Special Topic

New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events

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Abstract

The purpose of this article is to update the changes to the author's protocols used to manage acute filler related vascular events from those previously published in this journal. For lack of a better term, this new protocol has been called the High Dose Pulsed Hyaluronidase (HDPH) protocol for vascular embolic events with hyaluronic acid (HA) fillers. The initial protocol used involved many different modalities of treatment. The current protocol is exceedingly simple and involves solely the use of hyaluronidase in repeated high doses. Despite the simplicity of the treatment, it has proven itself to be very successful over the past two years of clinical use. There has been no partial or complete skin loss associated with this protocol since its implementation if the protocol was implemented within 2 days of the ischemic event onset. The protocol involves diagnosis and repeated administration of relatively high doses hyaluronidase (HYAL) into the ischemic tissue repeated hourly until resolution (as detected clinically through capillary refill, skin color, and absence of pain). The dosage of HYAL varies as the amount of ischemic tissue, consistent with the new underlying hypothesis that we must flood the occluded vessels with a sufficient concentration of HYAL for a sufficient period of time in order to dissolve the HA obstruction to the point where the products of hydrolysis can pass through the capillary beds. Although vascular embolic events are rare, it is important to note that the face has higher risk and lower risk areas for filler treatment, but there are no "zero risk" areas with respect to filler treatments. Even with good anatomic knowledge and correct technique, there is still some nonzero risk of vascular embolic events (including highly skilled, experienced injectors). However, with careful low pressure, low volume injection technique, and adequate preparation for treatment of acute vascular events, the risk is quite manageable and the vast majority of adverse events are very treatable with an excellent prognosis, with a few exceptions. This new protocol offers excellent results, but requires further research to determine optimal parameters for various HA fillers.

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ESSENTIAL CONCEPTS REGARDING RESOLUTION OF FILLER-RELATED VASCULAR ADVERSE EVENTS

This article summarizes a new approach to the management of acute accidental intravascular embolism with hyaluronic acid (HA) fillers. As with the former protocol previously published,[1] avoidance of complications is still the best strategy (Table 1). The old protocol involved a daily single treatment with hyaluronidase (HYAL) of 450 to 600 iu, as well as other modalities of treatment such as nitropaste, hyperbaric oxygen etc. In contrast, the new protocol involves HYAL dosing based on the volume of ischemic tissue, with hourly repeated dosing to maintain high concentrations of HYAL throughout the ischemic zone. Treatment is based on the clinical determination of the approximate surface area of ischemic tissue (as determined clinically by observation of

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Table 1. New Versus Traditional Treatment

	New	Traditional
Avoidance	Yes	Yes
Treatment timing	Immediate	Immediate
HYAL dosing strategy	Variable, based on volume of tissue affected	Fixed dose
Dose interval	Hourly	Daily
Ancillary Tx	None	Multipronged, vasodilators, NTP, hyperbaric 02, etc.
Outcomes	Excellent – complete resolution	Occasional partial treatment failures, scabbing, crusting, mild scarring, mild textural changes in the skin

NTP, nitropaste; Tx, treatments.

skin color and capillary refill), with larger doses of HYAL used for larger areas of involvement. This report is based on the author's clinical experience as a consulting physician with several dozen cases in the past two years using this new high dose protocol, in comparison to clinical experience in over 50 cases with previous protocols.

The author assumes that the pathology of filler related ischemia is due to arterial embolism of filler that typically occurs immediately at the time of filler treatment, and that the solution is to flood the tissues containing the obstructed vessels with HYAL in sufficient concentration for a sufficient length of time to relieve the HA obstruction. Rarely, the clinical history is that the patient was completely normal at the termination of treatment, and that signs of ischemia started at some time (typically hours) later. This phenomenon of "delayed onset" is discussed further below. The natural history of vascular embolic events (ie, untreated) progresses from momentary blanching (which may only last a few seconds), through livedo reticularis (up to a few days), to blisters (day 3), crusting, necrosis, slough, and finally healing by secondary intention – a process that may take six weeks or more. If untreated, it takes approximately 3 days before blisters appear on the skin (this seems to be a relatively consistent finding), and frank necrosis may not be evident for several days thereafter (typically after day 6), but the signs of ischemia are generally present right from the very beginning if you look for them. With appropriate treatment with the new High Dose Pulsed HYAL (HDPH) protocol, we typically see complete reversal of all the signs of ischemia and complete return to normal. Thus, instead of 6 weeks or more of slow healing by secondary intention, we see complete resolution with no signs of secondary problems within 3 days of the event, with patients typically suffering no more than a few bruises and so called "injection site reactions" (the normal sequelae of repeated needle injections). Diagnosis is completely clinical in nature. It involves examination of the skin, noting its color and in particular its capillary refill time. Typical cases of vascular obstruction may show some blanching, but this is often missed, since it is only momentary. A mottled skin appearance, termed livedo reticularis, is almost always apparent (except in cases of severe bruising). Capillary refill time is noted to be very slow. Using the finger holes of an instrument (such as the non business end of a pair of suture scissors, for example) help to assess the capillary refill (Figure 1).

The first major breakthrough in the treatment of vascular adverse events (AE), was the administration of HYAL (the author believes that the ancillary treatments such as nitropaste etc. probably did not contribute very much to the final outcome). With the old protocol, the author occasionally saw some blistering, crusting, and eventually some mild scarring, mild to moderate dyschromia (particularly in patients of color) despite treatment with HYAL. These occasional problems seemed particularly worse if more regions of the face had been originally involved in the vascular AE (eg, ischemia of the ipsilateral upper and lower lip, nose, and glabella) compared to single site (lip ischemia alone). This suggested to the author that perhaps we were not using enough HYAL in at least some of these patients (otherwise, why did some patients heal completely, while others had crusting and scars, dyschromia, etc?). This lead to the "*HYAL flooding hypothesis*" (further discussed below), namely that HA filler obstructed arteries needed to be bathed in high concentrations of HYAL for long enough periods of time to dissolve the filler. This concept is illustrated in Figure 2, showing that the recommended dosage of HYAL increases stepwise with the numbers of anatomical areas involved. If more parts of the face are involved with ischemia, then larger doses of HYAL will be needed to treat that individual. *We use ischemic surface area as a proxy for tissue volume* (not the volume of intravascular filler – the amount of filler within the intravascular space is essentially irrelevant, and not clinically observable at the bedside). *We can assume that all the arteries in the ischemic areas of the face are completely filled with HA filler.* In order to obtain a sufficient concentration of HYAL (ie, mg/cc^3) a larger volume of tissue (the denominator) means that a larger amount of HYAL is required.

