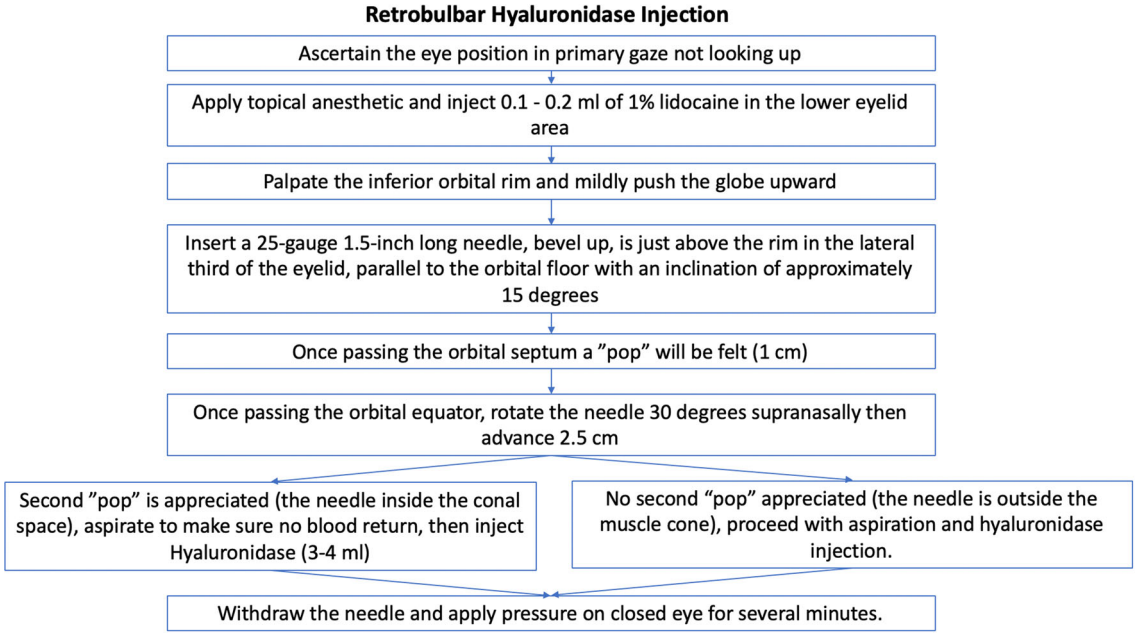

Fig. 5 Algorithm guide for the necessary steps to perform retrobulbar hyaluronidase injection

injection include globe perforation and penetration, optic nerve injury and retrobulbar hemorrhage [20, 39–41] (Video).

Treatment of IRVC

Those who inject fillers should establish a relationship with a local ophthalmologist/retinal specialist prior to the occurrence of complications.

If filler-induced visual compromise is suspected, visual acuity and pupillary testing should be performed immediately. Visual acuity is typically severely compromised, to the point of not being able to read the newspaper. Simply documenting the ability to read a printed magazine should sufficiently rule out an IRVC event requiring emergent retrobulbar injection. Visual fields can be assessed by finger counting in the peripheral vision. These findings should be documented prior to considering retrobulbar hyaluronidase injection. Accurate ophthalmic evaluation and documentation of true visual loss avoid putting a patient at risk from a retrobulbar injection unnecessarily. The decision on the pupil should be made by the ophthalmologist if possible. Some authors suggest a filler "crash cart" be available at all times and should include multiple vials of hyaluronidase, a 25 gauge 1 1/2″ needle or retrobulbar needle (a blunt-tipped 25G 1 ½″ needle) and a 5 mL syringe [10, 20, 23, 30]. In the majority of cases, symptoms of filler-induced blindness are immediate. Given that the incidence of this event is so rare and the occurrence is so sudden, delaying the patient's office discharge is probably not indicated.

As suggested by the successful salvage described by Goodman et al., if retrobulbar injection cannot be performed, an alternative supraorbital injection of 500–1000 U of hyaluronidase to the supraorbital region in quick succession could be attempted. [11]

Conclusion

Injection-related visual compromise (IRVC) is frightening to the injector and devastating to the patient and requires early recognition and treatment in an attempt to avoid irreversible blindness. To date, retrobulbar injection represents a direct method of hyaluronidase introduction to the region of the CRA, though without proven outcomes. This technique carries its own morbidity and should not be approached casually. Although many authorities suggest the presence of a crash cart, its value has not been established in the treatment of blindness. While the treatment of visual changes with hyaluronidase remains controversial, having it rapidly available for the treatment of non-blindness-related tissue ischemia is more difficult to refute.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Statement of Human and Animal Rights or Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

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