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ORIGINAL CONTRIBUTION

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The treatment of hyaluronic acid aesthetic interventional induced visual loss (AIIVL): A consensus on practical guidance

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Summary

Background: Visual loss (blindness) caused by injection of soft tissue fillers is a rare but devastating issue to both patient and practitioner. There is a lack of any structured protocol in the management of this problem

Aims: To produce a pathway for the management of hyaluronic acid aesthetic interventional induced visual loss that was based on the current available literature and guidelines. evidence proposed guidance for the practical management of this problem. was evaluated and a pathway has been developed for patient management and specialist advice

Method: A consensus group experts involved in aesthetic intervention, visual loss research and with experience in dealing with visual loss assessed the current literature and proposed guidelines available. Using the protocols available a pathway for the treatment of aesthetic interventional induced visual loss was proposed.

Results: The group produce a set of guidelines for the practitioner to use as an emergency situation and for use in a delayed presentation. The group also produced guidelines for specialists to use in a secondary care setting.

Conclusions: These recommendations are based on current publications and or consensus view as there is still a lack of robust Level I data to support any particular intervention therapy.

KEYWORDS
blindness, hyaluronic acid, hyaluronidase, patient management, vascular, visual loss

1 | INTRODUCTION

Blindness following soft tissue augmentation is a serious complication caused by occlusion of the branches of the ophthalmic artery to the eye.[1] In 2015, a review of the world literature on all reported cases of vision changes from fillers was conducted to highlight key aspects of the vascular anatomy, as well as discuss prevention and management strategies.[2] The results showed that 98 cases of vision changes from filler had been identified globally, with 65 of those leading to unilateral vision loss and only two cases being reversible. Autologous fat was the most common filler type to cause vision changes (47.9%) amongst the cases identified, while hyaluronic acid was indicated as the second most common cause, responsible for 23.5% of the complications. The sites that were high risk of complications were the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%), and forehead (12.2%). The literature reviewed also indicated that no treatments were found to be consistently successful in treating blindness. The authors concluded that, "although the risk of blindness from fillers is rare, it is critical for injecting physicians to have a firm knowledge of the vascular anatomy and to understand key prevention and management strategies." A similar complication of occlusion of the vascular system to the skin causing dermal necrosis has also been described with different

soft tissue augmentation materials with an estimated prevalence of 0.001% of procedures performed.[3]

Blindness (visual loss) following the injection of soft tissue augmentation materials appears to be due to the obstruction of the ophthalmic artery and its branches. The proposed theory is that of retrograde pressure induced embolization of material through the vascular anastomosis of arterial vessels in the facial region with a final common pathway ending in the end arteries of the retinal artery.[4,5] The Aesthetic Interventional Induced Visual Loss (AIIVL) Consensus Group came together in October 2016 including the following specialists: Consultant Plastic and Aesthetic Surgeons from the UK and China; and Consultant Ophthalmic Surgeons from the UK and United States. The group reviewed the current available reports on blindness associated with aesthetic procedures and developed a consensus opinion on the practical treatment for this condition. Reviewing the available evidence, it was observed that there was no consistent management pathway for this very rare but life-changing complication. Many aesthetic practitioners and specialists do not have any management pathway for this complication.

A report in 2017 recommended the availability a "blindness safety kit" with a protocol to follow if such a complication should occur.[6] A previous review also noted that practitioners ".must be trained to recognise symptoms, institute immediate actions and refer patients without delay to dedicated specialists for definitive and supportive management".[7] There is however a lack of a standard protocol for the treatment of this complication, and there are no Level I recommendations available for practitioners to follow. The guidance developed by the AIIVL Consensus Group is based on the scenario of visual loss due to soft tissue injection with hyaluronic acid (HA); the basic principles of the treatment pathway for non-HA products may be applied, although hyaluronidase would not be effective.

