

Midface rejuvenation with Hyaluronic Acid:
A critical appraisal of the vascular complication risks and the
development of evidence based protocols for their prevention and
management

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Abstract

Background: Fortunately rare, vascular complications causing skin necrosis or blindness are feared consequences of hyaluronic acid filler treatment. Cases of skin necrosis from intravascular injection of hyaluronic acid fillers or vessel compression have been reported worldwide, whereas cases of vision loss from hyaluronic acid fillers are largely limited to Asia. The author is gravely concerned about the inadequacy of current UK legislation surrounding dermal fillers and the lack of training for management of vascular complications.

Objectives: A review of the literature was conducted to assess the risk areas for filler treatment and compile evidence based methods for prevention and management in an aesthetic practice setting.

Methods: A comprehensive literature search was performed to include relevant articles based on specified inclusion and exclusion criteria. The type of filler was limited to hyaluronic acid, with a record of complications as skin ischaemia, soft tissue necrosis, visual disturbance or blindness.

Results and Discussion: Ten articles representing 41 patients with vascular compromise were identified. Data from these reports include injection site, symptoms, treatment and outcome. The treatment site associated with the highest incidence of vascular compromise is the nose, representing 42% of vision loss and 59% of skin ischaemia cases. 62% of skin ischaemia cases resolved completely, irrespective of time to presentation. The most successful management component for skin ischaemia appeared to be early intervention with hyaluronidase. None of the twelve vision disturbance cases showed improvement compared with their initial presentation with the treatment measures performed. For vision loss there appears to be no effective management.

Conclusions: Hyaluronic fillers are widely used in aesthetic practice. It is imperative for practitioners to be able to prevent, recognise and manage vascular compromise.

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I'd like to thank Ed, my business partner, who has helped me establish our facial aesthetics practice. And my cats, who are a welcome distraction to an otherwise upsetting topic.

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Introduction

The worldwide use of dermal fillers for rejuvenation and facial reshaping is showing an explosive increase over the last decade.

An 31% increase in dermal filler treatments, totalling 2,690,633 worldwide in 2014, was recorded by ISAPS since 2013. This steady increase has been seen since 2011 according to the American Society for Aesthetic Plastic Surgery, rising by approximately 30% year on year (Cavallini et al., 2016; ISAPS, 2016). Closer to home, in the UK, approximately 1.5 million botulinum and dermal filler treatments were performed in 2013, an increase of 4% from 2012 (Inglefield et al., 2014). The reason for this increase is simple: dermal filler injections are convenient, predictable, achieve good results and are largely safe (Hsieh, Lin, Huang, & Yeh, 2015).

The increase in the use of dermal fillers worldwide will mean an increase in the number of complications, especially since the complexity of the performed treatments is increasing from the simple treatment of perioral lines for which dermal fillers were originally approved by the FDA in 2003 (Abduljabbar & Basendwh, 2016; US FDA, 2016). Thus, it is imperative that awareness and knowledge to treat complications are increased in a bid to improve patient safety.

It is too easy and arrogant to say that the best way to manage complications is not to have any (Cavallini et al., 2016). Some complications are unpredictable and happen to even the most experienced clinicians. Selection of the appropriate filler, using it correctly and conducting the procedure safely are all factors which mitigate the risk of complications, as improper technique and misuse of filler account for many easily avoided complications. However, if complications still occur the practitioner has a duty to manage them to the best of their abilities in the interests of the patient.

Vascular complications are certainly disproportionate to the expected outcome of the procedure. Whilst the number of cases of blindness resulting from dermal filler treatment is approaching 100 worldwide, and the incidence of necrosis is thought to be less than 0.1% of

all procedures performed, underreporting by clinicians due to embarrassment means that the true incidence is unknown (Cohen et al., 2015; DeLorenzi, 2014; Sun et al., 2015).

Dermal Fillers

When selecting dermal fillers for patients in practice, it is important that the product is safe and effective, not allergenic and gives reproducible results. Furthermore, they should be noncarcinogenic, nonmigratory and nonteratogenic (Alijotas-Reig, Fernandez-Figueras, & Puig, 2013). On a purely aesthetic basis, fillers should provide supports and structure where the features of the face are affected by volume loss (Montes, 2012).

In the USA, the FDA regulates which dermal fillers may be used. There are currently 24 FDA approved dermal fillers in the USA, of which 13 are hyaluronic acid (US FDA, 2016). In Europe regulation is much less strict and practitioners can choose from many types of fillers – some of lesser quality than others due to lax regulations over production, distribution and use. There are over 160 types of filler and over 50 manufacturers in the world. Low quality products can contribute to the most serious complications and practitioners should remain vigilant, as cheap products are often those with least scientific research into the effects on the human body (Cavallini et al., 2016).

Hyaluronic acid

Hyaluronic acid (HA) are biodegradable fillers that injected under the dermis to cause a temporary change in appearance before being biodegraded (Funt & Pavicic, 2013). Hyaluronic acid is a fundamental component of the extracellular matrix of cells (Cavallini, Gazzola, Metalla, & Vaienti, 2013). It is a glycosaminoglycan (GAG) made of N-acetyl glucosamine and glucuronic acid to form a linear disaccharide polymer, a water retentive natural sugar that helps to hydrate and volumise the skin (Kassir, Kolluru, & Kassir, 2011).

HA fillers are the most commonly used fillers, accounting for 78.3% of all filler treatments and an increase of 253% since 2000 (Abduljabbar & Basendwh, 2016). Synthetically produced using bacterial cultures, HA is modified by a cross-linking and stabilising process with 1,4-butanediol diglycidyl ether (BDDE) to achieve the appropriate permanence in tissues and deliver products that can last between 4-12 months on average (Cavallini et al., 2016). They are described as either biphasic or monophasic, with a particle size of around 400µm. Biphasic HA fillers have little or no cross-linking, their particle size determining the product density (e.g. Restylane). Monophasic HA fillers are crosslinked to form homogenous gels where HA concentration combined with crosslinking determines filler density (e.g. Juvederm, Belotero) (Cavallini et al., 2016). Once in tissue, HA expands due to its hydrophilic properties (Grunebaum, Bogdan Allemann, Dayan, Mandy, & Baumann, 2009)

When injected into the tissues, HA can provide structure and elasticity by binding collagen and elastin (Kassir et al., 2011). The primary reason for its popularity in use is its biocompatibility and reversibility (Abduljabbar & Basendwh, 2016), which is a preferable property when the impact of HA on tissues can cause devastating consequences. However, this property is by no means a magic wand.

Hyaluronidase

Hyaluronidase can be used to manage unaesthetic outcomes and serious complications such as vascular compromise after dermal filler treatment.

Hyaluronidase is an endoglycosidase which depolymerises HA fillers by hydrolysis of the 1,4-N-acetylglucosaminidic bond in hyaluronic acid (Cavallini et al., 2013; Hilton, Schrupf, Buhren, Bolke, & Gerber, 2014). Originally licensed to improve permeation of intramuscular and subcutaneous injections and infusions, hyaluronidase increases drug diffusion into the extracellular matrix and increases blood vessel permeability (Cavallini et al., 2013; King, 2014). The action of hyaluronidase is rapid and complete within 24-48 hours. The disruption that is caused to the dermal barrier is transient, reforming after around 48 hours (Kassir et al., 2011).

The first report of the use of hyaluronidase to manage dermal filler complications was in 2007 by Hirsch et al (Hirsch, Cohen, & Carruthers, 2007) and early injection after a vascular complication significantly reduces the risk and extent of necrosis. It not only degrades the HA filler, but can also reduce pressure on the occluded vessels and reduce oedema (Beleznay, Humphrey, Carruthers, & Carruthers, 2014). Dosages in the literature remain varied, with some studies suggesting between 150U (Sun et al., 2015) to 200U repeated after one hour (Cohen et al., 2015), and even as high as 1000U (Cavallini et al., 2016). It is thought that although hyaluronidase is associated with a high incidence of allergy, too little can result in scarring (Cohen, 2008). Filler with higher HA concentrations may require more hyaluronidase (Cavallini et al., 2013).

There is much hype about the complication rate with the use of hyaluronidase, the incidence of which is reported at around 0.05-0.1%. However, this has been shown to increase to as high as 30% when high doses are administered. The mechanism of allergic reaction is Type I and Type IV mediated hypersensitivity, and can result in urticarial, erythema and oedema but also, more seriously, in rash, angioedema and anaphylaxis (Cavallini et al., 2013; Cavallini et al., 2016). For this reason, it is often advised to test hyaluronidase on the patient before administering it; however, in the case of impending necrosis it is thought that it would be more damaging to hesitate and direct administration of hyaluronidase is advised (Cohen et al., 2015).

The reason for its immunogenicity is the source of hyaluronidase. It is gained from ovine testis and thus contains animal products, but also contains lactose components in the hyaluronidase powder. In the UK, ovine hyaluronidase is available as Hyalase (Wockhardt) in a 1500 unit ampoule as powder for reconstitution with saline or with lidocaine to further vasodilation (Cohen et al., 2015; King, 2014). In America, a human recombinant formulation of hyaluronidase, Hylenex, is available which is safer and less immunogenic (Cavallini et al., 2013).

When using hyaluronidase in aesthetic practice, it is important to consider that it is antagonised by furosemide, benzodiazepines, dopamine, alpha-adrenergic agonists, antihistamines and phenytoin, some anti-inflammatories such as indomethacin and

antioxidants such as vitamin C (Cavallini et al., 2013; Cavallini et al., 2016; Glaich, Cohen, & Goldberg, 2006).

Hyaluronidase is not licensed for correcting problems resulting from filler treatment and is used off-label according to Article 87 of Directive 2001/83/EC. Therefore, informed consent is required from the patient, with a thorough outline of the medical and surgical alternatives (Cavallini et al., 2016; Cohen et al., 2015; King, 2014).

Complications with dermal filler injections

Non-surgical cosmetic interventions such as dermal filler treatments carry with them risks that the patient must be made aware of, as patient satisfaction is a significant outcome measure. Often, side effects accompany treatment, and discomfort, erythema, swelling and haematoma are commonplace and to be expected (Kassir et al., 2011). These are usually mild, transient and self-resolving, requiring no intervention except reassurance from the treating clinician as to their finite duration.

Complications from dermal fillers, on the other hand, are unexpected in nature and disproportionately negative to the intended therapeutic outcome even though the treatment has been administered correctly and the product used normally. These can be catastrophically severe and long lasting and may result in permanent injury or aesthetic deficits if not treated carefully and diligently (Cavallini et al., 2016; Y. Chen et al., 2014)

Vascular complications with dermal filler treatment

Vascular complications, although considered to be rare at a rate of around 0.1%, are the most frightening and serious consequences of dermal filler treatment (Sun et al., 2015). Embolisation of a vessel with filler material by direct injection, or compression of a vessel by the placement of product in close proximity, can progress to necrosis of tissue due to ischaemia (Cohen et al., 2015; Kassir et al., 2011). This can lead to areas of skin succumbing

to oxygen deprivation. Similarly, blockage of the vessels that supply the eye due to access of dermal filler particles to the ocular circulation can cause necrosis of the retina, leading to blindness.

Almost all filler materials in current and historical use have been linked to vascular complications and blindness, including paraffin, silicone oil, hyaluronic acid, polymethylmethacrylate, calcium hydroxylapatite and fat tissue (Hsieh et al., 2015).

In the case of occlusion of an artery, pain is often immediate and striking in nature with blanching of the supply tissue or loss of vision of the affected eye. When vision loss occurs, partial or complete loss of light perception, limited eye movement and retinal cherry-red spots may also be observed (Hsieh et al., 2015). When venous occlusion has occurred, it is often accompanied by a dull aching pain with dark violaceous patches at the vessel tributary site (Kassir et al., 2011). The patient may also report that there is pain disproportionate to the effected treatment (Inglefield et al., 2014). However, symptoms are not always the same and unusual or delayed presentations can occur as a result of swelling of the tissue or a hydrophilic filler leading to compression. Vascular complications are more likely to occur in areas where the blood flow is limited, or where there is a lack of collateral circulation affecting the tissues at risk. This is why the midface and nose are of particular relevance when treating with dermal fillers.

Midface rejuvenation and nose reshaping

The midface is subject to age-related changes, with loss of volume resulting in the descent of fat compartments and skin laxity, and deepened nasojugal and nasolabial folds. These changes in volume bring about an aged appearance, which is often the presenting complaint of a patient at an aesthetic practice. Replacement of volume to the fat pads of the face and lending improved structure with advancing age can result in high satisfaction rates of up to 75% at 2 years, with patients reporting an improvement in perceived age of up to 5 years (Few, Cox, Paradkar-Mitragotri, & Murphy, 2015).

The nose is not an area of the midface that is subject to extreme changes with age, but it is a part that is often the source of dissatisfaction in patients. Whether it is the shape or simply a defect in the nose such as a bump or an indentation, many patients seek to augment their noses. Dermal filler treatment of the nose is an excellent solution for patients who want to camouflage small to medium sized deformities of the nose but who are concerned with financial expense, aesthetic risk, surgery downtime or permanence of the effect (Humphrey, Arkins, & Dayan, 2009). Due to the nature of the nose tissue – it is non mobile and not subject to the same stresses as mobile and highly expressive parts of the midface – dermal fillers can last longer than in other areas.