This makes it easy for clinicians to remember that stepwise larger HYAL doses are used for stepwise larger numbers of ischemic areas. No prior knowledge of the amount of intravascular filler is required since we can assume that all the arteries are filled with HA in the ischemic zones. Only the clinical assessment of the number of ischemic regions (as a proxy for the volume of tissue we are to treat) alone is used to determine the HYAL dose, since all of these ischemic areas of the face will be injected with HYAL. In these cases of vascular AE, we never really know exactly where the embolic filler is located. We cannot see it; we can only see the ischemic skin involved. In the most basic terms possible, if you observe more ischemic skin

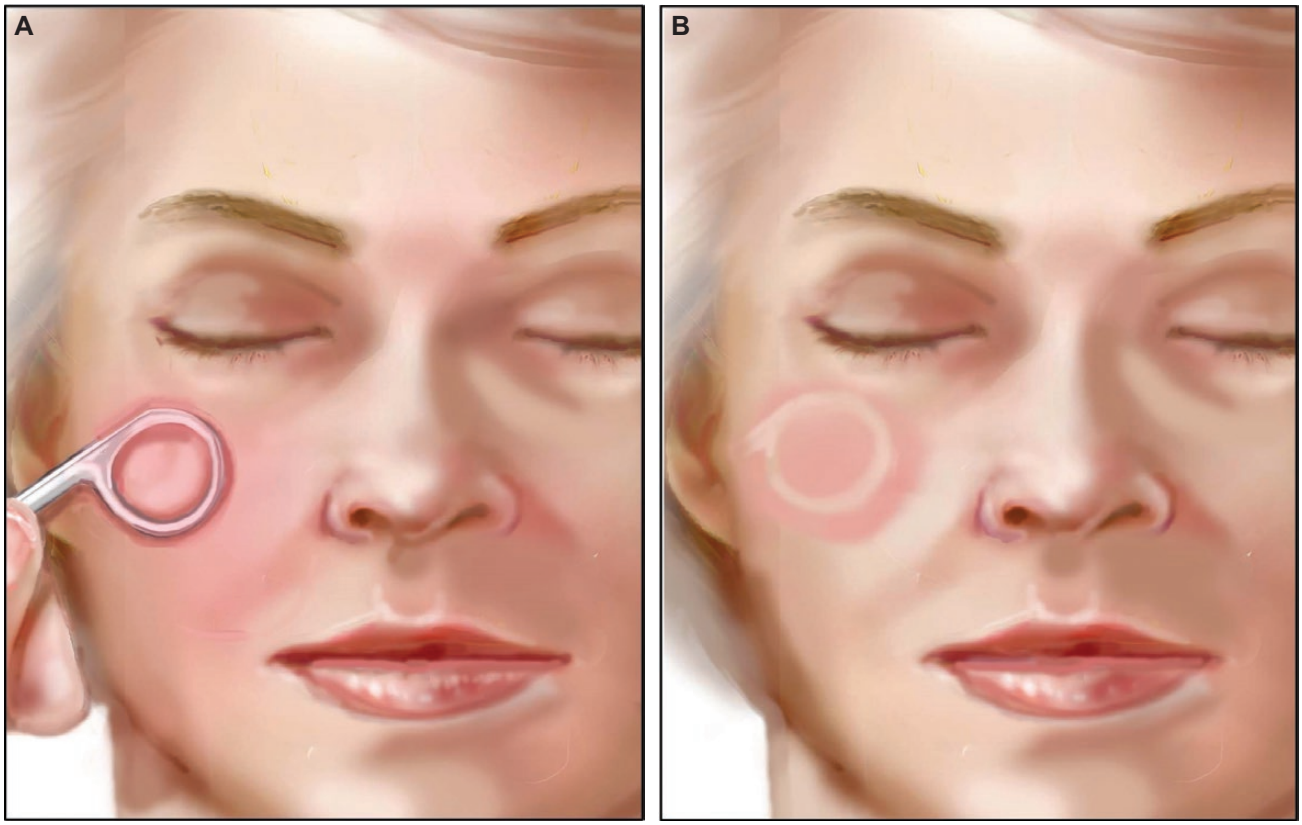

Figure 1. (A) When determining the status of the skin's capillary refill time, it is helpful to use and instrument to compress the skin. Patterns that are not typical in nature are more easily discernible. (B) The objective of this clinical test is to compare the refill time of the zone in question to normal skin either adjacent or on the contralateral side.

(on the face), you will need more international units of HYAL to inject into these areas of the face, because there is a larger volume of ischemic flesh involved. We need to reach a minimum concentration of HYAL in that ischemic tissue (that can then diffuse into obstructed arteries, and break down the filler). Thus, more ischemic skin means larger doses of HYAL.

ANALYSIS OF HDPH PROTOCOL

The newest protocol for the treatment of filler embolism involves several important changes. First came the realization that HYAL was the critical factor in treatment. None of the ancillary treatments previously recommended (topical nitropaste, hyperbaric oxygen, etc.) are used at all any more, except for one baby aspirin per day for seven days (ASA is given to reduce platelet activity, but direct evidence for its benefit is lacking in this situation). The author has not recommended or used any of the ancillary treatments for over 2 years now. With experience came the second important observation that dosing should depend on the *quantity of tissues adversely affected* (ie, one dose does not fit all). This is based upon the assumption that HYAL has to be used in quantities sufficient to bathe the obstructed vessels in a concentration sufficient to hydrolyse the filler causing the obstruction. A vessel that can no longer transport fresh blood because it is blocked by HA must be bathed (flooded) by a sufficient concentration of HYAL to diffuse across the arterial wall and then break down the HA to metabolic products small enough to pass through the capillary system. We cannot possibly know where the obstructed vessels are within the block of ischemic tissue. We must assume that all the vessels within the zone of ischemia are obstructed, and treatment must involve flooding the entire zone with sufficient HYAL concentration to promote complete hydrolysis of the HA filler (which, again, could be anywhere within the ischemic zone's arterial system). With this view, partial breakdown of HA is insufficient, because partial breakdown products can still obstruct blood flow (although they may be pushed further downstream by arterial pressure). Thus when we are advising "HYAL flooding" what we mean to say is that we want to ensure that the obstructed vessels are soaking in a sufficient concentration of the enzyme to promote complete hydrolysis of the HA within the vessels. We assume that partial