In reviewing the evidence base, blindness following injection was initially described in 1963[8] and more recent reports show that the pattern of involvement of the surrounding periocular tissues is variable.[9] The ophthalmological literature describes a clinical condition of Central Retinal Artery Occlusion (CRAO).[10,11] Patients who smoke, are hypertensive, have a high body mass index, high serum lipid levels, diabetes, and cardiac disease, have important modifiable risk factors associated with retinal emboli; it can be hypothesized that these patients may bear the higher risk for AIIVL.

The guidance of the AIIVL group draws on the corollary between this clinical condition and that of the complication by occlusion by an embolus of HA.

2 | CONSENSUS GUIDANCE

The group provides guidance on separate aspects:

1. Pre- and peritreatment advice to minimize the risk of general and specific complications;
2. Immediate management of patients with visual loss at the clinic and at home;
3. Specific advice that specialist units may follow;
4. Further advice to the practitioner.

2.1 | General advice

The group felt that the following was important for all practitioners injecting products in the head and neck region:

The potential for visual loss and skin necrosis must be on consent forms and be explicitly discussed with the patient. Although this complication is very rare, informed consent requires that the practitioner discusses this potential life-altering condition with the patient. Surgeons who perform surgical blepharoplasty will discuss the potential of visual loss and in not doing so would be deemed below the standard of practice of a reasonably competent practitioner on that field. The consequences of visual loss are so devastating that the group felt that this aspect of the potential complication should be openly discussed with the patient (Consensus Recommendation).

All practitioners performing injectable treatments in the head and neck area must have a thorough knowledge of facial anatomy with respect to vessels (layers of face and where vessels may be found). There is much information available and being reported regarding the potential anastomosis of vessels in this region; it is essential that practitioners are aware of the—"normal" anatomy/variations/alterations following surgery (eg, rhinoplasty). The whole head and neck region should be viewed as an area of high risk and not segmented into "danger zones." Injections into the incorrect layer represent the "danger layer." Understanding this concept will help reduce the risk of inappropriate placement of products and the potential adverse events associated with this (Good Medical Practice Guidelines).

Careful, aseptic skin preparation and cleaning of the whole face prior to injection of injectable implants (dermal fillers) are essential. This will reduce the potential risk of early and late implantation of skin commensals with associated risks of infection. It is also perceived to fall within the area of good clinical practice to ensure the environment is kept clean and clinical; aseptic nontouch techniques (ANTT) are practiced and that the practitioner maintains a clinically clean personal approach ("bare below the elbows") (Clinical Guidelines).

When using a cannula (single-entry sites), care should be taken to minimize adjacent skin contact on cannula entry so as to avoid the introduction of skin commensals at each entry. Practitioners should consider keeping the cannula clean between passes through the skin. With multiple injection points (eg, needle), it may be applicable to consider further skin cleaning between injections to reduce bacterial load and change the needle for patient comfort (Clinical Guidelines).

While performing injections, these should be delivered slowly with minimal pressure, to minimize trauma and also the potential for embolism if a vessel has unknowingly been breached. There should be caution with mechanical injection systems to avoid high pressure injections. The precise pressure required to cause an embolic phenomenon has not been verified (Consensus Recommendations).

TABLE 1 General guidelines

General Advice on avoiding complications:

1. Essential knowledge of facial anatomy in respect to vessels (layers of face and where vessels may be – potential anastomosis – "normal "anatomy/Variations/alterations following surgery (rhinoplasty) *? High Risk sites - ? whole face?*
2. Potential for visual loss and skin necrosis on consent form and discussion with patient.
3. Careful, aseptic skin preparation
4. For single-entry sites, care should be taken to minimise adjacent skin contact on cannula entry so as to avoid the introduction of skin commensals at each entry
5. Multiple injection points – consider further skin cleaning to reduce bacterial load and change needle for patient comfort
6. Injections should be delivered slowly with minimal pressure, to minimise trauma and also the potential for embolism if a vessel has unknowingly been breached. *Caution with mechanical injection systems- need to have pressure sensor and cutoff?*
7. Inject small volumes less than 0.1 ml per bolus
8. Cannula size 25G or greater bore
9. Smaller Needle diameter (27 G or less) may enter vessels and also need high pressure to initiate flow – controversial point as smaller needle makes it difficult to deliver large volume in one bolus quickly so may make it less likely to cause visual loss
10. Caution with injections especially with 27 G or smaller gauge needles/cannulas

There have been reports that when injecting a bolus, the volume of injectate should be a limited volume of less than 0.1 mL per bolus[12] (Publication).