The midface and nose are considered amongst the highest risk areas for vascular complications in dermal filler treatment.

The anatomy relative to vascular complications

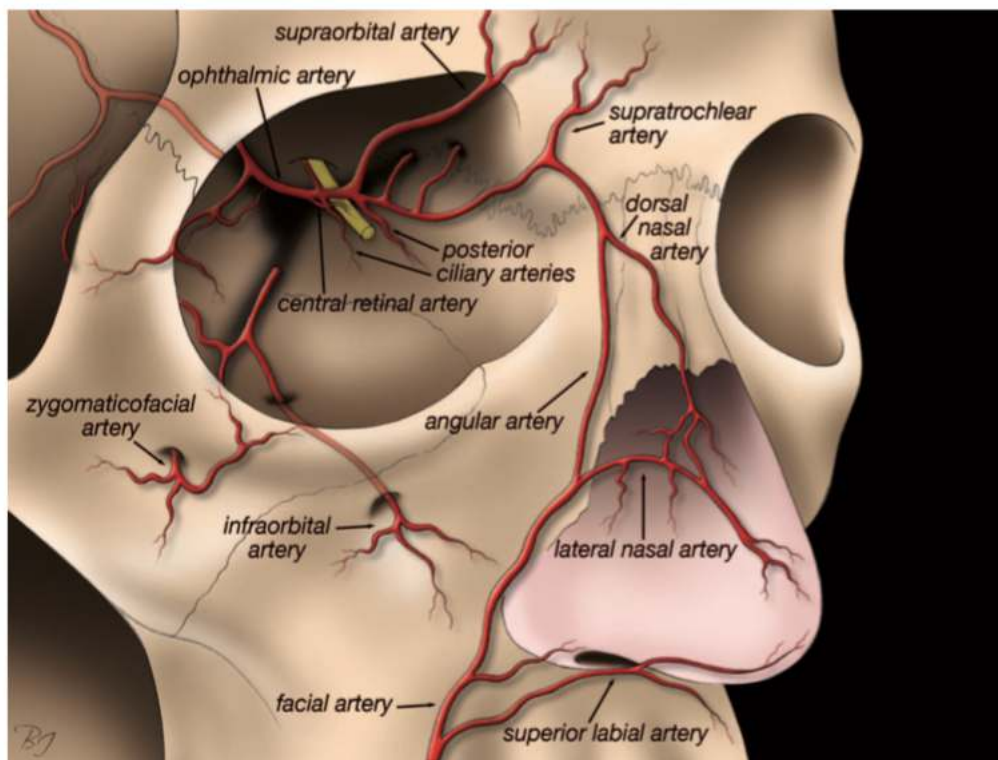


Figure 1: The vasculature of the midface (from (D. Lazzeri et al., 2012))

The facial artery, a branch of the external carotid, is the major vessel supplying blood to the superficial face. At the mandible, the facial artery crosses diagonally towards the nose, running a tortuous path at the nasolabial fold, before advancing to the lateral nasal wall in the alar crease and terminating in the angular artery. This runs towards the medial orbital rim. At the junction between the facial and angular arteries lies the lateral nasal artery, which supplies the 78% of the blood to the nose (nasal tip and ala), and blood to the remaining 22% of the nose via the dorsal nasal artery. Compression or occlusion of the facial artery in the nasolabial fold or further on at the angular or dorsal nasal artery can lead to alar necrosis or necrosis of the tip of the nose (Kassir et al., 2011).

The facial vein, which runs alongside the facial artery, lies at a distance of around 2-3cm lateral to the ala of the nose and similarly at the level of the oral commissure. The facial vein also demarcates the medial border of the medial fat pad of the face, which is triangular and often subject to volumisation with fillers (Chinnawong, Tansatit, Phanchart, & Rachkaew, 2015; Cotofana et al., 2015). Compression or occlusion of the facial vein or its tributaries can lead to a dull ache, dusky grey/mottled appearance and progressive ischaemia of the tissues (Inglefield et al., 2014).

The anastomosis of the dorsal nasal arteries with the ophthalmic arteries occurs at the medial canthus and from here blood can access the central retinal arteries via the ophthalmic arteries (Kassir et al., 2011; Y. J. Kim, Kim, Song, Lee, & Yoon, 2011). The ophthalmic artery is a branch of the internal carotid, and in turn supplies its orbital group, consisting of lacrimal, supraorbital, posterior ethmoidal, anterior ethmoidal, internal palpebral, frontal and nasal arteries, and the ocular group, consisting of long ciliary, short ciliary, anterior ciliary, muscular and central retina arteries (S. N. Kim et al., 2014). Excess pressure on the plunger above systolic during injection of fillers to the midface can overcome the anastomosis between facial and ocular circulation and reflux through to the ophthalmic artery or its branches (Tansatit, Moon, Apinuntrum, & Phetudom, 2015). Resulting ischaemia of the ophthalmic artery by blockage with dermal filler leading to lack of blood supply of any of the branches that it supplies can cause palsy of oculomotor nerves, blepharoptosis, exotropis, palsy of ocular muscles and loss of vision (Kwon et al., 2013). A further catastrophic consequence of pressure overcoming the anastomosis is a resulting cerebral event from filler product retrograde flow

into the internal carotid artery (Y. Chen et al., 2014; D. Lazzeri et al., 2012). Furthermore, high injection force deposits higher volumes of filler at speed, which can also lead to sudden compression of vessels, causing ischaemia and subsequent necrosis of skin (Y. Chen et al., 2014; D. W. Kim et al., 2011).

The glabella has limited collateral blood flow, so it represents another area at high risk of vascular compromise. Branches from supratrochlear and supraorbital arteries supply the glabella and inferior central forehead and the nasal root, with very superficial vessels (Glaich et al., 2006; Kassir et al., 2011). Injection of filler into either of these can result in direct entry into the ocular circulation and resultant blindness, but also consequences such as necrosis of the skin of the forehead and scalp (Kassir et al., 2011).

Related studies

The study that inspired this review is the case series report by Beleznavy et al about vascular complications in dermal filler treatment. Various fillers were analysed and methods for the management of vascular complications leading to impending skin necrosis were devised. This study is interesting as the protocols devised were simple, clearly set out and easy to follow, and the cases documented all had favourable outcomes (Beleznavy et al., 2014). These protocols can be utilised in aesthetic practice rather than a hospital setting and piqued the author's interest in devising management protocols for both skin and ocular complications from filler occlusion that can be utilised in practice in the UK.

Some similar reviews of the literature have been completed. In 2014, Carruthers et al compiled a literature review of blindness. The focus was on prevention and therapy. Autologous fat was identified as the main cause of filler blindness, but also that any attempted interventions were unsuccessful. A technique for retrobulbar injection of hyaluronidase was developed, in the hope that hyaluronidase injected directly into an ophthalmic artery would catabolise the clogged vessel. Unfortunately, this technique would need to be completed by a neuroradiologist or ophthalmologist only and would not be suitable for the aesthetic practice (Carruthers, Fagien, Rohrich, Weinkle, & Carruthers, 2014).

Lazzeri et al completed a literature review in 2012, in which 29 articles representing 32 cases of vascular complication leading to blindness were analysed. 47% were due to autologous fat injection, and precaution protocols were suggested. Treatment protocols included lowering the intraocular pressure by incision with a blade, IV diuretics, carbogen (5% carbon dioxide and 95% oxygen) rebreathing alongside corticosteroids, but all proved to be fruitless (D. Lazzeri et al., 2012).

A further review of the literature was conducted by Ozturk et al in 2013, where 61 cases of vascular occlusion other than autologous fat were considered dating from 1991 to 2012. This study associated the nose with the highest risk with 33.3% of complications having treatment at this site. A variety of fillers are considered and several complication types other than vascular are included and guidelines for the management of filler complications in general were developed which included in-practice management and referral (Ozturk et al., 2013).

It appears that no reviews have focused exclusively on the prevention and treatment of vascular complications of HA filler in an aesthetic practice setting that include papers published past 2012. Since HA is the most widely used filler, it seems pertinent to consider cases that have resulted from its use. Evidence based guidelines that are easy to implement developed from this review can be used to favourably influence the outcome of vascular complications and inspire further research.

Current treatment standards

Currently there are no reliable standard treatment protocols for vision loss as a result of dermal filler treatment (Hsieh et al., 2015) and prevention is a much more effective strategy.

Management of impending skin necrosis is a much more widely appraised topic, with many papers outlining guidelines for management. Protocols, such as those published by Inglefield et al in 2014, or Beleznyay et al in 2014 focus on the use of hyaluronidase, massage, hot compresses and anti-inflammatory measures as a treatment (Beleznyay et al., 2014; Inglefield

et al., 2014). These recommendations appear to be realistic and the success rates and outcomes adequate.

Practice implications

Patients commit to dermal filler every day, believing that it is a simple and quick procedure. This is indeed the case if the procedure is performed safely, by an experienced clinician, in the right environment. In the UK, the legislation surrounding the use of dermal fillers is lax and patients are potentially at very high risk of harm. Practitioners do not need to hold any formal qualifications to practice dermal fillers, and do not need to be healthcare professionals to gain access to dermal filler products or advertise to and treat patients (Keogh et al., 2013).

As the midface is the most at risk area for dermal filler complications, so it would not be a far-fetched tale to suggest that a vascular complication could occur in aesthetic practice for a medically healthy patient undergoing cheek or nose augmentation. The patient would require immediate, medium term and long term care. In order to give the patient the best possible care and mitigate any long term sequelae, it is important for all aesthetic practitioners to be familiar with the prevention, identification and management of vascular complications.

It was simple for the author to achieve training, completing a one or two-day course in order to be certified competent in the use of dermal fillers. However, initial training had little focus on the prevention and management of dermal filler complications; indeed after reviewing the course material, it seems to have no mention of it whatsoever. It therefore seems that many courses designed to offer practitioners a new scope of practice are leaving them poorly equipped to deal with any potential serious complications, of which necrosis and blindness are the most worrying.

The author is gravely concerned about the safety of medical aesthetics in the UK. She chose the topic of complications to demonstrate the risks associated with various procedures and

also in the hope that it might be taken up as a guide for practitioners to mitigate any unintentional harm they may do their patients.

In light of the governments total failure to take on board the findings of the Keogh Report, there is a long way to go before a serious regulatory framework can be established. A great deal of relevant regulation in our industry was directly or indirectly influenced by Europe, and our recent break with the EU can only further harm the prospects for a sensible regulatory regime in the near future.

It is the unfortunate case that action from governments and regulators does not come from careful planning and consideration but as a knee-jerk reaction to public and media outcry arising from serious harm being done to patients.

Most of the worse cases in this research come from overseas but be assured that similarly appalling adverse events will start appearing in the UK before long. It will not be the wealthy or enlightened patients who will suffer but the patients of limited means and insight, who are arguably those who need protecting the most.

Ask yourself this question; *what am I doing, as a thought-leader and expert in this field to mitigate risk?* Similarly ask *what am I doing to spread ideas that might protect both practitioners and patients from harm?*

Illegal practice is one issue but *substandard* practice must also be addressed as a growing problem. Perfectly good dentists and GPs are 'trying their hand' at facial aesthetics and are still very capable of causing harm, just as someone who picks up a needle for the first time is capable of causing harm. The only difference being that patients will have no reason not to trust the absolute clinical integrity of a medical practitioner.

Every day the author sees complications from legal and illegal practitioners, the severity and frequency of which are increasing month on month. One of the most harrowing facts is that patients come to the author's practice because their treating practitioners have often disappeared, cannot be traced or even deny having been the treating practitioner at all!

The author encourages practitioners to take up the advice found in this research and use it to make sure they are offering patients a safe and effective service in a consistent and appropriate way. Evidence based guidelines have been produced in such a format that they can simply be taken and put in surgeries for reference and guidance in an incident.

The author also encourages readers of this research to join her in campaigning for a safe and regulated industry because the position as it currently stands is woefully inadequate.

Those who say facial aesthetics is a profitable enterprise either lack commercial insight or lack personal integrity. Aesthetics is about the subtle pursuit of perfection and strong clinical skills and judgement. Those undertaking it in the hope of making money should be actively discouraged, for they represent the greatest risk.

Example Clinical Scenario

A patient attends an aesthetic practice seeking rejuvenation of the mid face, complaining of volume loss and aged appearance of the nasolabial folds. Hyaluronic acid filler treatment is suggested and commenced. During treatment the patient complains of pain. Immediately after treatment the patient complains of further pain and a violaceous patch to the left nasolabial fold and the left side of the nose is observed.

Immediate and long term management strategies must be invoked to appropriately manage this patient. What are the effective ways to manage this situation? Could anything have been done to prevent this complication?

Aims and Objectives

The aims of this dissertation are to ascertain the current treatment recommendations for cases of vascular compromise and loss of vision as a result of dermal filler injection and to search the current literature for cases relating to vascular compromise and blindness after

treatment of the midface. A particular interest was the treatment guidelines for the management of both vascular compromise and blindness, and whether there have been any changes in the commonly accepted protocols to deal with vascular compromise since the advent of the use of hyaluronidase in 2007. Furthermore, since there is very little evidence that visual loss as a result of dermal filler treatment can be effectively treated in the clinic setting, or indeed even in the hospital setting, research was conducted to assess whether any useful treatment modalities for vision loss from HA fillers exist or attempts have been documented.