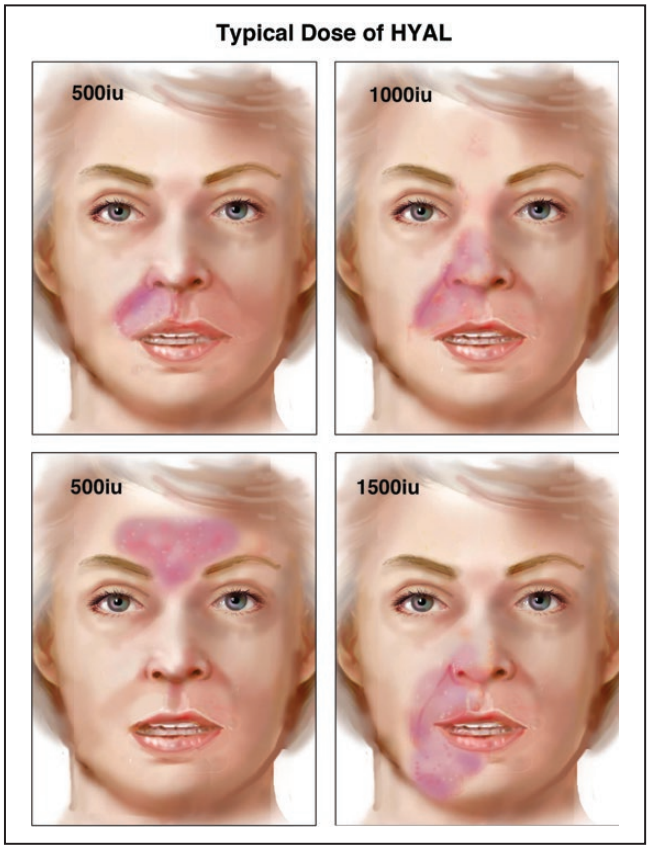

Figure 2. Some common patterns of injury, and the typical doses used by the author for each. HYAL is injected into the ischemic tissues and gentle massage is then used to maximize the contact time between the ischemic tissues and HYAL. The tissues may be edematous, but gentle massage following injection of HYAL will tend to decrease this. Massage is important to help maximize contact between HYAL and the filler causing the obstruction.

hydrolysis is insufficient. The author also suggests that partial breakdown may result in further obstruction downstream. In fact, in this view, partial breakdown may result in new areas of ischemia (or at least, a zone of injury of a different shape than at presentation, as is sometimes seen), as these breakdown products may be carried downstream past areas where collateral vessels are bypassing the initial obstruction. In fact, this is the mechanism by which we posit that the phenomenon of "delayed onset" ischemia occurs, when dilution or blood pressure moves an embolus further downstream. A vessel containing an embolus of filler might not be yet causing ischemia, since collaterals may initially be completely by-passing the obstruction. As the filler makes its way downstream, it may then block the collaterals and then manifest the ischemia.

Clinical assessment of the patient must be ongoing and persistent. The goal of treatment is complete dissolution of the offending filler obstruction. To accomplish this, there must be sufficient concentration of HYAL in the right location long enough to result in (sufficiently) complete hydrolysis (Figure 3). The number of qualifications specified here are intentional, since a deficiency in any one of these elements is a recipe for failure to achieve the stated goal of complete resolution of the obstruction. In vitro, the response time for hydrolysis depends on the actual filler being tested. Let's assume that a filler will take, roughly speaking, a few hours to break down, since the HYAL has to diffuse across the intact arterial wall and hydrolyse the filler. (Crosslinked fillers will take longer times to degrade with HYAL, whereas in contrast, in the author's in vitro testing, non-crosslinked HA was hydrolyzed almost instantaneously, with complete liquefaction within just a few seconds of direct contact). It is known that HYAL itself is actively metabolized by the human body, so it is being deactivated at some rate as soon as it is injected. As swelling fluid accumulates from leaky capillaries in the ischemic environment, the HYAL is also being diluted. Finally, we know that as HYAL degrades the ground substance, it begins to diffuse away from the original injection site. Thus we can see that the amount of HYAL we originally injected into a region will be partially deactivated (by natural anti-HYAL agents), diluted by swelling fluids, and will physically diffuse away from the region where we want to maintain a high concentration. These three factors all act to reduce HYAL action, and the author suggests that these are reasons that we should act to top up the HYAL on a frequent basis to maintain the desired high concentration (Figure 4). The frequency of this topping up has to be determined in laboratory studies, but for now, the author has been using an hourly dosing schedule. This seems clinically to be safe and effective, but it may be overdoing it and dose ranging studies in a validated model are needed.

The remaining objections to this kind of treatment involve nebulous concerns about destruction of naturally occurring HA in the tissues, with the stated fear that we will cause a permanent deficiency of HA, despite the fact that this is not seen in actual clinical cases, with perhaps two notable exceptions. First, if ischemia is allowed to persist for a period of time such that cell death occurs (fat cells in particular), then permanent tissue deficiency is to be expected (in other words, under-treatment will likely cause permanent subdermal fat atrophy and secondary skin changes). The second example is under treatment of infection, especially clinical abscess. These are the only times that the author sees permanent deficiency of tissues, ie, under-treatment or delayed treatment of ischemia, or when chronic infection with abscess has been mismanaged. When an abscess has been allowed to fester for periods of time without incision and drainage, the resulting inflammation has resulted in sub dermal fat

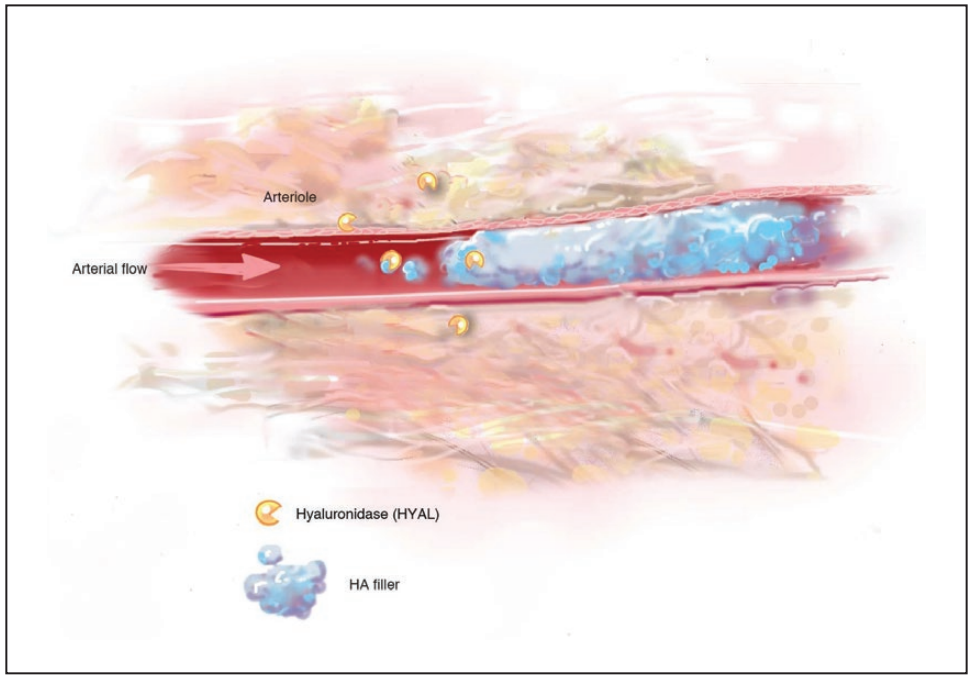

Figure 3. Hyaluronidase diffuses through the arterial wall at some concentration dependent rate. Low concentrations are far less effective clinically. It seems probable that high concentrations of HYAL can result in higher intra-arterial concentrations, and therefore more efficient HA hydrolysis.