The cannula size used to inject should be 25G or greater diameter. There is opinion and views that a 27G cannula has a great potential to penetrate arterial walls. Cannulas with a gauge of 25 or larger diameter may have less risk of puncturing the arterial wall. Thin needles and cannulas (diameter 27G or less) may enter vessels and also need high pressure to initiate flow. This is, however, not acknowledged by all the experts. Alternatively, a thinner needle makes it difficult to deliver large volume in one bolus quickly so may make it less likely to cause visual loss (Table 1).

The group went on to consider possible scenarios in which a patient may present following an injection of HA-based filler. The two possible presentations are as follows:

1. Immediate visual loss with patient in clinic; and
2. Delayed presentation—patient not in clinic.

2.2 | Immediate visual loss

In the eventuality of a patient presenting with immediate visual loss, the first action of the practitioner should:

- stop injecting immediately;
- Ask the patient to start to rebreathing into a paper bag to increase the carbon dioxide concentration in the bloodstream. This is in keeping with recommendations for CRAO. The principle of retinal artery vasodilatation was considered as a priority to encourage the movement of the emboli into the peripheral portions of the vascular system (Publication for CRAO);
- Give oral aspirin immediately as an oral regimen of 2 pills of 325 mg daily to try to prevent further clot formation due to vascular compromise (and an antacid to prevent aspirin-associated gastritis). The duration of aspirin treatment would depend on the clinical scenario and whether improvement is seen, but a one week course is recommended (Publication for Vascular Occlusion);
- Sublingual GTN may be administered of potentiate further vascular dilatation and encourage movement of the product toward the periphery of the retinal system (Publication for Vascular Occlusion);
- Commence ocular massage to theoretically cause the embolus to travel physically displace emboli toward the periphery of the retinal system. This should be instituted immediately in conjunction with the above maneuvers.

Without any additional delay, the patient should be transferred to a specialist facility (Eye Hospital/A&E). There is some evidence from the literature on CRAO to suggest that after 90 minutes there is irreversible loss of vision that is progressive. Specialist treatment at an appropriate facility should be instituted as soon as possible to optimize all possible treatment pathways and provide professional support to the patient (Publication on CRAO).

2.3 | Delayed presentation—patient not in clinic

The group felt that the same management pathway as for immediate visual loss should be instituted: rebreathing, oral Aspirin, and ocular massage. The practitioner would need to give advice to the patient remotely to ensure that this protocol is instituted as soon as possible (Consensus Recommendation).

The practitioner will also need to coordinate the immediate transfer of the patient to the specialist center (Eye Hospital/A&E Department). The practitioner should also take full responsibility in terms of informing the facility of the impending arrival of the patient. It is important that the practitioner ensures the facility who know all details including interventions performed, time of injection—onset time—delay of transfer, and all relevant medical history (Good Medical Practice).

2.4 | Specific interventions at specialist facility

The group were concerned that in many cases patients who presented at emergency facilities were met by specialists who were not up to date with any of the specific guidelines. The AIIVL group looked at the possible interventions and have drawn up some guidance that would assist the specialist centers in starting emergency treatments.