The goal of this review was to evaluate and construct evidence based guidelines for the management of vascular complications – both impending skin necrosis and blindness – after treatment with hyaluronic acid fillers in the aesthetic practice setting in the UK. The hope is that they will be simple and accessible to practitioners, assist them in the case management and reduce a small portion of the stress felt by patient and practitioner in such a potentially disastrous event and assist in the management of the acutely compromised patient.

The aims were defined as follows;

- To evaluate the high risk areas for treatment of the midface
- To evaluate the risk posed by hyaluronic acid fillers
- To assess the outcome of intervention strategies in the literature
- To formulate evidence based prevention protocols for aesthetic practitioners in the UK
- To formulate evidence based management protocols for vascular occlusion that can be effectively used in the practice setting
- To make recommendations for improvement in the UK practice setting

Methods

This is a review of the relevant literature in order to draw conclusions about current aesthetic practice, the risks to vasculature and sight associated with HA filler treatment of the midface and to construct evidence based guidelines for the management of such complications. The complication rate and their management is an area that is gaining significant interest in the field of aesthetic medicine due to a steep increase in the number of patients treated. Unfortunately, due to the loose legislative framework in the UK relating to the use of dermal fillers, patients are at a significant risk of harm (Keogh et al., 2013).

A comprehensive MEDLINE, Cochrane database and PubMed electronic database search was performed to include journals published between 2011 and 2016, in a five-year date range. Aesthetic Medicine is a fast evolving field and as such a narrow date range has been selected for this reason; HA fillers were not commonly used until 2003 and the rapid increase in their use was not until later. Ozturk et al conducted a study on dermal filler complications with date ranges 1991-2012, so a later date range would serve as a fitting development, albeit limited to HA filler. No empirical research was conducted for the findings in this review.

The initial broad search in PubMed (carried out 01 Feb 2016) included keywords “dermal filler” and “complications” and resulted in 51 results. A brief assessment of the search results revealed that many of the papers included different types of dermal fillers, but also technique specific papers.

The criteria for inclusion as a key paper was for primary data to be published, for example clinical trials or case studies. Secondary reviews of the literature were excluded. Aesthetic medicine has a notoriously weak yet fast growing evidence base due to the worldwide scientific and financial interest in it.

The BestBETs methodology was used in order to formulate a three-part question for the purposes of literature research. This was to include the target population, the possible intervention, and the outcome.

The following BET was devised;

In [dermal filler treatment] which [management strategies] result in [improved outcome for vascular complications]

This was then revised to a more focused target population and intervention, as follows;

In [patients seeking rejuvenation of the midface] how are [VASCULAR complications managed] after treatment with [hyaluronic acid dermal fillers]

The original search of dermal filler complications was refined to include the midface. In a search of MeSH terms, this included the cheek, tear trough and nose and was defined as “the portion of the face comprising the nasal, maxillary and zygomatic bones and the soft tissues covering these bones” (Mosby, 2013). Further narrowing of the search criteria was performed to focus on Hyaluronic Acid fillers only, as these constitute over 75% of all fillers used in modern aesthetic practice (Abduljabbar & Basendwh, 2016).

Only English journals were considered for the literature review. In order to formulate evidence based guidelines for the management of vascular complications and to assess the effect of dermal fillers and their risk in aesthetic practice, studies not conducted on humans were excluded. The area of interest in the midface is the anastomosis of the nasal vasculature with the ocular vasculature, and this is not represented in an animal model. Cadaver studies have been evaluated for the embolic channel, however these do not provide useful interventions that can be utilised on a patient (Tansatit et al., 2015). Due to the nature of the intervention, it was thought unlikely for randomised controlled trials to be published for a human population.

The search terms were refined as follows:

(midface[All Fields] OR “mid face”[All Fields] OR “mid-face”[All Fields] OR cheek[MeSH Terms] OR cheek[All Fields] OR “tear trough”[All Fields] OR “nose”[All Fields])

AND

("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields])

AND

("complication"[All Fields] OR "complications"[All Fields] OR "necrosis"[All Fields] OR "blind*" [All Fields] OR "ocular"[All Fields] OR "vascular"[All Fields])

AND

("2011/05/02"[PDat] : "2016/05/02"[PDat] AND "humans"[MeSH Terms] AND English[lang])

42 articles were found in the above search.

In order to include and exclude papers from analysis, titles and abstracts were read to check for relevance. The final date for inclusion and research was 02 May 2016.

Exclusions were made on the following basis:

- 7 papers were not related to aesthetic medicine
- 19 papers focused on techniques in the treatment of the midface rather than on complications or their management
- 4 papers were not related to HA fillers
- one paper dealt with a complication that was not vascular
- one paper dealt with imaging techniques in dermal filler complications rather than their management

Ten papers were included from the initial search. Of these, two were not available online.

In order to make sure that all relevant papers had been found, two further searches were conducted, featuring skin necrosis and blindness as the main key words. Limitations were placed on the date range only, to include papers after 2011 (a five year range).

Further search 1:

"Skin necrosis after dermal filler injection" in Pubmed

((("skin"[MeSH Terms] OR "skin"[All Fields]) AND ("necrosis"[MeSH Terms] OR "necrosis"[All Fields]) AND after[All Fields] AND ("dermal fillers"[MeSH Terms] OR ("dermal"[All Fields] AND "fillers"[All Fields]) OR "dermal fillers"[All Fields] OR ("dermal"[All Fields] AND "filler"[All Fields]) OR "dermal filler"[All Fields]) AND ("injections"[MeSH Terms] OR "injections"[All Fields] OR "injection"[All Fields])) AND ("2011/05/02"[PDAT] : "2016/05/02"[PDAT]))

returned 11 papers

Further search 2:

“Blindness after dermal filler injection” in Pubmed

("blindness"[MeSH Terms] OR "blindness"[All Fields]) AND after[All Fields] AND ("dermal fillers"[MeSH Terms] OR ("dermal"[All Fields] AND "fillers"[All Fields]) OR "dermal fillers"[All Fields] OR ("dermal"[All Fields] AND "filler"[All Fields]) OR "dermal filler"[All Fields]) AND ("injections"[MeSH Terms] OR "injections"[All Fields] OR "injection"[All Fields])

returned 7 papers

Two further papers were identified and included for consideration and evaluation. A further evaluation of these papers and their references showed significant overlap in the source papers and the search was deemed to have been carried out to its fullest.

Ten papers were finally selected, as follows:

Beleznay, K., Humphrey, S., Carruthers, J., & Carruthers, A. (2014). Vascular Compromise from Soft Tissue Augmentation. *Journal of Clinical and Aesthetic Dermatology*, 7(9), 6. *Clinical case series, Canada.*

Chen, Q., Liu, Y., & Fan, D. (2016). Serious Vascular Complications after Nonsurgical Rhinoplasty: A Case Report. *Plast Reconstr Surg Glob Open*, 4(4), e683. doi:10.1097/GOX.0000000000000668

Single case report, China/London.

Chen, Y., Wang, W., Li, J., Yu, Y., Li, L., & Lu, N. (2014). Fundus artery occlusion caused by cosmetic facial injections. *Chin Med J*, 127, 1434-1437. doi:10.3760/cma.j.issn.0366-6999.20133254

Clinical case series, China.

Kassir, R., Kolluru, A., & Kassir, M. (2011). Extensive necrosis after injection of hyaluronic acid filler: case report and review of the literature. *Journal of Cosmetic Dermatology*, 10, 224-231.

Single case report, USA.

Kim, S. N., Byun, D. S., Park, J. H., Han, S. W., Baik, J. S., Kim, J. Y., & Park, J. H. (2014). Panophthalmoplegia and vision loss after cosmetic nasal dorsum injection. *J Clin Neurosci*, 21(4), 678-680. doi:10.1016/j.jocn.2013.05.018

Single case report, South Korea.

Kim, Y. J., Kim, S. S., Song, W. K., Lee, S. Y., & Yoon, J. S. (2011). Ocular ischaemia with hypotony after injection of hyaluronic acid gel. *Ophthal Plast Reconstr Surg*, 27(6), e152-155. doi:10.1097/IOP.0b013e3182078dff

Single case report, South Korea.

Kwon, S. G., Hong, J. W., Roh, T. S., Kim, Y. S., Rah, D. K., & Kim, S. S. (2013). Ischemic oculomotor nerve palsy and skin necrosis caused by vascular embolization after hyaluronic acid filler injection: a case report. *Ann Plast Surg*, 71(4), 333-334. doi:10.1097/SAP.0b013e31824f21da

Single case report, South Korea.

Park, S. W., Woo, S. J., Park, K. H., Huh, J. W., Jung, C., & Kwon, O. K. (2012). Iatrogenic retinal artery occlusion caused by cosmetic facial filler injections. *Am J Ophthalmol*, 154(4), 653-662 e651. doi:10.1016/j.ajo.2012.04.019

Clinical case series, South Korea.

Park, T. H., Seo, S. W., Kim, J. K., & Chang, C. H. (2011). Clinical experience with hyaluronic acid-filler complications. *J Plast Reconstr Aesthet Surg*, *64*(7), 892-896. doi:10.1016/j.bjps.2011.01.008

Clinical case series, South Korea.

Sun, Z. S., Zhu, G. Z., Wang, H. B., Xu, X., Cai, B., Zeng, L., . . . Luo, S. K. (2015). Clinical Outcomes of Impending Nasal Skin Necrosis Related to Nose and Nasolabial Fold Augmentation with Hyaluronic Acid Fillers. *Plast Reconstr Surg*, *136*(4), 434e-441e. doi:10.1097/PRS.0000000000001579

Clinical case series, China.

Results

Ten studies were finally selected as representing vascular complications from HA filler in the midface. As these vascular complications can result in tissue necrosis and blindness, studies were selected that showed instances of both.

Out of the ten papers selected, five involved ocular complications as a result of dermal fillers in the midface and five involved skin compromise. An initial review of the papers involved ascertaining which elements would prove useful to the central question of how vascular complications with HA fillers arise and how to manage complications in the midface.

The initial review of the included papers can be found in *Table 1*.

All papers found were CEBM Level 4 evidence, with most being single or multiple case reports. No randomised controlled trials were found. Due to the fortunately rare incidence of vascular complications in dermal filler practice, sample sizes are small, ranging from reports of a single patient in practice to 13 patients in the ocular complications group and 28 cases in a further study including vascular compromise affecting skin. However, with ocular complications papers it was found that whilst the single cases focused on HA fillers in the midface, papers with multiple cases included an array of filler products, including autologous fat and collagen (Y. Chen et al., 2014; S. W. Park et al., 2012). The studies that dealt with vascular complications involving skin only were similar, with the Belezny et al reporting on a combination of HA, CaHA and particulate fillers (Belezny et al., 2014). Further to this, Park et al explored all types of complications in a much larger sample size of 28 treated with HA filler only, of which three were found to be vascular complications affecting the skin (T. H. Park, Seo, Kim, & Chang, 2011).

In order to closer evaluate the data gained from the included studies, it was necessary to assimilate the relevant cases from each study in one table. Factors that were considered to be important for the evaluation of the data and subsequent formation of any guidelines were the following:

- Injection site – in order to evaluate procedure risk and formulate protocols for the prevention of vascular complications an assessment of the sites most affected must be made
- Practitioner – it would be interesting to ascertain whether certain professions are associated with a higher risk in vascular complication and outcome
- Injection volume – higher volumes injected are associated with increased risk of vessel compression, increasing the risk of ischaemia
- Injection technique – using larger bore needles is associated with an increased risk
- Symptoms – to recognise the complication in relation to the area treated and whether there is a standard presentation or warning sign for vascular compromise
- Time to presentation – delaying presentation for emergency treatment may result in worse prognosis
- Diagnosis – a diagnosis should include the vessel affected and the result of the occlusion. There may be a difference between the intervention and outcome if the vessel suffers frank occlusion or compression
- Treatment – in order to formulate evidence based guidelines for the management of vascular compromise, any effective treatment modalities must be assessed
- Outcome – to judge whether an intervention or treatment has been effective, the outcome must be measured

The subjects isolated from the ten studies that meet the criteria of vascular compromise with HA filler in the midface causing skin or ocular symptoms are presented in *Table 2*.

It soon became clear that the qualification of the treating practitioner was rarely recorded. SN Kim et al, YJ Kim et al and Kwon et al recorded a general surgeon and two physicians (exact specialty undisclosed) as the treating practitioners out of 12 considered ocular complications. From the group of vascular complications affecting the skin and a total of 28 cases, only two papers listed treatment providers, with Kassir et al stating the procedure was completed by a plastic surgeon and Chen et al made a point of advising that the license and registration status of the practitioner was unknown, without making reference to whether it was in fact a medical professional. Thus with such limited data on the performers, it would be difficult to

evaluate the risk associated with different professionals undertaking aesthetic procedures in the midface. As such, this criterion was removed.