atrophy, presumably because of the white cell "regurgitation on feeding" phenomenon, where fat cells as innocent bystanders are killed accidentally. If the abscess had been promptly diagnosed and treated with incision and drainage (if any remaining reservoir of the invading organism removed from the tissues) the tissue deficit would have never occurred in the first place. In these situations, we do in fact see permanent tissue deficiency unfairly blamed on HYAL, when in actuality the blame lies squarely on the shoulders of the inadequacies of the clinical treatment. HYAL does not seem to cause permanent atrophy of the tissues. HYAL does break down natural HA, there is no doubt about this fact. However, tissues are naturally resilient and promptly restore the natural balance of HA within a short period of time (typically a few days). Thus the two undisputed causes of permanent tissue deficiency are both iatrogenic in nature and involve conservative management, NOT aggressive management.

Consider a vessel filled with HA filler, with all blood flow obstructed. The tissues are ischemic, and products of metabolism are building up in the tissues, and acidosis begins. Pain starts only when the included lidocaine is metabolized. Let us begin treatment with a dose of HYAL. Some of the HA is broken down into smaller pieces, but the pieces are still too large to pass through the capillaries, which as you recall are on the order of 5 to 10 microns (recall how erythrocytes have to deform to pass through the narrowest capillaries). As time progresses, the HYAL is diluted with serum leaking from the capillaries, reducing its effectiveness. Further, the HYAL diffuses away from the sites of high concentration towards lower concentrations. At the same time, there is of course active deactivation of HYAL by naturally occurring anti-HYAL enzymes. Thus, by dilution, diffusion, and deactivation, HYAL activity is gradually reduced (Figure 4). Meanwhile, the huge molecules of HA have been broken down to slightly smaller particles, and there may be some shifting of the obstruction further downstream, and the zone of ischemia may actually change somewhat. However, when the concentration of HYAL drops below a critical level, and further HA degradation occurs only at the much lower rate of natural breakdown, and the obstruction stabilizes once again (until more HYAL is injected). We do know that it takes a couple of hours to break down some modern HA fillers to a point where they may pass through the capillary beds, if, and only if, the concentration of HYAL is sufficient (this probably varies somewhat from filler to filler, and this is yet another area ripe for research). It is imperative that HYAL be refreshed in the system to maintain a higher rate of degradation if we want the obstruction to be relieved in a timely fashion. Thus we need to keep adding more HYAL to the zone of ischemia to keep the HA degradation on track to restore normal blood flow in the zone of ischemia. Typical hourly doses of HYAL used for various sized ischemic injuries are shown in Figure 2. In a way, it's like trying to fill up

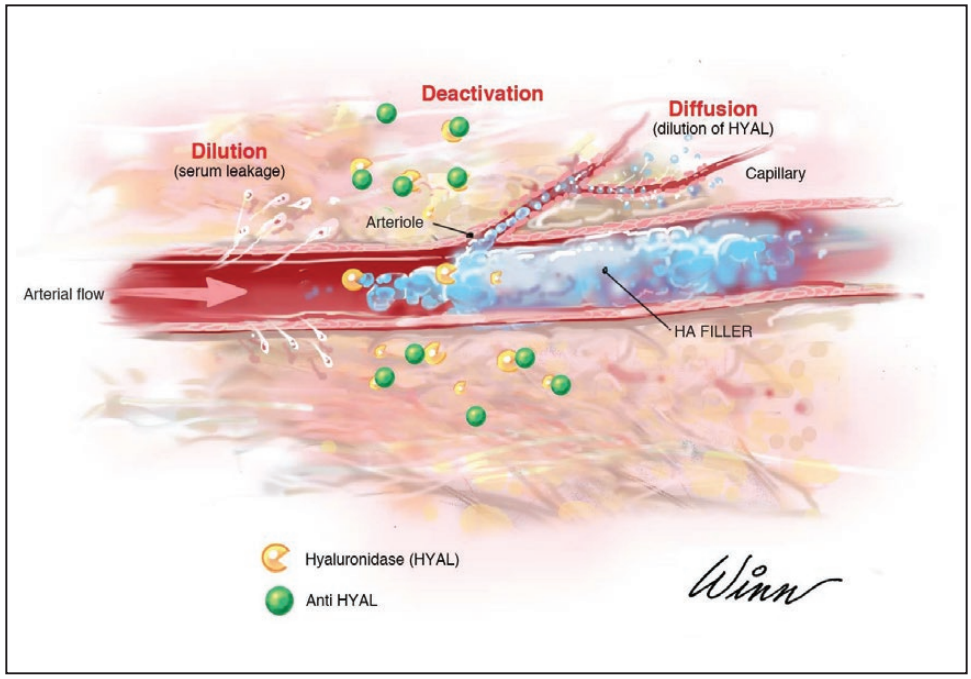

Figure 4. As soon as HYAL in injected into the tissues, its concentration is decreasing through several concurrent processes. Serum is leaking out into the ischemic tissues, diluting the HYAL, as tissue anti-hyaluronidase agents start breaking down the enzyme. Simultaneously, diffusion occurs, reducing the local concentration.

a leaky container, since we need to keep topping up the HYAL in the system as it is simultaneously being reduced by dilution, diffusion, and deactivation.