In addition to the guidance proposed for the initial care, the specialist facility should consider the following interventions. As time is of the essence, it is important that the patient care is not delayed to perform any specific investigations. It is important that the retinal vascular occlusion as recorded accurately at presentation and a

TABLE 2 Consensus guidance

	Scenario 1 **Immediate blindness patient in clinic** **Signs/symptoms** **Note time of onset**	**Scenario 2** **Delayed presentation** **Patient not in clinic** **Time of signs symptoms - to be noted**
Action/Advice	1. Stop injecting! 2. Rebreathing (paper bag) 3. Start oral aspirin 4. Ocular massage	1. Rebreathing (paper bag) 2. Ocular Massage 3. Start oral aspirin 4. Call for emergency transfer
Who to contact inform	1. Immediate transfer to Eye Hospital/A&E Facility (BLUE LIGHT) emergency Golden hour	1. Arrange immediate transfer to Eye Hospital A&E Facility 2. Inform Facility of arrival of patient 3. Ensure facility know all details and possible intervention time of injection – onset time - delay of transfer (see first column
Advice to give other specialist/practitioners Ophthalmology/A&E	1. IV acetazolamide 2. Inferotemporal peribulbar injection of Hyalase – specialist intervention 3. Dose 1500 IU 4. Hourly repeat? 5. Anterior chamber paracentesis and withdrawal of 0.1-0.2 ml aqueous. 6. Sublingual GTN 7. Superselective Intra-arterial thrombolysis - no reperfusion High risk CV haemorrhage 8. ? IV Urokinase & Hyalase - High doses 9. High dose infiltration of Hyalase around supratrochlear notch 10. No cases of revascularisation reported	
Manufacturer contact	1. Inform Manufacturer of product – type dose etc. 2. MHRA (Regulatory body) to be informed	
Patient support advice	1. Inform patient of possible outcome – seriousness 2. Support for patient family 3. Liaise with hospital re visual loss 4. Keep close contact with patient	
Medicolegal	1. Inform indemnity cover 2. Keep accurate notes 3. Relevant photographs 4. Record all intervention – treatment schedule product use/ volume & site injected needle/cannula inc size 5. Notes on all interactions with patient/family/facility	
Other interventions	Hyperbaric chamber - no evidence.. and difficult to reach location in time NB Retrobulbar injections also risky – no confirmed evidence of effectiveness – but makes sense as narrowest portion of CRA is as it pierces dura of optic nerve intraocular injection Hyaluronidase– no evidence	

baseline retinography are performed. Intravenous acetazolamide (500 mg I.V.) would further enhance retinal arterial vasodilatation and blood flow and can be used by the appropriate specialists. Anterior chamber paracentesis and withdrawal of 0.1-0.2 mL aqueous may also be performed to reduce the intraocular pressure and allow movement of the emboli distally along the arterial tree (In combination with IV Mannitol—see below) (Publication on CRAO).

Another intervention would be to administer sublingual glyceryl trinitrate (GTN) to further enhance vasodilatation on the retinal venous system and reduce pressures in this region, although opinions vary on the advisability of nitroglycerin[13] (Publication).

It may also be advisable to increase the pressure differential between the ischemic tissues and arterial blood pressure. This may be achieved by intravenous Mannitol to increase the preload, combined with anterior paracentesis may reduce the local pressure at the ischemic site (retina)(Publication for CRAO).

Other interventions have been described in the literature, and the group looked at these in detail. The use of hyaluronidase has been advocated as a retrobulbar or (Inferotemporal) peribulbar injection. This is a specialist procedure, and it is unlikely that most practitioners would be competent to perform this procedure in an emergency situation. There are also risks of: retrobulbar hemorrhage, ocular perforation, vascular retinal occlusion, and other local and systemic effects that an aesthetic practitioner may not be competent on discussing and managing in an acute situation. The available evidence for clinical efficacy of this technique is not strong, although experimental evidence is

available demonstrating the spread of hyaluronidase in the orbital region from retrobulbar and peribulbar infiltration; the clinical results of this technique in reversing visual loss form HA fillers are limited to a few case reports only[14] (Publication).

If this intervention were to be attempted, it must be considered in the context that, retrobulbar injections pose a risk to the patient. Inferotemporal peribulbar injection of hyaluronidase is probably less of a risk than retrobulbar injection (although there is no confirmed evidence of effectiveness). However, it could be attempted in a specialist setting. The inferotemporal area represents the narrowest portion of CRA is as it pierces the dura of the optic nerve and would be a target area for the enzyme to penetrate the CRA. The specific doses of hyaluronidase have not been elucidated; however, it would appear appropriate to consider injecting 2-4 mL (1500 IU). It would be advisable to consider repeated retinal arterial observation and repeated infusion of hyaluronidase on an hourly basis (although this is only a consensus opinion).