The classification of injection technique was also removed. It is well documented that a smaller gauge needle is thought to cause a lower incidence of vascular events, with the use of a cannula reducing this risk further. However, from the evidence in these studies alone this conclusion cannot be drawn, as the injection technique was only recorded twice for the ocular complications patients by Chen et al recording the use of a 30G needle, and Beleznyay et al recording needle gauge of 28G to 30G in their treatment. The method of injection, whether retrograde or anterograde, or whether the product was placed in a bolus, fanning or other pattern, was not recorded in any studies. As such it would be difficult to establish evidence based guidelines on these cases alone (Beleznyay et al., 2014; Y. Chen et al., 2014).

It is clear that there is a great variation on the inclusion criteria for each of the studies. It is also clear that a large study of the vascular complications affecting both sight and skin in relation to performing treatment with HA fillers in the midface has not been done on a scale that would normally net reliable data for the formulation of proper evidence based guidelines. However, as aesthetic medicine is such a fast evolving and as yet unexplored field, the data from the individual cases, when collected and evaluated together will provide a useful framework from which to draw up guidelines for complication management.

Table 1: Overview of the ten selected papers, their basic outcomes and weaknesses

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|--|---|---|----------------------------|--|--|
| (Y. Chen et al., 2014) VASCULAR / OCULAR Study Number: 1 | 13 patients with fundus artery occlusion from dermal filler treatment resulting in loss of vision, women, age range 23-47 | CEBM Level 4 Case reports Retrospective | Type of filler | Autologous fat 7/13 cases Collagen 1/13 cases HA 5/13 cases | <ul style="list-style-type: none"> • Small study sample • Follow up period short or inconsistent • No evidence of injection technique or volume injected • Statistical assessment vague due to high number of variables, tabulated only • No treatment or prevention strategies • Vague description of site as “frontal” |
| | | | Symptoms and presentation | Immediate partial or complete vision loss unilateral Ophthalmic artery occlusion presents with severe pain | |
| | | | Associated Site and vessel | Frontal area 5/13, Periocular 2/13, Temple 2/13, Nose 4/13 Ophthalmic arteries and branches | |
| | | | Resolution | No improvement in 10/13 cases (7 autologous fat, 1 collagen and 2 HA) No improvement if Ophthalmic artery occlusion 3 patients in HA filler group showed improvement | |
| | | | Treatment / intervention | Nitroglycerin, massage, eye drops to lower intraocular pressure, aspirin, prednisolone. No relationship between treatment and symptom resolution | |
| (S. N. Kim et al., 2014) VASCULAR / OCULAR Study number: 2 | Single case, female, age unknown (“healthy young woman”) | CEBM Level 4 Case report Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Single case • No dosage or treatment outlined • No conclusions for treatment can be drawn |
| | | | Symptoms and presentation | Immediate vision loss unilateral Severe pain | |
| | | | Associated site and vessel | Nose: non-surgical rhinoplasty Occlusion of Ophthalmic artery | |
| | | | Resolution | No improvement | |

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|---|-----------------------------------|---|----------------------------|--|--|
| | | | Treatment and Intervention | None recorded | |
| (Y. J. Kim et al., 2011) VASCULAR / OCULAR Study number: 3 | Single case, female, 30. | CEBM Level 4 Case report Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Single case • No discussion or exploration of treatment modalities |
| | | | Symptoms and presentation | Vision loss unilateral Pain not specified | |
| | | | Associated site and vessel | Nose: non-surgical rhinoplasty Central retinal artery occlusion | |
| | | | Resolution | No improvement | |
| | | | Treatment and Intervention | IV Methylprednisolone 1g per day 3D, Oral prednisolone, aspirin 100mg, dressing skin lesion No relationship between treatment and resolution | |
| (S. W. Park et al., 2012) VASCULAR / OCULAR Study number: 4 | 12 cases, female, age range 18-66 | CEBM Level 4 Case reports Retrospective | Type of filler | Autologous fat 7/12 cases Collagen 1/12 cases HA 4/12 cases | <ul style="list-style-type: none"> • No attempt at treatment • Short follow up of 16 days and under in 5 cases • Mixed retrospective study not just HA filler |
| | | | Symptoms & presentation | Loss of vision unilateral with or without pain. | |
| | | | Associated site and vessel | Glabella 7/12 cases, Nasolabial fold 4/12 cases, Combined G/NL 1/12 cases Ophthalmic artery occlusion 7/12 cases (1/7 HA) Central retinal artery occlusion 2/12 Branch retinal artery occlusion 3/12 (3/3 HA) | |
| | | | Resolution | IAT (urokinase) did not improve symptoms No relationship between intervention and improvement in symptoms; No improvement in OAO group and no improvement in patients with severely decreased sight | |

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|---|--------------------------|--|----------------------------|--|--|
| | | | Treatment and intervention | Intra-arterial thrombolysis 4/12 cases Anterior chamber paracentesis 4/12 cases Conservative management 3/12 cases No hyaluronidase | |
| (Kwon et al., 2013) VASCULAR / OCULAR Study number: 5 | Single case, female, 20. | CEBM Level 4 Case report Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Single patient study • Use of unlicensed treatments |
| | | | Symptoms and presentation | Loss of vision unilateral, skin necrosis Warning sign ignored by practitioner | |
| | | | Associated site and vessel | Nose: non-surgical rhinoplasty Occlusion of retinal artery | |
| | | | Resolution | Improved visual acuity from 20/70 to 20/30 | |
| | | | Treatment / intervention | Nicergorline | |
| (Kassir et al., 2011) VASCULAR / SKIN Study number: 6 | Single case, male, 52. | CEBM Level 4 Case report Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Single patient only • Reference to unrelated studies • Mechanism of vascular event not identified exactly • Appreciation of common treatment modalities which have not been implemented |
| | | | Symptoms and presentation | Skin necrosis: Late presentation after large filler volume | |
| | | | Associated site and vessel | Compression of facial artery, transverse facial artery and buccal branch of maxillary artery | |
| | | | Resolution | Healed with scarring | |

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|--|---|---|----------------------------|--|--|
| | | | Treatment and intervention | Conservative: antibiotics, scar management | |
| (Sun et al., 2015) VASCULAR / SKIN Study number: 7 | 20 cases with nose and nasolabial fold augmentation, 1 male (21), 19 female (21-52) | CEBM Level 4 Case reports Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Dosages not recorded • Experimental medicine / herbal remedies used which are not licensed in US/EU |
| | | | Symptoms and presentation | Impending skin necrosis of nose and glabellar tissues | |
| | | | Associated site and vessel | Nose: nonsurgical rhinoplasty in 15/20 cases NL fold augmentation 5/20 cases | |
| | | | Resolution | 13/20 cases with full recovery early treatment showed better outcome | |
| | | | Treatment and intervention | Previously undocumented interventions Treatment with hyaluronidase all except 2 late presentation cases | |
| (T. H. Park et al., 2011) | 28 cases, all filler | CEBM Level 4 | Type of filler | HA | |

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|--|---|---|----------------------------|--|--|
| VASCULAR / SKIN Study number: 8 | complications. 3/28 skin necrosis | Case reports Retrospective | Symptoms and presentation | Various, but 3/28 patients skin necrosis | <ul style="list-style-type: none"> • All types of complications considered • Number of vascular complication cases considered low • Conventional treatment approaches not used |
| | | | Associated site and vessel | Nose, nasal sidewall and mentum for sites of necrosis | |
| | | | Resolution | Not documented for necrosis cases | |
| | | | Treatment and intervention | Antibiotics and surgical excision | |
| (Belezny et al., 2014) VASCULAR / SKIN Study number: 9 | 12 cases with vascular compromise from soft tissue augmentation, aged 26-69 | CEBM Level 4 Case reports Retrospective | Type of filler | Various, including 5/12 with HA | <ul style="list-style-type: none"> • Single centre results • Long duration of study (10 year span) – developments in treatment and products in this time +++ but also shows risk related to total number of treatments |
| | | | Symptoms and presentation | Immediate (hours) or delayed (1-5) violaceous reticulated patches | |
| | | | Associated site and vessel | Cheek, NLF, alar crease | |
| | | | Resolution | Complete, without scarring in all HA cases | |
| | | | Treatment and intervention | Warm compress, hyaluronidase, massage, GTN paste 2%, aspirin and prednisolone, daily follow up | |
| (Q. Chen, Liu, & Fan, 2016) VASCULAR / SKIN | Single case, female, 32. | CEBM Level 4 Case reports Retrospective | Type of filler | HA | <ul style="list-style-type: none"> • Single case • No protocol that has been tested • Poor outcomes |
| | | | Symptoms and presentation | Intense pain and skin blanching, followed by necrosis of skin | |

| Author / Date / Category | Patient Group | Study Type (level of evidence) | Outcomes | Key Results | Study Weaknesses |
|--------------------------|---------------|--------------------------------|----------------------------|--|--|
| Study number: 10 | | | Associated site and vessel | Nose: non-surgical rhinoplasty | <ul style="list-style-type: none"> • Contradiction of commonly used methods for resolution of HA filler complication without significant evidence |
| | | | Resolution | Healing with scarring | |
| | | | Treatment and intervention | Surgical decompression nasal tip, suction drainage, hyperbaric oxygen, thereafter wound management | |

Table 2: case collection from key papers

| Reference | Paper category | Age | Sex | Inject. site | Injection vol. | Symptom | Time to presentation | Diagnosis | Treatment | Outcome |
|---|----------------|-----|-----|-----------------------|------------------------------|--|----------------------|-------------------------------------|---|---|
| Y. Chen et al., 2014 | ocular | 44 | F | Nose | unknown | headache, vision loss | immediate | anterior ischaemic optic neuropathy | nitroglycerin, digital massage, eye drops to lower intraocular pressure, aspirin, prednisolone. | small improvement BCVA |
| Y. Chen et al., 2014 | ocular | 45 | F | Periocular | 1.0ml | vision loss although not fully described | immediate | central retinal artery occlusion | | reduced sight but not loss, no improvement |
| Y. Chen et al., 2014 | ocular | 25 | F | Frontal area | 2.1ml | vision loss although not fully described | immediate | unknown | | resolution from hand movement to improved visual acuity |
| Y. Chen et al., 2014 | ocular | 38 | F | upper eyelid | 0.6ml | Ptosis, ophthalmoplegia, dizzy, vomiting, vision loss | immediate | ophthalmic artery occlusion | | no light perception - no improvement |
| Y. Chen et al., 2014 | ocular | 23 | F | Nose | 0.9ml | Ptosis, ophthalmoplegia, dizzy, vomiting, vision loss | immediate | ophthalmic artery occlusion | | no light perception - no improvement |
| S. N. Kim et al., 2014 | ocular | NA | F | Nose | unknown | Ptosis, ophthalmoplegia, vision loss right eye | unknown | central retinal artery occlusion | High dose IV corticosteroids | no light perception - improvement in lateral eye movement but not sight |
| Y. J. Kim, Kim, Song, Lee, & Yoon, 2011 | ocular | 30 | F | Nose | 0.8ml (symptoms after 0.2ml) | toothache, headache, pain in left upper face, vision loss left, necrosis of skin glabella and nose | immediate | central retinal artery occlusion | IV methylprednisolone, aspirin 100mg, wound dressing. | no scarring, eyeball movement returned to normal, permanent vision loss |
| S. W. Park et al., 2012 | ocular | 32 | F | Nasolabial / glabella | unknown | vision loss right eye, ocular pain, ptosis, exotropia, ophthalmoplegia, corneal oedema | immediate | ophthalmic artery occlusion | intra-arterial thrombolysis | no light perception - no improvement |
| S. W. Park et al., 2012 | ocular | 26 | F | Nasolabial | unknown | inferior visual field defect, no ocular pain | 2 weeks | branch retinal artery occlusion | not recorded | visual acuity 1 at presentation, no change (20/20) |