LOW VOLUME EVENTS (LVE) VERSUS HIGH VOLUME EVENTS (HVE)

The author defines low volume embolic events (LVE) as emboli consisting of 0.1 mL of HA filler or less. These are by far the most common types of accidental intravascular events actually encountered in the field with experienced injectors. High volume vascular embolic events (HVE) consist of emboli of more than 0.1 mL. HVE are more commonly associated with worse prognoses and injuries to multiple systems, such as loss of vision, loss of hearing, or even stroke. The author's experience with HVE is limited, since most of the physicians are aware of embolic events in Canada and thus practice to a higher degree of clinical safety. However, occasionally one encounters a HVE when a half cc or more has been injected as a bolus directly into an artery. In the laboratory, under direct vision in cadavers, is not a realistic reproduction of the phenomenon in the living patient. We can typically see the filler agent filling the distal vessel first, then we can see the filler flow retrograde into the larger proximal vessel and then start to fill the proximal branches. In the living patient, there would be an arterial pressure gradient that would alter the path of filler flow. In cadavers, the speed and pressure used for injection does not materially affect the flow pattern, but one can reasonably assume that in the living patient that arterial pressure would affect the flow of the filler within the arterial system (the author unsuccessfully tried to reproduce constant artificial blood pressure with an indwelling intra-arterial catheter and an IV bag held at an appropriate height above the specimen). This is why "low and slow" with a small bolus is the preferred technique. There is much work to be done regarding the physiology of these events, but there are of course modern sensibilities regarding live animal experimental studies in the modern world and getting approval for these types of necessary studies is proving more difficult for scientists today. Larger volumes of emboli could be expected a priori to be more difficult to treat, and in fact they are. A larger volume of filler requires a longer period of hydrolysis, and maintaining a high enough concentration of HYAL for a long enough period of time throughout a larger volume of tissue presents greater challenges. In the central face, particularly the nose and glabella, where the average intra-arterial volume of the supraorbital, supratrochlear, and dorsal nasal vessels approaches 0.1 mL, it becomes apparent that a large bolus of HVE could easily fill the named vessels as well as the proximal ophthalmic artery as well as the even more proximal intracranial arteries. In the temple region, there have been incidents involving the anterior branch of the superficial temporal artery, flowing back to the middle cerebral, for example, then affecting hearing as well as causing embolic stroke. When reviewing these cases, it

is clear that avoidance strategies are paramount, since the retina and the brain are markedly oxygen dependent, and there is only a limited period of time to reverse the obstruction before the ischemic injury is nonreversible.

INTRA-ARTERIAL HYAL VERSUS EXTERNALLY APPLIED HYAL

HVE involve large bolus injections into the arterial system, and these typically require more vigorous treatment with HYAL because the zone of ischemia is larger, and dissolving the embolus takes longer. There is also the question regarding intra-arterial injection of HYAL, as opposed to the current strategy of simply bathing the external surface of the obstructed vessels with HYAL. With an arterial obstruction, as when clot busting drugs are used in intra-arterial treatments, there is the problem of maintaining the concentration of the drug where it is most needed. If the obstruction is complete, there is no flow past or through the obstruction, thus injecting HYAL into an occluded artery causes the HYAL to flow proximal to the obstruction. HYAL does work on the obstruction, but only at the site where it is exposed in the lumen of the vessel. In contrast, when flooding the entire zone of obstruction, the HYAL seems to break down the HA filler all along the vessel pathway, affecting the entire embolus at once. This hypothesis has not been tested however, and it remains to be proven whether external application of HYAL to the outside of a vessel is more or less effective than intra-arterial application of HYAL. Certainly for ease of use, external application of HYAL is very simple and appears to be safe and effective treatment, but there have been sporadic case reports at international meetings of treatment failures reversed with intra-arterial application of HYAL. This involves either a cut down procedure (to cannulate an artery) or super-selective angiography procedures that are not typically available except in tertiary care centers. For the time being, until evidence shows otherwise, external application by simply injecting HYAL into the affected areas and flooding the affected vessels through indirect diffusion appears to be a safe and effective solution in most cases. Clinical experience over that past few years has shown that the use of indirect soft tissue injection of HYAL alone without *any* ancillary treatments (ie, no nitropaste or hyperbaric oxygen etc.) has provided excellent results, superior to the previous protocol[1] recommended.

TIME OF ONSET

Embolism probably most often happens contemporaneously with filler treatment, except in rare cases. There are some cases that report no evidence of problems at the end of treatment, but obvious signs of ischemia a few hours later. The author believes delay of onset of ischemia is rare, and at least some cases are likely due to perceptual blindness – ie, the injector simply is concentrating on the goals of symmetry, aesthetics, balance, and so on, and missing the signs of vascular ischemia.[2] On occasion though, the author has heard of cases where the practitioner is adamant that the patient was completely fine at the end of treatment (ie, when the physician was actively assessing the patient for ischemia), only to discover rather obvious ischemia a few hours later. In these uncommon situations, the author hypothesizes that filler may be trapped in a vessel, perhaps at a bifurcation or branch point, with NO signs of distal ischemia because collateral vessels bypass the obstruction. At some point, this globule of filler may become dislodged by whatever mechanism, and then pass downstream to the precapillary arterioles, thus causing tissue ischemia. Despite the obvious violation of Occam's Razor (where the simplest solution is usually correct), this two step process may turn out to have some validity in rare cases, but once again this is purely conjecture and the author has absolutely no hard evidence. In the typical event, the simple truth appears to be that the material seems to flow downstream within the arteries until it is constrained by size and can pass no further. It then simply blocks one or more arterial blood vessels, recalling that vessels can back fill towards a branch point by retrograde flow, and the filler can thus also obstruct nearby branches or even be passed towards a more distal zone through a main branch of a vessel. The zone of ischemia may be large or small sized depending on the amount of intravascular filler injected, and the relative importance of the specific blood vessel to the tissues in question. One could think of the vascular system as analogous to an Interstate highway system, where all points are connected, and it is quite possible to reach a distant exit ramp from any particular on ramp.

MECHANISM OF INJECTION: HOW DOES FILLER GET INTO THE ARTERY?

It may be that most of these events are a result of direct intra-arterial injection, with the opening of the needle or cannula directly within the lumen of the vessel. Clearly, aspiration before injection might provide good feedback if bright red blood is seen, but a negative result may be misleading.[3] In areas of scarred tissues, as from previous trauma, or even from a long series of former filler treatments, some special considerations may come into play. As a needle or cannula is passed into the tissues, this may create an artificial pathway for the filler to flow. In fact, this is a technique used called pre-tunneling, where

a needle or cannula is passed through the tissues, and the filler is slowly injected upon withdrawal. If the tissues are scarred, then the needle track acts as a conduit for filler to flow through (Figure 5). A possible mechanism for embolism becomes apparent. If a vessel is penetrated by a needle or cannula, even if the filler is deposited at some distance beyond the vessel, the filler may back track along the needle pathway and then enter directly into the vessel, following a pathway of least resistance.