Superselective Intra-arterial thrombolysis has also been considered[15,16]; however, there has been no convincing evidence of reperfusion. There is also a high risk of adverse events including cerebrovascular hemorrhage.

Direct intraocular injection of hyaluronidase has been attempted in an animal model in an attempt to deliver the enzyme directly near to the site of the embolus.

Recent use of IV Urokinase & hyaluronidase in high doses has been shown to be very effective in an animal model.[17] This has been reported to be effective in one case report.[18] The presumed mechanism is that proximal to the emboli, there is vascular stasis, which results in a thrombus. The thrombolytic agent allows the hyaluronidase to reach the HA emboli, and therefore, the combined approach is more effective than the agents when administered separately.

Overall, the results for patients presenting with no light perception following an HA emboli have been very poor. It is however imperative that any intervention is instituted within an hour of injury. Indirect evidence from rhesus monkeys with CRAO reveals that the retina could recover after 98 minutes; however after 105 minutes, the retina was irreversibly damaged.[19]

2.5 | Patient support/administration

The group considered that the follow-up of the patient including support was important and the injecting practitioner should take on this responsibility in collaboration with the specialist facility.

Following the adverse event and institution of the management plan as discussed above, the following aspects should be addressed (Consensus Recommendations):

- Inform the product manufacturer (medical affairs) regarding the adverse event and the product(s) used, volumes, and all details of the product.
- The national medical device authority (MHRA in the UK) must be informed regarding this adverse event.
- Liaise with the specialist facility and discuss the potential serious outcome of the adverse event. The practitioner has a duty of candor to be transparent in their actions concerning this event.
- Provide ongoing support for the patient's family and keep in close contact with the patient during this period. The patient may feel vulnerable and angry, and it will be important to provide support to them.

There will be important administrative aspects that the practitioner will need to address (Good Medical Practice):

- The relevant medical indemnity provider must be informed.
- Details of all the events preceding and the interventions/action taken must be accurately recorded including: treatment schedule product use/volume & site injected needle/cannula including size.
- All relevant photographs of the patient should be available.
- All communications between the specialist facility, patient and practitioner should be documented (Table 2)

3 | DISCUSSION

HA Injection Aesthetic Interventional Induced Visual Loss is an extremely rare but serious adverse event associated with injection of soft tissue augmentation in aesthetics. Our review of the available reports, our experience, studies, and opinions indicated a lack of any specific Level I guidelines in managing this condition.

Although in general the outcome is poor, it is imperative that treatment is attempted in the "Golden Hour" to try and reestablish retinal vascular flow. We have looked at the clinical condition of Central Retinal Arterial Occlusion and provided guidance that may be of practical use to the practitioner, specialist, and continuing support of the patient should this devastating adverse event occur. There continues to be discussion on the role of retrobulbar infiltration of hyaluronidase; the risks of this technique and lack of efficacy in recent reports[17] when balanced with the guidance for CRAO have led us to provide guidance that has some clinical basis including techniques that are readily available to the practitioner and specialist.

The experimental studies using IV hyaluronic acid and thrombolytic therapy may provide more specific treatments and we await further developments in this area. The most important aspect in this is the essential knowledge of head and neck vascular anatomy and the techniques of injection to avoid this adverse event.

4 | CONCLUSION

An immediate diagnosis and treatment of visual loss using the guidance provided may be of critical importance in managing this adverse event. Unfortunately, the prognosis for vision return is

grave. There is no robust Level I evidence-based treatment that can restore vision and no clear evidence that the complication of vascular occlusion can be avoided even with optimal technique in expert hands. We hope that the guidance we have provided will be evaluated and encourage further clinical research.

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