| Reference | Paper category | Age | Sex | Inject. site | Injection vol. | Symptom | Time to presentation | Diagnosis | Treatment | Outcome |
|---------------------------------|----------------|-----|-----|--------------|----------------|---|----------------------|--|---|---|
| S. W. Park et al., 2012 | ocular | 26 | F | Glabella | unknown | inferior and central visual field defect, no ocular pain | 5 hours | branch retinal artery occlusion | massage and anterior chamber paracentesis | visual acuity decreased from 0.7 to 0.15 over review period |
| S. W. Park et al., 2012 | ocular | 26 | F | Nasolabial | unknown | inferotemporal visual field defect, no ocular pain | 3 weeks | branch retinal artery occlusion | not recorded | visual acuity 1 at presentation, no change (20/20) |
| Kwon et al., 2013 | ocular | 20 | F | Nose | unknown | partial visual disturbance right eye, orbital pain, nausea, vomiting, headache, blepharoptosis, diplopia, dizziness | immediate | branch retinal artery occlusion | Aspirin, Nicegorline, eye drops, IV steroids, hyaluronidase for skin lesion, wound care, IV antibiotics | visual acuity improvement from 0.3 to 0.6, partial resolution blepharoptosis, partial resolution limitation of eyeball movement, minimal scarring of skin |
| Kassir, Kolluru, & Kassir, 2011 | skin | 52 | M | Cheek scar | 2.0ml | persistent pain, slough, necrosis, poor capillary refill | 5 days | compression of facial, transverse facial, buccal branch of maxillary artery supply areas | topical antibiotic, IM antibiotic, wound care (silicon) | healing with scarring |
| Sun et al., 2015 | skin | 24 | F | Nose | unknown | Nose skin impending necrosis | 7 days | compression of vessel causing ischaemia | No hyaluronidase | Necrosis of skin, healing with scarring |
| Sun et al., 2015 | skin | 22 | F | Nose | unknown | Nose and NLF impending necrosis | 7 days | embolism of vessel | Hyaluronidase, antibiotics, Tanshinone, Papaverine, topical magnesium sulphate, infrared radiation, hyperbaric oxygen, aspirin. | Necrosis of skin, healing with scarring |
| Sun et al., 2015 | skin | 24 | F | Nose | unknown | Nose skin impending necrosis | 4 days | compression of vessel causing ischaemia | | Necrosis of skin |
| Sun et al., 2015 | skin | 28 | F | Nose | unknown | Nose, NLF, glabella, forehead impending necrosis | 1 day | embolism of vessel | | Necrosis of skin, healing with scarring |
| Sun et al., 2015 | skin | 25 | F | Nasolabial | unknown | Nose, NLF, lip reticulated erythema skin | 3 hours | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 25 | F | Nose | unknown | Nose reticulated erythema skin | 1 day | compression of vessel causing ischaemia | | Full recovery |

| Reference | Paper category | Age | Sex | Inject. site | Injection vol. | Symptom | Time to presentation | Diagnosis | | Outcome |
|------------------|----------------|-----|-----|---------------------|----------------|--|----------------------|---|---|------------------|
| Sun et al., 2015 | skin | 38 | F | Nose | unknown | Nose, glabella, forehead reticulated erythema | 1 day | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 24 | F | Nose | unknown | Nose, NLF, glabella, forehead impending necrosis | 9 days | embolism of vessel | No hyaluronidase | Necrosis of skin |
| Sun et al., 2015 | skin | 25 | F | Nose | unknown | Nose reticulated erythema skin | 2 days | embolism of vessel | Hyaluronidase, antibiotics, Tanshinone, Papaverine, topical magnesium sulphate, infrared radiation, hyperbaric oxygen, aspirin. | Full recovery |
| Sun et al., 2015 | skin | 52 | F | Nasolabial | unknown | Nose, NLF reticulated erythema | 1 hour | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 21 | M | Nose | unknown | Nose reticulated erythema skin, pustules | 2 days | compression of vessel causing ischaemia | | Full recovery |
| Sun et al., 2015 | skin | 22 | F | Nose and nasolabial | unknown | Nose, NLF, glabella, forehead reticulated erythema | immediate | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 31 | F | Nose | unknown | Nose reticulated erythema skin, pustules | 2 days | compression of vessel causing ischaemia | | Full recovery |
| Sun et al., 2015 | skin | 21 | F | Nose | unknown | Nose, glabella, forehead reticulated erythema | 5 days | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 35 | F | Nasolabial | unknown | Nose, NLF reticulated erythema, pustules | 1 day | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 39 | F | Nasolabial | unknown | Nose, NLF, lip reticulated erythema skin | 3 days | embolism of vessel | | Full recovery |
| Sun et al., 2015 | skin | 33 | F | Nasolabial | unknown | Nose, NLF, lip reticulated erythema skin | 2 days | embolism of vessel | | Full recovery |

| Reference | Paper category | Age | Sex | Inject. site | Injection vol. | Symptom | Time to presentation | Diagnosis | | Outcome |
|--|----------------|-----|-----|--|----------------|--|----------------------|---|---|---|
| Sun et al., 2015 | skin | 34 | F | Nose | unknown | Nose skin impending necrosis | 5 days | compression of vessel causing ischaemia | | Necrosis of skin |
| Sun et al., 2015 | skin | 26 | F | Nose | unknown | Nose skin impending necrosis | 2.5 days | compression of vessel causing ischaemia | | Necrosis of skin, healing with scarring |
| Sun et al., 2015 | skin | 37 | F | Nose | unknown | Nose, NLF reticulated erythema | 1 day | embolism of vessel | | Full recovery |
| T. H. Park, Seo, Kim, & Chang, 2011 | skin | ? | ? | Nose | unknown | tissue necrosis | 3 months | not made | Oral antibiotics | not described |
| T. H. Park, Seo, Kim, & Chang, 2011 | skin | ? | ? | Nasolabial | unknown | alar necrosis | 7 days | not made | Oral antibiotics | not described |
| Beleznay, Humphrey, Carruthers, & Carruthers, 2014 | skin | 69 | ? | Pre-jowl sulcus, lip corner, right lateral cheek | 1.0ml | violaceous reticulated patch right NLF, pain right upper lip, numbness, ecchymosis | 2 days | vascular compromise - presumed compression of vessel or embolisation (if immediate) | Massage, warm compress | complete resolution |
| Beleznay, Humphrey, Carruthers, & Carruthers, 2014 | skin | 65 | ? | Nasolabial | 1.0ml | violaceous reticulated patch left NLF, pain | 2 hours | vascular compromise - presumed compression of vessel or embolisation (if immediate) | Massage, hyaluronidase | complete resolution |
| Beleznay, Humphrey, Carruthers, & Carruthers, 2014 | skin | 31 | ? | Nasojugal | 2.0ml | violaceous reticulated patch right cheek, pain | 5 days | vascular compromise - presumed compression of vessel or embolisation (if immediate) | Massage, warm compress, hyaluronidase | complete resolution |
| Beleznay, Humphrey, Carruthers, & Carruthers, 2014 | skin | 50 | ? | Nasolabial | 2.0ml | violaceous reticulated patch left NLF and alar crease, pain | 1 day | vascular compromise - presumed compression of vessel or embolisation (if immediate) | Massage, warm compress, hyaluronidase, prednisolone | complete resolution |

| Reference | Paper category | Age | Sex | Inject. site | Injection vol. | Symptom | Time to presentation | Diagnosis | Treatment | Outcome |
|---|----------------|-----|-----|----------------------|---|--|----------------------|---|---|---------------------------------|
| Beleznay, Humphrey, Carruthers, & Carruthers, 2014 | skin | 58 | ? | Nasolabial and cheek | 0.5ml HA but also 3ml CaHA to NLF and cheek | violaceous reticulated patch and blanching left NLF | immediate | vascular compromise - presumed compression of vessel or embolisation (if immediate) | Massage, warm compress, nitroglycerin paste, hyaluronidase, prednisolone, aspirin | complete resolution |
| Q. Chen, Liu, & Fan, 2016 | skin | 32 | F | Nose | unknown | grey discolouration forehead, nasal sidewalls (bilat), nasal triangles (bilat) | 2 days | vascular compromise | surgical decompression, suction drainage, hyperbaric oxygen, wound management | healing with extensive scarring |

Discussion

Vascular complications are fortunately rare, and occur at a rate of around 0.001% of all performed dermal filler treatments (Cohen et al., 2015).

Beleznay et al report a risk rate of around 0.05% for vascular complications in their practice, which may be due to a higher complexity of procedures undertaken (Beleznay et al., 2014). However, when the adverse event requires referral to a centre such as that by Park et al, around 10% of all those referred are necrosis cases (T. H. Park et al., 2011).

Whilst arterial occlusion is of sudden onset, often accompanied by severe pain and blanching of the affected skin, venous obstruction can result in delayed presentation of violaceous, reticulated patches on the area of tissue drained by the obstructed vein (Daines & Williams, 2013). Vision loss is often the former, where an embolus occludes an ocular supply artery leading to ischaemia of the orbit and associated muscles, whereas complications involving the skin can be either due to filler embolus affecting an artery, or compression of an artery or vein causing ischaemia of the tissue with delayed onset. Pressure necrosis can result from the sheer volume of filler introduced into the target tissue, such as the case by Kassir et al where 2.0ml of HA filler injected into an already poorly perfused scar resulted in necrosis, further exacerbated by delayed expansion to HA filler as a result of its hydrophilic properties (Grunebaum et al., 2009; Kassir et al., 2011; Sun et al., 2015). The time to presentation is a useful indicator of the nature of the vascular accident – in the study by Beleznay et al for example, three out of the five HA filler cases presented at 24 hours or more, suggesting that the complication is due to compression or embolization of a vein, which is of slower onset (Beleznay et al., 2014). Sun et al specified the difference between vessel embolization and compression in their findings, however how these were distinguished has not been elaborated upon – it is assumed that imaging procedures were used to identify the cause of the compromise in addition to the area supplied being demarcated by the area which the vessel should supply. As far as the author is aware, there is no hard and fast way to easily distinguish between embolization and compression at the point of diagnosis. However, compression may be easier to resolve with liberal injection of hyaluronidase to relieve pressure on the vessel in question.

All studies examined were retrospective case reviews. Chen et al, Park et al and Beleznyay et al all reported larger sample size in the papers analysed, with 13, 12 and 12 cases, respectively. However, these studies all considered various types of fillers, including autologous fat, collagen, unidentified particulate fillers and HA (Beleznyay et al., 2014; Y. Chen et al., 2014; S. W. Park et al., 2012). The only study to focus entirely on HA filler complications was by Sun et al, with 20 subjects recorded in a retrospective case series examining impending necrosis of facial tissues (Sun et al., 2015). Conclusions relevant to the clinical question could only be drawn from cases that were treated with HA fillers in the midface, which have been presented in Table 2 and which will be referred to henceforth. There were a total of 12 ocular complications and 29 skin complications associated with HA filler treatment in the ten studies included for analysis. All cases were accounted for from presentation to outcome.

Filler types

The relevance of different filler types is in their capacity to occlude vessels of the eye. The particle size of HA fillers is around 400µm, which is of sufficient size to block the smaller vessels such as the retinal arteries measuring around 160µm diameter but not large enough to block the main ophthalmic arteries at around 2mm diameter, unless a large bolus is injected at speed. In cases of vision loss resulting from HA filler, the retinal artery and its branches were involved in 64% where the affected vessel was documented. Chen et al and Park et al compared this with the occlusion of vessels by other types of filler, especially autologous fat where the particle size is extremely variable and often larger, and noted that autologous fat occluded larger vessels such as the ophthalmic artery more frequently. HA filler occlusion of the ocular vessels is therefore associated with better outcome as the initial blockage of the vessel is likely to be a smaller one, supplying less tissue (Y. Chen et al., 2014; S. W. Park et al., 2012).

The studies by Park et al and Chen et al consider very similar cases of ocular complications. When comparing the two, the incidents of ocular complications for the different types of fillers resulted in similar percentages for incidents of HA versus Autologous fat fillers. HA

fillers represent five and four cases in each series, respectively. Autologous fat accounts for seven cases out of the 13 cases by Chen and seven out of 12 cases by Park (Y. Chen et al., 2014; S. W. Park et al., 2012). Autologous fat therefore accounts for more cases of vision loss in both referral centres, even though the number of HA filler treatments far outweigh the number of autologous fat treatments. Comparing this with the 2014 ISAPS data, there were 965,727 treatments with autologous fat versus 2,690,633 with HA filler. However, the instances of reported vision loss for autologous fat in the studies by Chen et al and Park et al are higher than HA filler by a factor of almost 2. If the patient group in these two studies can be used as a representative average of what really occurs in terms of complication rate, then extrapolating these values relative to the ISAPS data means that autologous fat is approximately five times more likely to cause blindness than HA fillers (ISAPS, 2016).

High risk areas and the effect on vessels

The results gained from the included papers gave a very clear indication of the high risk areas for treatment with dermal fillers. Sun et al in their study focusing on HA fillers, 75% of the cases of skin necrosis were due to treatment of the nose and the remaining 25% due to treatment of the nasolabial area, and all of the subjects presented with skin necrosis of the nose, regardless of where in the midface the treatment site had been (Sun et al., 2015). In the collated 12 ocular complications cases from all papers considered, the nose was treated in 42% of cases, with nasolabial and glabella treatment both being responsible for 25% of vision loss cases each. A staggering 59% of the collated 29 skin necrosis cases from all considered key papers had had treatment of the nose, followed by treatment of nasolabial folds with 34% of cases. This clearly outlines the nose, nasolabial and glabella as top three sites to result in vascular complications.

Nose augmentation is therefore classed as the highest risk procedure in the midface. It is perhaps no coincidence that several of the papers hail from China and Korea, where nose reshaping in order to westernise the patient's appearance is a procedure that is on the increase (S. W. Park et al., 2012). Whilst the nose is regarded as a treatment area that only experienced practitioners should approach, nasolabial fold augmentation is one of the first

treatments taught on many one-day courses, especially in the UK – this poses a serious risk for patients and a worry to experienced practitioners receiving referrals for complication management.

It has already been established that treatment of the nose is usually due to a desire to reshape, rather than for rejuvenation purposes. Considering the incidence of ocular complications however, there does seem to be a weighting towards complications in younger individuals – all subjects documented with vision loss as a result of HA filler treatment were under the age of 45. This may not be a coincidence. It is thought that younger individuals may be at increased risk of ocular complications due to an increased number of patent cutaneous arterial anastomoses. In a cadaver study by Tansatit et al, injection of facial arteries with dye led to the dye being extruded into the globe. In much the same way, filler can cause ocular complications. Large facial cutaneous arteries can be easily accidentally cannulated in filler treatment. When pressure is exerted on the plunger, and this is sufficient to cause retrograde flow, the ophthalmic artery can be reached from augmentation sites in nose and nasolabial areas (Y. Chen et al., 2014; Tansatit et al., 2015).