There were three competing hypotheses (Table 2) regarding the pathophysiology relating to ischemia. Vascular compression relates to the idea that high pressures adjacent to an artery can compress it, analogous to stepping on a garden hose while watering your flowers. Vascular spasm relates to tightening of the muscle layers in blood vessel walls in response to a chemical stimuli (eg, cocaine, tobacco products; note that vascular spasm is known to result in skin loss in susceptible patients in response to low temperatures, mechanical irritation, or inflammatory vasculopathies). Generally, the chemicals or drugs which can cause significant vascular spasm are noxious, and HA is anything but noxious (in fact, HA was selected in large part because it is rather innocuous and unlikely to irritate tissues). Mechanical irritation or stimulation of a blood vessel can sometimes cause it to spasm, but that is usually a temporary condition, and only in certain exceptional circumstances (eg, surgical replantation) is this an important mechanism in the otherwise healthy typical filler patient. That we are dealing with an acute vascular embolic event as has several lines of evidence supporting it. First, we know that in the lab in animals, several centers have not been able to get vascular insufficiency by external compression.[4,5] Second, the most direct evidence is seen when looking at the histopathology from affected ischemic tissue where we can see the filler in the lumen of the arteries in the tissues.[6] Thus we have some direct histological evidence (filler in the vessels) as well as indirect evidence (being unable to reproduce the phenomenon in the lab in animal models) and in addition we have extensive indirect evidence with respect to tissue expander experience. Thus we have quite a bit of evidence for the vascular embolism of filler material, and almost no evidence for vascular spasm or external vascular compression. The author does not believe that the other mechanisms have any significant role in the pathology (except in the rarest of circumstances), and that when ischemia is seen in relationship to an HA filler treatment, then it should be assumed that there has been an intra-arterial obstruction, and restoring circulation by dissolving it with HYAL should be the immediate goal of treatment. Where the filler ends up will depend on several factors including but not limited to the volume of the filler, the pressure of injection, the type (cohesivity) of filler, the patient's

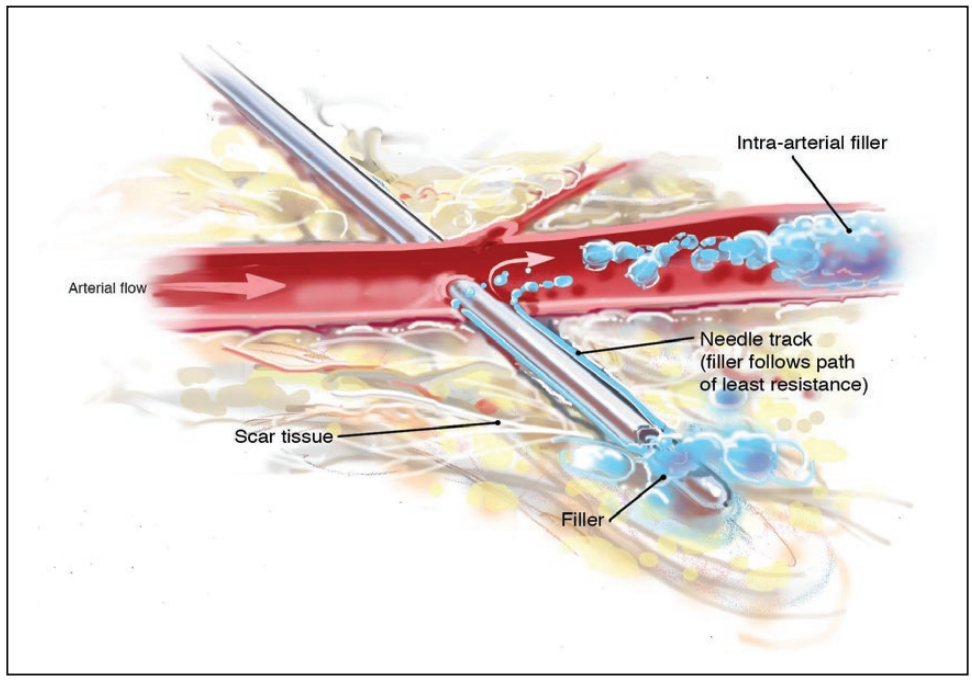

Figure 5. How penetration of a vessel might cause intravascular embolism, even though the tip of the cannula or needle is far past the lumen of the vessel. This is assumed to be more likely to occur when there is scar tissue present in the soft tissues. Penetration of scar tissues with a needle or cannula creates a pathway for filler to flow. The author hypothesizes that this type of problem may be become more prevalent with long term patients, since each filler treatment causes a small amount of scarring in the soft tissues.

Table 2. Possible Causes for Filler Associated Ischemia

External vascular compression	Analogous to stepping on a garden hose, results in decreased flow. Not reproducible in the lab on animals.
Vascular spasm	Acute spasm of vascular smooth muscle, usually associated with noxious drugs and chemicals as well as after replantation surgery.
Intravascular embolism	The pathophysiology best supported by the evidence (direct evidence of filler inside arterioles on pathology); reproducible in the lab on animals.

local blood pressure at the site, and the exact anatomic location of the vessels involved (location of collaterals, blood flow pattern, etc.).

AVOIDANCE

The current clinical practice recommendation is to use a maximum aliquot of 0.1 mL of filler per pass in any one area of the face, and then to move the needle tip slightly before injecting another similar volume, such that if you happened to be in an artery, no more than 0.1 mL of filler would enter the vessel.[1,7] We reached that number many years ago by estimating the volume of a small artery from typical injection sites on the face to the height of the orbit (unpublished cadaver data), so that if you did happen to put filler into the arterial system, there would not be sufficient volume to flow into the internal carotid territory and thence into the central retinal artery. More recent data on the volume of the Supratrochlear artery (as a representative example of this principle) showed that the average volume is approx. 0.085 mL.[8] The filler should be injected under low pressure, since high pressure and high flow rates could cause filler to travel to undesirable areas. Finally, it is wise to avoid scarred tissues, and to treat all scars as higher risk areas. If you penetrate an artery by passing a needle or cannula through it and into scarred tissues, you may create a pathway for the filler to pass into the vascular system (Figure 5). The filler may flow retrograde along the needle pathway, and then enter into the lumen of the vessel since this may be the path of least resistance. The author has noted the gritty nature of tissues in long standing filler patients, and is concerned that we may see more vascular AE in the future in our long standing patients, since each subsequent filler treatment adds a little more scar to tissues.[1]

Venous outflow obstruction: for most areas of the face, this is a non-issue. Most areas have reliably redundant venous pathways, and if one is blocked, an adjacent one is easily brought into play. The exceptions to this are axial pattern or free flaps, but these are rarely, if ever, the subject of filler treatments.