Chen et al reported that in addition to loss of vision in one case, the patient exhibited signs of a cerebral accident as a result of filler treatment, evidenced by magnetic resonance imaging (Y. Chen et al., 2014). Cerebral infarction has previously been documented in a further study by Hsieh et al, thought to be caused by pressure exceeding systolic on injection causing reflux of filler embolus to the middle cerebral artery. This can have truly devastating consequences (Hsieh et al., 2015). Excess pressure on injection is therefore a significant risk factor in dermal filler treatment.

The first case of permanent vision loss as a result of HA filler non-surgical rhinoplasty was 2011 by Kim et al (Y. J. Kim et al., 2011). By 2013, the total number of cases of vision loss associated with all types of filler treatment was around 60. There are a range of warning signs for vision loss as a result of filler treatment, with ocular pain and ptosis presenting in a large number of cases. Associated loss of movement of the eye is due to occlusion of the ophthalmic artery and lack of perfusion to the oculomotor nerves (Y. Chen et al., 2014). In the study by Kwon, the practitioner documented a “bursting” sensation after initial injection,

which was ignored, shortly after which the patient reported loss of vision (Kwon et al., 2013). Other symptoms included toothache and pain on one side of the face (Y. J. Kim et al., 2011). Park et al linked occlusion of the ophthalmic artery to severe pain, whereas central retinal artery occlusion and branch retinal artery occlusion can present without pain (S. W. Park et al., 2012). It appears that the smaller the vessel occluded, the less pain results due to less tissue supplied. Examination of the retina in the studies by Kim et al and Chen et al revealed cherry-red spots associated with ophthalmic artery occlusion and thinning of the fundus. The outcome for these patients was no improvement in light perception, with ophthalmic artery occlusion having the worst prognosis and most severe symptoms (Y. Chen et al., 2014; Y. J. Kim et al., 2011).

Interventions

Skin ischaemia / necrosis

Early intervention with impending skin necrosis is linked to a favourable outcome; Sun et al claim that when treatment is started within two days, the patient suffers a significantly reduced incidence of scar formation (Sun et al., 2015). Out of the 29 cases of impending necrosis of the skin analysed from the literature, 17 were treated in two days or less. Of these 17, two, or 12%, suffered a degree of scarring after healing. This can be compared to those that received treatment after two days, after which 58% of patients suffered scarring after vascular compromise. Although two days is an arbitrary time span, this does appear to mark the divide between excellent and mediocre outcome for resolution of necrosis of skin. However, the correlation between treatment time and outcome needs to be more extensively studied to demarcate optimum outcome versus time to presentation (Sun et al., 2015).

A study conducted in 2007 by Hirsch et al was the first case in literature that Hyaluronidase was used to successfully manage vascular complication from HA filler and it has been used to routinely treat vascular complications endangering skin since (Hirsch et al., 2007). It has been shown effective in the management of impending skin necrosis, but not in the management of ocular complications. Out of the 29 cases affecting the skin, 22 (76%) were treated with

hyaluronidase, of which 17 (59%) had a good outcome. The remaining five patients who did not have a good outcome with necrosis and scarring a consequence of the vascular complication, presented at 1 day, 2.5 days, 4 days, 5 days and 7 days post treatment. Sun et al advised that early treatment is essential, and describe this as within two days of treatment. Considering the results from the collected studies, there is a significant improvement in outcome when treatment is started with hyaluronidase in the early presenter. Comparing this with the individuals in the case groups that did not receive hyaluronidase, only one out of 7 patients had a good outcome without scarring. The lack of use of hyaluronidase seems to be in part due to the late presentation of the patients of 5 days post-operatively or more. At this stage tissue necrosis is most likely at an advanced stage and the prognosis is severely compromised (Beleznay et al., 2014; Sun et al., 2015). It can therefore be concluded the incidence of scarring and long term sequelae can be reduced when hyaluronidase is administered immediately or at the very least within two days of the procedure to improve outcome.

In their case report series investigating impending skin necrosis, Sun et al explored the use of Tanshinone and Papaverine alongside commonly used methods to improve vascular compromise (Sun et al., 2015). Tanshinone is a Chinese herbal remedy derived from *Salvia miltiorrhiza*, which has been used to treat a variety of cerebral and cardiovascular disorders. Tang et al investigated its effectiveness in reperfusion of cerebral ischaemia in rats, showing that it has a protective effect and improves cerebral blood flow in the animal model (Tang et al., 2014). However, its use in prevention of necrosis as a result of HA filler has only been documented in the study by Sun et al. Papaverine is an opium alkaloid antispasmodic and cerebral and coronary vasodilator (Fusi, Manetti, Durante, Sgaragli, & Saponara, 2016), and was presumably by Sun et al to improve perfusion of the ischaemic tissue. Unfortunately, as the variables have not been separated and all interventional methods including hyaluronidase, papaverine and tanshinone were all combined on the same subjects, it is difficult to ascertain whether the two novel interventions had any significant effect on the outcome for the patient. In the absence of data to the contrary, and given that the outcomes in the study by Beleznay et al were similarly good with complete resolution of the skin lesions without scarring, it must be assumed that tanshinone and papaverine did not significantly improve

outcome for the patients above and beyond what would have been obtained with the use of hyaluronidase and standard treatment methods alone (Beleznay et al., 2014; Sun et al., 2015).

In their single case report, Chen et al illustrated how over-aggressive management without implementing commonly used protocols for the management of vascular complications can lead to poor outcome. The patient presented moderately late, at 2 days, and instead of using hyaluronidase, massage or any vasodilating treatments, surgical decompression and suction drainage was performed. It is debateable whether this surgical intervention may have caused further tissue swelling, leading to exacerbation of the area of ischaemia. The outcome for the patient was extensive scarring to the nose and glabella. Chen et al considered, much to the patient's detriment, that the use of hyaluronidase at day two would not be of use. This is contrary to the results achieved by Beleznay et al where in the case of two individuals with a similar pattern of ischaemia at 2 days and 5 days, complete resolution was achieved with the use of hyaluronidase and a defined management protocol (Beleznay et al., 2014; Q. Chen et al., 2016).

In cases where ischaemia has led to necrosis of skin, the outcome can be positively influenced by appropriate wound management. Silicone dressings have been shown to improve healing of the necrotic tissue and wounds (Lansdown & Williams, 2007). Furthermore, where accessible, hyperbaric oxygen treatment can improve skin resolution. It is often used in graft healing after cancer or trauma surgery and for the treatment of nonhealing wounds by increasing endothelial cells, fibroblasts, keratinocyte migration and differentiation, but can pose an excess cost, risk and inconvenience (Grunebaum et al., 2009; Kassir et al., 2011). With small areas of necrosis it is thought that it poses no additional benefit. Indeed, the study by Sun et al failed to provide any concrete evidence that recovery was better than the straightforward protocol applied by Beleznay et al in terms of healing without scarring. Whilst it may supply some benefit as an adjunctive treatment, using hyperbaric oxygen as a first line treatment in the case reported by Chen et al showed worse outcome. It would certainly represent a significant financial involvement; low cost interventions including hyaluronidase, massage and aspirin have been shown to have more favourable outcomes which are more easily implementable (Beleznay et al., 2014; Q. Chen et al., 2016; Sun et al., 2015).

Vision loss / disturbance

Urokinase was administered to one patient in the case series by Park et al in order to achieve intra-arterial thrombolysis and reduce clot formation within the vessel walls (S. W. Park et al., 2012). In much the same way as when administered for the treatment of ischaemic strokes within the first few hours after the cardiovascular accident, it was hoped that reperfusion of the vessel would be achieved, leading to the patient regaining some or all of their sight (Wardlaw, Murray, Berge, & del Zoppo, 2014). However, there was no improvement in light perception and no improvement in sight for this patient, leading to the conclusion that urokinase was ineffective. Indeed, it would be unlikely to remedy a HA filler embolus as urokinase would not be able to degrade hyaluronic acid. In order to rule this intervention out fully, however, further interventions with intra-arterial thrombolysis would need to be documented.

Nicergoline was used by Kwon et al to manage a case of branch retinal artery occlusion and subsequent decreased sight resulting from HA filler treatment. Nicergoline was used in conjunction with aspirin, IV steroids and hyaluronidase for the skin lesion (Kwon et al., 2013). It is a drug that can decrease vascular resistance and has been used to treat cerebral infarction and acute and chronic peripheral circulation disorders, amongst others. It acts to promote cerebral metabolic activity, resulting in increased metabolism of glucose and oxygen, and is antithrombotic by inhibiting platelet phospholipase and interfering with platelet aggregation. The patient treated with the combination of steroids, aspirin and nicergoline showed improvement in sight and partial resolution of blepharoptosis and eyeball movement. Unfortunately, however, the European medicines agency have restricted the use of all ergot derivatives including nicergoline due to concerns about the safety profile of these drugs. Whilst the treatment combination may have been effective for this patient, a further larger case series would need to utilise this treatment; even if this proved successful the use of nicergoline would be restricted in the UK (Kwon et al., 2013; Saletu, Garg, & Shoeb, 2014).

Chen et al presented a case series in which treatment with nitroglycerin, digital massage, eye drops, aspirin and prednisolone was used. In one case, a patient showed an improvement in

best corrected visual acuity (BCVA). A second case in this series improved in sight from hand movement to “improved visual acuity”. It is not specified whether nitroglycerin was applied topically, as it is often with skin ischaemia, or systemically. Nitroglycerin relaxes vascular smooth muscle leading to vasodilation, which is thought to assist in reperfusion of the tissues affected by vascular compromise (Kukovetz, Holzmann, & Romanin, 1987). The role of aspirin is antiplatelet, whereas eye massage is thought to help dislodge the clot and prednisolone to reduce inflammation. Unfortunately, the improvement may also be a coincidence – the case was diagnosed as anterior ischaemic optic neuropathy, and therefore much less severe than full occlusion of the ophthalmic artery. For the second case, the data on diagnosis is missing and the outcome is rather vague, so conclusions about the effectiveness of the intervention cannot be drawn. The remaining cases in the same series by Chen et al that were treated with the same protocol after diagnosis with ophthalmic artery occlusion or central retinal artery occlusion showed no improvement in symptoms (Y. Chen et al., 2014). Indeed, considering the three cases of central retinal artery occlusion and three cases of ophthalmic artery occlusion from the studies considered, none of the interventions brought about an improvement.

An intervention best performed in a hospital setting by a specialist ophthalmologist, Park et al described the use of anterior chamber paracentesis to treat vision loss as a result of filler treatment (S. W. Park et al., 2012). Anterior chamber paracentesis has since been used in a study by Rajabi et al to alleviate central retinal artery occlusion in a patient who had undergone orbital tumour resection. However, in this study, the intervention was performed immediately, in addition to systemic mannitol and intravenous acetazolamide therapy, and partial resolution to 1m counting finger was achieved (Rajabi, Naderan, Mohammadi, & Rajabi, 2015). Chen et al were unable to achieve improvement for their patient who had vision loss as a result of dermal fillers. The difference between the two cases may be due to the time to treatment – Rajabi’s patient was treated immediately (indeed was already in a hospital setting), whereas Chen’s patient had a five-hour delay, but also due to the occluding material – filler versus blood clot. It is known that retinal ischaemia becomes irreversible after 90 minutes, so quick action on behalf of the referring practitioner may have improved the outcome. This is certainly a hospital-based procedure and not one that can be suggested for use in practice, but it may have scope yet.

Unfortunately, no interventions have been found that will reliably influence the outcome of visual disturbance as a result of HA (or any) filler treatment and can be used in practice. Even large centres such as those by Chen et al and Park et al have shown that the development and implementation is not related to funding, but simply because there does not currently seem to be a reliable remedy for filler-induced blindness (Y. Chen et al., 2014; S. W. Park et al., 2012).

Outcomes

In all cases considered, the exposure to the filler treatment preceded the vascular complication, and no other factors could have brought about the onset of symptoms. It is known that injection of filler can lead to vision loss or tissue ischaemia.

Out of 29 cases of skin ischaemia, 62% progressed to a full recovery. Considering the twelve cases of ocular complications, three cases (25%) showed slight improvement in sight from a state of decreased sight, but no cases returned to normal and no cases with vision loss showed any improvement. A case of loss of vision is therefore significantly more concerning for the patient's long term wellbeing.

Unfortunately, the three cases of decreased sight that showed improvement had a high number of variables including intervention and follow up and little documentation about the doses involved in treatment. Also, the vessels involved were smaller and the symptoms less severe (or simply unrecorded in one case), which could mean that the intervention had no effect or the body simply dealt with the occlusion.

There has been no reproducibility in the outcome of vision loss as a result of HA filler treatment. Therefore, rather than attempt to change guidelines to novel interventions that have been sparsely studied, it may be better to continue with existing interventions that are not considered harmful to the patient (but may also result in little benefit). Impending skin necrosis treatment on the other hand has been studied and adequate, reproducible

interventions have been performed and documented by Beleznyay et al and Sun et al especially. Parts of the study by Sun et al which consider novel herbal remedies should be further investigated for safety and efficacy (Beleznyay et al., 2014; Sun et al., 2015).

Beleznyay et al report five cases of HA filler induced vascular complication over a ten year span. Whilst the management resulted in adequate resolution for all of their cases, the author raises the following observations for this case series. The first is that the treating practitioners in this case series are extremely experienced and perform a very large number of dermal filler treatments, yet they appear to have a higher than average vascular complication rate, at 0.05%. This could be due to higher numbers of high risk procedures performed by this centre, although all of their cases were related to treatment of the nasolabial fold and not the site considered to be the highest risk (the nose). Given the experience of the practitioners in question, it is unlikely to be due to technique. This risk rate may be the actual “honest” risk rate for vascular complications; honesty in reporting is an issue that is a cause for concern in the aesthetic industry, and many suspect that the actual incidence of vascular complication is much higher than the 0.001% quoted by Cohen et al (Cohen et al., 2015). The author has certainly never heard of non-healthcare providers of aesthetic treatments coming clean willingly about their complications. A further observation about this case series is the time span over which the cases were reported. Technology in dermal fillers has come along significantly over the 10-year time period in which the cases considered by Beleznyay et al presented; unfortunately, the presentation of the cases along this time span is not recorded. Modern fillers may now perform better for the purpose for which they are intended, and as suggested by Inglefield et al, a factor in minimising complications is selecting the appropriate filler – with so many on the market, filler performance is improving.

The larger centre studies with multiple cases in this review demonstrated clearly defined outcomes, whereas the smaller studies included in the review are usually one-off case reports of adverse outcomes which were less reliable due to the small amount of data collected. None of the studies had comparison groups for the intervention. In order to arrive at reliable intervention strategies, further investigation with a larger amount of cases would need to be completed for vision loss as a result of HA filler treatment.

Practitioner status

Unfortunately, the studies that were considered did not give adequate insight into practitioners most at risk of causing vascular complications, as this was only documented in 9 out of the 41 cases included in the analysis, and in these the practitioners were medically qualified, i.e. surgeons or physicians. Indeed, no research has focused specifically on this. Chen et al briefly touched on the questionable licensing status of the performing practitioner in their study. However, in this study it became evident that even those with specialist medical training can prove ill-equipped to deal with the complication at hand. In this case it appears that whilst medically qualified, the surgeons were not trained to deal with filler complications. The patient was passed from one inadequate practitioner to the next, failing to implement simple protocols including hyaluronidase in favour of a surgical approach, resulting in a poor outcome for the patient

Especially in the UK, where Keogh described fillers as “a crisis waiting to happen” (Keogh et al., 2013), dermal filler treatment can be performed by anyone, whether medically trained or not. Non-medically qualified individuals often practice with no clinical support whatsoever, and indeed they may practice anywhere (Bruce & Jollie, 2014). Unfortunately, non-medical practitioners often do not feel bound by the same code of ethics that medical professionals must subscribe to, and clinical data on the outcomes of treatment by lesser licensed individuals may be difficult to achieve.

Evidence based guidelines for the prevention and management of vascular complications

Vascular complications involving HA fillers can result in permanent disfigurement. The following guidelines have been devised by assessing the relevant literature in relation to favourable outcomes. The author does not consider it reasonable to experiment with novel techniques in practice setting, and any interventions have been devised in line with techniques and treatments that have been demonstrated as effective.

Prevention protocols

Prevention strategies should be constantly referred to by the aesthetic practitioner. Table 3 outlines how simple measures can avert serious complications.

Table 3: Prevention protocols for vascular compromise

| Prevention strategies and in-treatment precautions for Vascular Complications | |
|---|--|
| Patient | <ul style="list-style-type: none"> • Detailed medical and psychological history • Aesthetic treatment history – previous rhinoplasties increase risk • Assessment of anatomical sites • Valid informed consent • Documentation of risks, benefits and discussions • Pre-operative photographs |
| Filler | <ul style="list-style-type: none"> • Viscosity / properties correct for treatment area • Reversibility with hyaluronidase |
| High Risk Areas | <ul style="list-style-type: none"> • Know your anatomy • Nasal ala: avoid if possible, extremely high risk • Nasolabial and nose: caution, relative risk |
| Technique | <ul style="list-style-type: none"> • Smallest possible needle size prevents excess product injection • Aspiration prior to injection to check for intra-vascular position • Retrograde injection • Low injection force – smaller syringes require less pressure • Smallest possible volumes • Stop and reassess if needle becomes blocked or injection requires higher pressure than anticipated • Cannula use decreases trauma to vessel, especially in nose • Placement of product at midline in nose, below musculoaponeurotic layer • Superficial injection technique in nasolabial fold • Compression of supply artery during procedure: upper nasolabial fold, side of nose, oral commissure, • Compression of anastomosis site during procedure: superior nasal corner |
| Pain | <ul style="list-style-type: none"> • Investigate pain that is disproportionate with treatment • Counsel patient to report pain • Sharp, sudden pain: query arterial occlusion • Dull, throbbing pain: query venous occlusion |
| Patient Observation and Aftercare | <ul style="list-style-type: none"> • Blanching or skin changes must be monitored to resolution • Counsel patient to report skin or sensory changes • Full post-operative instructions given verbally and written • Out of hours emergency number available to patients |

Management protocols

Unfortunately, few studies have been published that focus on the development of new or improved protocols rather than just reporting cases. Even with the cases examined in this review, high numbers of variables and low numbers of subjects make the development of any novel guidelines very difficult. Management protocols can be formulated from those cases that show favourable outcome, combined with historically effective interventions.

Loss of vision

This is likely to be a terrible day for both the patient and the practitioner.

Retinal necrosis becomes irreversible some 90 minutes after treatment and early recognition of the complication and rapid treatment induction is essential. The goal is to regain sight and reperfusion of the retina is central to this; all efforts must be central to this (S. Lazzeri et al., 2013).

Unfortunately, office based remedies that aesthetic practitioners are likely to have at their disposal prove to be largely fruitless if occlusion of the ocular vessels has occurred. It is impossible to remove the embolus as it is simply not accessible and hyaluronidase is not suitable for lysis of emboli in vessels (Kwon et al., 2013). Whilst hyaluronidase is recommended immediately, it will most likely only act on the area of ischaemia affecting the skin rather than remedy the loss of vision.

Reducing intraocular pressure is difficult in practice; eye massage, also known as eye-CPR, can be performed in order to attempt to dislodge the clot (Y. Chen et al., 2014). Any blade or needle incisions to reduce intraocular pressure should be left for consultant ophthalmologists. It is perhaps better to not attempt any heroic interventions in practice – practitioners should act within their competence and scope of practice and recognise the need for early referral. It is important to have an immediate referral pathway to an ophthalmologist or the nearest emergency room where treatment with IV

methylprednisolone 1g for 3 days, high dose oral prednisolone and aspirin 100mg per day can be started. This is however likely to simply reduce the accompanying effects on the skin (Y. J. Kim et al., 2011). The practitioner should accompany the patient and explain what has caused the vision loss and how this may have happened.

Table 4 outlines the limited possible treatment options available to practitioners in the practice setting.

Table 4: management of vision loss

| Management of vision loss | |
|----------------------------------|---|
| Identify the complication | Check for eye movement Check for decreased or loss of vision +/- pain |
| Immediate management | <ul style="list-style-type: none"> • Stop treatment • Hyaluronidase up to 1000U along injection site • Aspirin 2x 325mg • Eye-CPR to attempt to dislodge clot |
| Immediate Referral | <ul style="list-style-type: none"> • To A&E / Ophthalmology • Accompany patient and assist to explain how event occurred |

Impending necrosis of skin

When the vascular occlusion occurs, treatment should be swift and aggressive. Belezny et al produced effective and simple guidelines for treatment that can be used in aesthetic practice without being too costly or confusing for the practitioner (Belezny et al., 2014).

The protocol in table 5 and following algorithm in figure 2 is devised to enable a threefold approach to tissue recovery, including dissolution of the product, vasodilation and increased blood flow. The immediate application of heat with a warm compress will aid blood flow to the area. Whilst effective for vasodilation, the use of nitroglycerin (GTN) paste is controversial – it may cause orthostatic hypotension, potentiation of vasodilation with alcohol and other vasodilators such as sildenafil, and can cause rashes, dizziness and headaches (Cohen et al.,

2015; Glaich et al., 2006). Nevertheless, the risk of the likely outcome of necrosis and scarring is thought by many to be greater than the transient side effects from its application (Edwards, Wiholm, & Martinez, 1996).

Hyaluronidase reverses HA filler and should be used without delay to dissolve filler and decompress vessels. An allergy test is not thought to be necessary in an emergency situation. Figure 3 outlines the dilution and use of hyaluronidase when reconstituting 1500iU powder, such as Hyalase(Wockhardt) in the UK. Some authors, namely Cavallini et al, advocate the use of much higher doses in order to achieve dissolution and improve outcome (Cavallini et al., 2016).

Aspirin blocks platelet aggregation and is an anti-inflammatory. It should be given without delay. Adjunctive treatment may also consider the use of prednisolone to further reduce the inflammatory response. Other, less widely used interventions may include the use of the vasodilator sildenafil to further increase blood flow, or low molecular weight heparin in order to prevent thrombosis (Beleznay et al., 2014)

Where necrosis is large or wounds are exhibiting signs of healing by secondary intent, referral for hyperbaric oxygen treatment may be considered (DeLorenzi, 2013).

Similarly to the situation of vision loss, it is important for the practitioner to recognise when improvement is not being achieved. If the patient does not seem to be getting better within 30-60 minutes, it is advisable to follow the guidance in figure 2 and refer to an emergency room. The practitioner should accompany the patient to advise and assist instead of sending an anonymous referral. It is advisable to prior to such a situation occurring, practitioners explore their options for referral – preparation and communication with the nearest hospital prior to such a situation will alleviate significant stress in the real event.

Table 5: Management of skin ischaemia / necrosis

| Management of impending skin necrosis | |
|--|---|
| Identify the complication | <p>Check for warning signs!</p> <p>Blanching and pain: possible arterial occlusion</p> <p>Violaceous reticulated: possible venous occlusion</p> |
| <p>Immediate management</p> <p>Threefold approach: Dissolution Vasodilation Increased Blood flow</p> | <ul style="list-style-type: none"> • Stop treatment • warm compress • topical 2% nitroglycerin GTN paste or GTN patch • massage affected area firmly • hyaluronidase: injected deep dermal and subcutaneous along path of vessel and filler injection area • 2x 325mg aspirin • if no improvement in 60 minutes: repeat hyaluronidase and consider referral (see figure 2 below) • High flow oxygen • Consider oral prednisolone 20-40mg |
| Adjunctive treatment | <ul style="list-style-type: none"> • High flow oxygen • Consider oral prednisolone 20-40mg, 3-5 days • Consider sildenafil for vasodilation |
| 24 hours | <ul style="list-style-type: none"> • 75mg aspirin daily • review and reassure • continue prednisolone, if started |
| Day 1-7 | <ul style="list-style-type: none"> • 75mg aspirin daily • Apply GTN every day until resolved • Daily follow up appointment • Wound care if necrotic tissue and eschar formation • Continue prednisolone until day 5, if started |
| Wound care if necrosis | <ul style="list-style-type: none"> • Silicone dressing • Minimize bacterial contamination • Observe for secondary infection, treat if appropriate with topical or oral antibiotics • Consider Hyperbaric oxygen if slow healing or large necrosis (if accessible) |
| Day 7-14 | <ul style="list-style-type: none"> • Aspirin 75mg • Daily follow up until resolution (may take more than 2 weeks) |