HIGH DOSE PULSED HYAL PROTOCOL FOR LVE

The protocol is very simple, but relies on the assumptions on Table 3. For a "single area" (eg, one half of the upper lip) low volume vascular event (LVE, by definition less than 0.1 mL of filler embolus), the dose of HYAL is 3 mL (about 450 iu) for an area of half an upper lip. If the nose is also involved, then the dose would be 6 mL (900 iu). The dose goes up dramatically with the size of the ischemic tissue. The author argues that as the volume of ischemic tissue increases, then the dosage of HYAL must also increase, since the goal is to attain a minimum effective concentration of HYAL throughout the entire block of ischemic tissue (see Figure 2 for hourly general dosing suggestions). We do not know exactly where the obstruction is – we only can see its clinical extent by judging the color of the skin and by assessment of the capillary refill. *We need to wet the entire volume of ischemic tissue with HYAL, because we need to hydrolyze the filler throughout the entire block of tissue.* If there is only a small obstruction remaining, and hydrolysis breaks it up partially and it moves downstream on the vessel, it may still be enough to block blood flow. So it is important that wherever the obstruction ends up, there is still a high enough concentration of HYAL (the minimum effective concentration, whatever that may be) throughout the entire zone. By this means, whatever vessels are filled with the HA filler throughout the ischemic tissue, the tissues are "wet enough" with HYAL to break it down to components small enough to pass through the capillaries. Once the byproducts are through to the venous system, they will no doubt continue to be broken down or be filtered out in the pulmonary capillary bed (except in the rare case of a right to left shunt somewhere in the system). In summary, the goal of treatment is to flood the ischemic tissue with sufficient HYAL to breakdown the HA filler. Because HYAL is being continuously removed from the system, we have to keep replenishing it, hence the hourly dosing schedule.

TISSUE VOLUME ESTIMATION

The author guess-timates the volume of HYAL (150 iu/cc) to be given to be about 3cc for an area of half an upper lip (a very rough approximation that seems to work, clinically). One can try to estimate the volume of tissue involved, and then work to the tissue volume, which seems at first to be the most scientific approach (the HYAL dose should be *titrated to* a *certain volume of tissue*). When first deciding on how much HYAL to utilize, the author estimates the volume of tissue is involved, ie, not merely the surface area of the zone of injury. Thus, if the thick tissues of the lateral cheek below the zygoma radial to the upper molar

Table 3. Assumptions Regarding Acute Filler Associated Ischemia

Ischemia is secondary to mechanical blood flow obstruction by HA filler inside the lumen of arteries
Flooding the tissues around the obstructed vessels with HYAL results in hydrolysis of the HA, relieving the mechanical obstruction to arterial blood flow. The HA fillers break down into smaller and smaller pieces, and eventually these products of HA hydrolysis can pass through the capillaries and allow blood flow to resume
HYAL activity is degraded by various means in a time related fashion (dilution, diffusion, and deactivation). Therefore, its effectiveness decreases rapidly following injection.
The hydrolysis of the filler material is dependent on the concentration of the HYAL in the surrounding tissues, and diffusion into the vessel lumen.
The hydrolysis of the filler material is dependent on the length of time that the obstructed vessel is bathed in a HYAL solution of sufficient concentration to promote diffusion into the vessel.
Products differ in their resistance to HYAL. Crosslinking HA is done to make the product HYAL resistant, so that the benefits of the filler last longer. In general, longer lasting filler products are more HYAL resistant, and are thus more difficult to dissolve with HYAL in this situation.

teeth (which measure about 25 mm in cadaver measurements the author has taken, ie, just over twice the thickness of an upper lip) are involved, then more HYAL must be used per unit surface area in comparison to an upper lip (which measures about 12 mm), or glabella (which measures about 6 mm in thickness). In other words, the physician should make some attempt at estimating the volume of ischemic tissue, with a view to using more HYAL if thicker tissues are involved. The underlying assumption is that the blood volume per unit of tissue is approximately uniform in the face. By extension, the intra-arterial space is similar per given volume of tissue. Despite the considerations given above, and the likely benefits of better dosing through better volume estimates, even the very rough dosing based on surface area alone can be sufficient for success (Figure 2).

The author wants to stress that these numbers have arisen through clinical practice alone, and not through scientific testing of any sort. No doubt, these doses will certainly be changed with further investigations. The truth of the matter is that no one really knows the minimum effective dose to use. However, the downside risk of treatment has been very low, and the upside has been high, with full uneventful recovery as the norm, excepting only those cases with delay of onset of treatment or when insufficient HYAL has been used (as in the former protocol).

This protocol relies on the assumptions posted on Table 3. We assume that the embolus of HA material is inside the arterial system, and we assume that by bathing the obstructed vessel in a solution of HYAL of sufficient concentration for a sufficient length of time, the contained HA material will be hydrolyzed by the HYAL (Table 3). The process of breakdown is not likely to be linear. The initial breakdown products of hydrolysis are likely to still be large enough to cause obstruction to blood flow, but it may cause some clinical changes in the shape of the injury as some of the product is "dissolved" and perhaps some corollary vessels open up. It is important to review each case during the treatment, and adjust the injection of HYAL to match the volume of ischemic tissue seen clinically. In some cases, for example, an area of ischemia may involve the upper lip and ipsilateral nose, but after a period of time, the lesion may involve only the part of the original lesion, say the nose in this example. Thus it would be reasonable to reduce the dose of HYAL and to re treat the nasal area only in this example. The author does not know the minimum effective HYAL concentration required to treat the average HA filler embolus (ie, the dose of HYAL that is effective to hydrolyze a given quantity of filler emboli). The effective working strategy of flooding the tissues is almost certainly not the most efficient one. It may be that a lower concentration of HYAL may be equally effective. However, the author argues that higher dosing regimens appear to be clinically safe, and the outcomes better, than when more conservative dosing is used. It appears that we have everything to gain, and little to lose, by using this strategy.

SOURCE OF HYAL DISCLAIMER

Another critical factor is that the author uses HYAL 150 iu/cc compounded in a local pharmacy (York Downs Pharmacy, 3910 Bathurst St, Toronto, Canada) because we do not have any pharmaceutical grade HYAL available legally in Canada. It may be that the HYAL we use in Canada is less or more effective than other brands, despite the fact that the potency given by the pharmacy is 150 iu/cc. Further, it may be that there is more batch to batch variability in a compounded preparation of HYAL in contrast to a strictly controlled pharmaceutical process. The author is assuming that the bovine testicular HYAL prepared at our local compounding pharmacy is actually what it purports to be, and it pharmacologically equivalent to any other equivalent HYAL, but this has not been proven.