Figure 2: Algorithm for the management skin ischaemia / necrosis

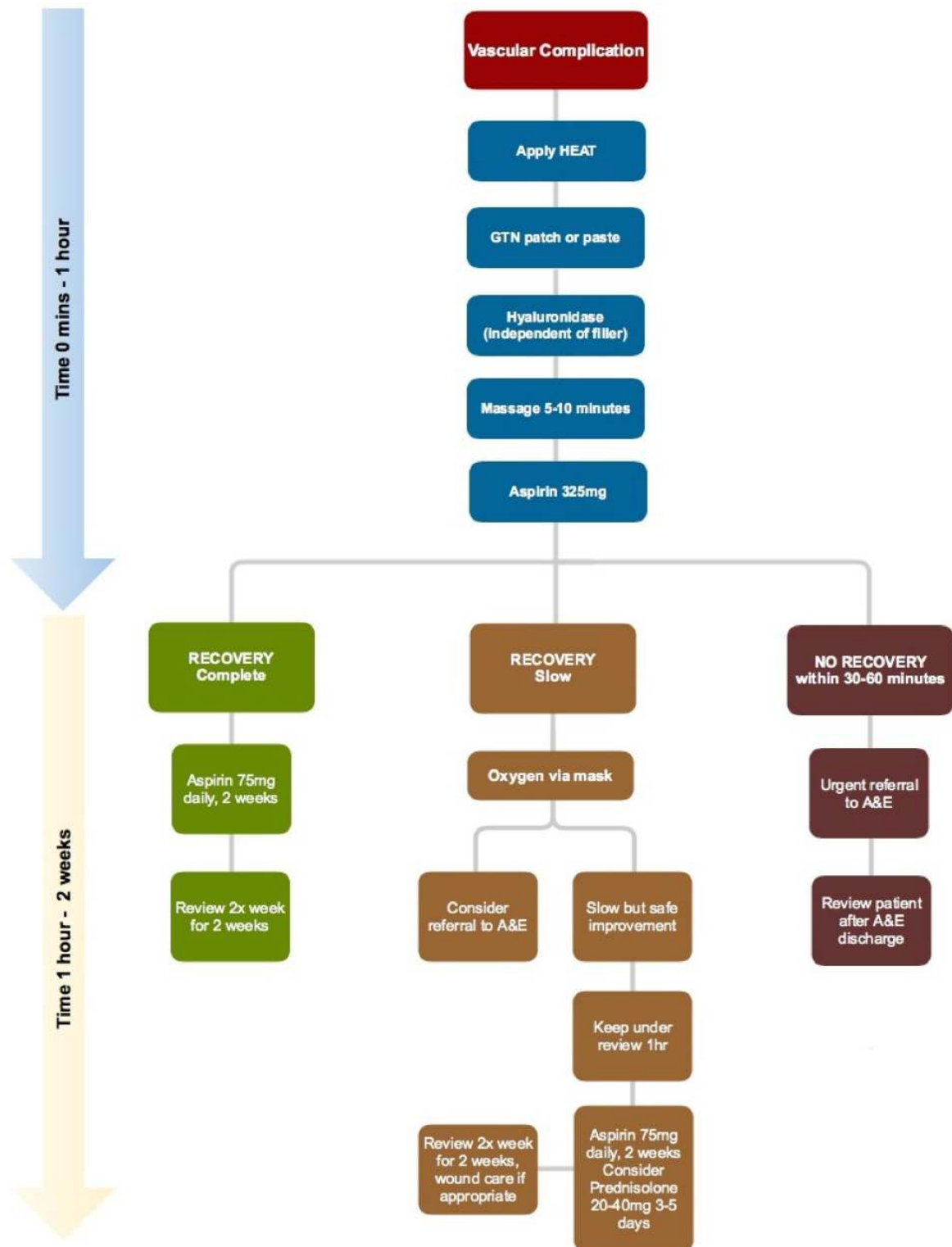
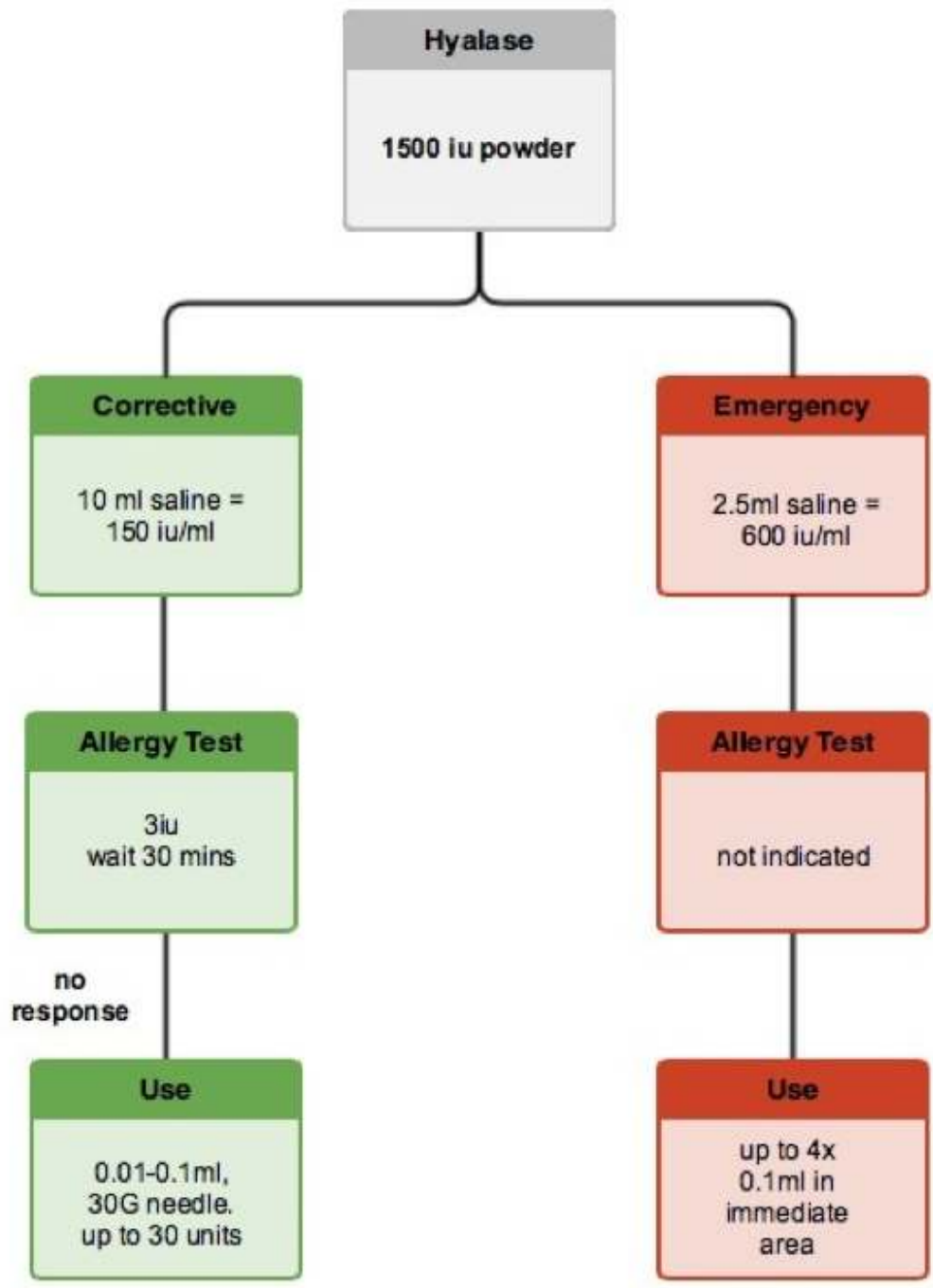


Figure 3: reconstitution and dosage of hyaluronidase (Hyalase / Wockhardt)



The Emergency kit

In order to manage a complication effectively, an emergency bag for vascular occlusion should be available in the practice, and suggested components are outlined in Table 6 below.

Table 6: Emergency Kit for vascular compromise

| Emergency Kit Bag for Vascular Compromise | |
|---|---------------------------------|
| Drug | Action |
| Hyaluronidase | Dissolution of HA filler |
| GTN paste | vasodilator |
| Aspirin | Anti-inflammatory, antiplatelet |
| Prednisolone 20mg tablets | Anti-inflammatory |
| Oxygen (sufficient for 15-20 minutes high flow, recommended CD cylinder size) | Improved tissue perfusion |
| Sildenafil (optional) | vasodilation |
| Antihistamines | In case of allergy |
| Adrenaline | In case of allergy |

Further studies suggested

Most of the studies recording vascular complications involve a very small sample of patients. The larger case numbers by Chen et al, Park et al, Sun et al and Beleznyay et al were mostly referral centres for dermal filler complications, whilst isolated centres document single case reports.

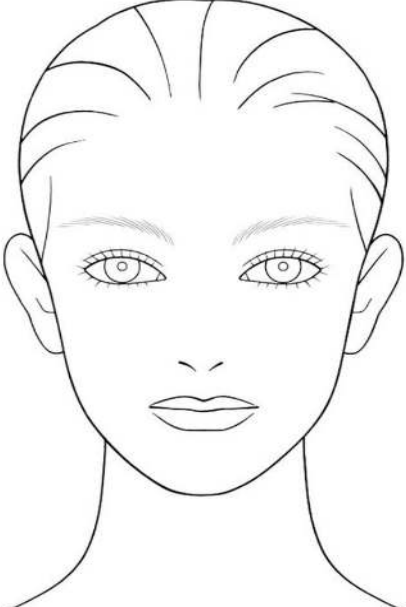
Unfortunately, all studies that have been analysed for this review have been conducted outside the UK and may not be an accurate representation of the protocols that UK-based practitioners are aware of. In addition to this, the UK has some of the laxest regulations governing the use of dermal fillers and many practitioners are completely unlicensed and have very little formal medical or any other training, making the risk rate in the UK potentially higher (Keogh et al., 2013). This makes gathering any useful information for study purposes extremely difficult.

In order for UK-based research into the prevention and management of vascular complications affecting vision and skin to be completed, the following are suggested:

1. A UK-wide dermal filler complications referral centre, consisting of a range of appropriately trained and experienced professionals from dental, medical and nursing backgrounds. A “centre” does not necessarily have to be one location, but more a body who will accept referrals, treat to a prescribed consistent guideline, share information, and from this information develop and enhance interventions for complications. Recommendations and guidelines could be formulated from this.
2. A UK-wide complications reporting method, which requires completion of a reporting card which can be sent to a data collection centre (this may be the referral centre). A similar system has been developed by the MHRA, known as the yellow card scheme, to report adverse reactions to medicines (MHRA, 2016). A structured form, such as the example developed by the author seen in figure 4, could be used to report the incident or refer the patient to the referral centre, should this be necessary. Detailed forms such as this would focus the referring practitioner to report the relevant data and assist in any onward treatment. Practitioners should be encouraged to report; the option of an anonymised form may improve practitioner compliance. Awareness

of such a scheme could be promoted by using organisations such as Safe Face, IHAS, cosmetic insurance providers and pharmaceutical companies. It does not, however, commit unscrupulous practitioners to reporting adverse events and the cooperation from non-healthcare practitioners should be encouraged at the point of product sale.

Figure 4: vascular complication reporting form

| Vascular Complication Reporting Form | | |
|--|--|--|
| About the Patient | | |
| Name (Only for treatment referral; anonymise if using this form to report data) | Age | Sex |
| About the treatment | | |
| Dermal Filler used | Batch Number | |
| Please use diagram below to detail injection sites and quantities | | Injection site |
|  | | Injection method (needle / cannula) |
| | | Injection volume |
| | | |
| About the complication | | |
| Symptoms | Diagnosis | |
| Time to symptoms / presentation | Treatment already administered and outcome | |
| About the practitioner | | |
| Name | | |
| Profession / Qualification | | |
| Referrals for treatment: send patient with form, accompany where possible Referrals for data collection: omit names of practitioner and patient | | |

Conclusions

It is time to face the real issue: filler blindness in the UK is not a matter of *if* but *when*. Cases of skin necrosis are already increasing in incidence. Practitioners must do better in order to prevent a devastating outcome for the patient.

As aesthetic medicine advances, so does the complexity of treatments; filler rhinoplasties are not only blurring the line between surgical and non-surgical, but are fast becoming the most dangerous procedure in the midface, an already high risk area.

The author has recognised significant shortcomings in approaches to vascular complication management in the aesthetic practice as a result of this review. Progress is slow, with little useful input since the development of the first protocol by Hirsch et al in 2007 (Hirsch et al., 2007). Nevertheless, effective protocols for the management of impending necrosis have been developed, and further documented in this review. Early intervention within two days of the event with use of hyaluronidase is a proven way to reduce the long term sequelae for the patient. The treatment of vision loss as a result of filler, however, is a proverbial stab in the dark. There are no proven and effective methods to combat filler blindness that can be effectively used in the aesthetic practice setting. The prognosis is often hopeless and there appear to be no remedies for this on the horizon as novel concepts have not been proven enough to integrate into practice. Hospital interventions are equally untested, and the onus is on the referring practitioner to convey the patient to an appropriately qualified ophthalmologist with the right experience before irreversible ocular damage sets in. Recognising the complication early is therefore a central pillar to management.

Guidelines have largely been developed in a responsive fashion, with the increasing number of dermal filler casualties prompting a move towards development of prevention protocols. Hyaluronic acid filler may be reversible, but it is still dangerous, and practitioners should do everything in their power to mitigate the risk to the patient.

The state of UK legislation is a matter of concern. Practitioners embark on treatment with little or no formal training, and due to lax laws surrounding the use of dermal fillers non-

healthcare providers with little accountability are a further risk to patients in an already potentially dangerous field. Ignorance is bliss, and many practitioners attempt treatments that are simply outside of their competencies and without proper prevention or management strategies in place. It is for this reason that the evidence based guidelines and charts in this review were devised as simple, easy to understand protocols to use in aesthetic practice.

As we embrace aesthetic treatments in the field of medicine, we must be prepared to encounter the vascular complications that will undoubtedly come with it. A UK-wide support or referral system would serve as an effective help for the patients who are most at need, whilst providing data for the development of strategies to improve outcome for those affected by vascular events.

There is a difficult road ahead with the true incidence of vascular complications unknown but undoubtedly rising. It is hoped that this review will clarify and facilitate their treatment, and take away some of the stress and anguish felt by practitioner and patient by providing structure and guidance in a time of chaos.

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