CONSEQUENCES FOR CENTRAL RETINAL ARTERY EMBOLISM

It has been reported that retrobulbar injection of HYAL should be considered for treatment of accidental central retinal artery embolism with HA fillers[9] (it is a given that prevention is far preferable to treatment, as discussed previously). However, clinical discussion with physicians who have actually tried this technique has not been encouraging (unpublished data) and to date there have been no published reports of successful recovery of vision in any patient who arrived with no light perception at onset. We know that experimental occlusion of the central retinal

artery in rhesus monkeys showed strict time limitations of about 97 minutes[10] before onset of permanent injury. In this strict sense, there is a definite time limit of about an hour and a half from the onset of visual loss until circulation is restored. If restoration of circulation is delayed for only a few minutes beyond this limit, for example 105 minutes, some degree of damage is permanent in monkeys (and probably also in humans). Given that HYAL would have to be prepared, injected into the retrobulbar space, and then diffuse throughout the space (and thus far no one has even demonstrated that HYAL can even diffuse through the sclera), it seems rather unlikely that this treatment would be effective. This technique is likely only effective if the vascular obstruction occurs in the extra ocular portion of the central retinal artery (or if the obstruction was of some other part of the system such as the long and short ciliary arteries, or of the vessels supporting the optic nerve itself), it is uncertain if there would be enough time for the HYAL to hydrolyze the HA filler within these strict time limitations. To whatever time required for hydrolysis of the particular HA filler being used, we must add the time for HYAL diffusion to the emboli. This is an area that obviously requires further research, and although the author does not want to dissuade anyone from trying this technique, expectations of success should be tempered by the facts. If the filler has already entered the globe and settled in the retina, the prognosis is likely to be poor. The reasons we have such good success with emboli in the skin are precisely because these tissues are rather resistant to prolonged bouts of ischemia, whereas the retina has very limited and apparently strict time limitation on its ischemic survival. The retrobulbar injection technique is rather simple to perform, and the author has been trained to do it in cadavers. Using a 25 g 1.5 inch long needle, the orbit is approached through the lateral lower eyelid below the canthus. The needle tip is directed slightly upwards and temporally (laterally), and the needle tip is "walked" along the lateral orbital wall until about 2/3 to 3/4 of the length of the needle (about one inch) has been inserted. One then encounters a slight depression at this location and then about 3 cc of HYAL can be slowly injected (range of 2 to 4 cc total).

CONCLUSIONS

There has been a significant improvement in the qualitative nature of the results with this high dose protocol. With the previous vascular AE protocol, some patients had blisters, mild to moderate epidermal slough, and often had at least some degree permanent mild dermal scarring, as well as long lasting dischromia (particularly in patients of color). We used to consider this kind of mild scarring as a successful treatment, since it did not involve the serious degrees of tissue loss and the protracted healing by secondary intention that we had formerly observed in the completely untreated cases (often involving 6 weeks or more of dressing changes and aftercare). The author suggests redefining what a successful treatment entails. With this new protocol, we define successful treatment as complete resolution of ischemia with no epidermal scabs, scarring, or any secondary changes whatsoever.

The evidence from laboratory studies is that these events are a result of filler embolism occurring at the time of filler treatment. The working hypothesis is that flooding the tissues with a sufficient concentration of HYAL results in dissolution of the obstruction. We cannot know from clinical observation alone how much filler is present within the arterial system, nor can we know the precise location of the obstruction. For all practical purposes, we can assume that all the vessels in the affected areas are completely filled with HA filler. In order to relieve the obstruction, we need to ensure that a sufficient concentration of HYAL is present around the affected vessels for a period of time sufficient to ensure that diffusion can occur across the vessel wall. Thus there are several constraints on this system: the concentration of HYAL (which is degraded by deactivation by naturally occurring anti-HYAL factors in the tissues, dilution by leaking serum, and diffusion away from the site of obstruction; see Figure 4), the length of time the concentration is above the minimum required, the diffusion of HYAL into the vascular lumen, the resistance of tissues to hypoxia (which varies by tissue type). Since we cannot know where the obstruction is, exactly, we should assume that all the arteries in an ischemic area are obstructed, and that we need to treat that entire volume of tissue with sufficient HYAL to relieve the obstruction. We use the appearance of ischemia on the skin surface as a proxy for the volume of tissue that we must treat with HYAL. This is a complex system, with several time dependant variables and rates of change. In order to simplify treatment until a better system comes along, the author has been using a set of simple rules to govern treatment. These are not rigid rules, but rather flexible guidelines to help make clinical decisions. In general, larger areas of ischemia will require larger doses of HYAL given more frequently. Specifically, larger volumes of tissue will require more HYAL than smaller volumes of tissue.

We present a rough rule of thumb, using the lip, nose, and forehead as dose multipliers, with the standard dose of about 500 iu per area (Figure 2). For a single region, we recommend starting with a dose of about 500 iu every hour or so, until the ischemia is resolved (until skin color has returned and capillary refill time has returned to normal). For two areas, 1000 iu, and 1500 iu for three areas. We recommend keeping the patient in the clinic for observation, and retreating every 60 to 90 minutes until normal skin color returns. Typically, most will resolve after about

three or four treatment sessions, but rarely there have been up to 8 or 9 re-injections of HYAL. Occasionally, because of exhaustion of both the patient and the clinician, the patient has been sent home overnight to return for more treatment the following day. It is important to realize that although treatment is urgent, it is not an emergency, as the soft tissues are relatively resistant to ischemia. As long as treatment is completed within about 72 hours (about 3 days) of onset of ischemia, success is common. These high, repeated doses of HYAL have been used for approximately 2 years in several dozen cases with excellent results, defined as complete resolution to normal, with no scabbing or other long lasting secondary changes (apart from the normal injection site reactions expected due to repeated injections). This is a clinical guideline that is done at the patient bedside with no special equipment or diagnostic laboratory requirements. Diagnosis is entirely clinical, done in the typical fashion with history and physical examination through observation and capillary refill tests.

It's possible that lower doses, or less frequent re-injections of HYAL, may be equally satisfactory for different HA preparations, and that different preparations of HYAL may differ in their effectiveness. However, the author developed this protocol because of dissatisfaction with the results of less aggressive treatment (particularly with the newer, longer lasting HA filler formulations) and has found consistently good results using this more aggressive approach with both highly experienced clinical injectors as well as clinical neophytes. The benefits of this new protocol include that it is easy to use and remember, and that it is implemented equally well by experienced surgeons as well as by those with less detailed anatomical knowledge.

Disclosures

Dr DeLorenzi is Medical Director for Allergan Canada (Markham, Ontario, Canada) and Merz Canada (Burlington, Ontario, Canada), and an Advisory Board Member for Kythera Biopharmacueticals Inc. (Westlake Village, CA, USA), Suneva Medical Inc. (San Diego, CA, USA), and Valeant Pharmaceuticals (Laval, Quebec, Canada).

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