Nitroglycerin: A Review of Its Use in the Treatment of Vascular Occlusion After Soft Tissue Augmentation

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BACKGROUND Skin necrosis after soft tissue augmentation with dermal fillers is a rare but potentially severe complication. Nitroglycerin paste may be an important treatment option for dermal and epidermal ischemia in cosmetic surgery.

OBJECTIVES To summarize the knowledge about nitroglycerin paste in cosmetic surgery and to understand its current use in the treatment of vascular compromise after soft tissue augmentation. To review the mechanism of action of nitroglycerin, examine its utility in the dermal vasculature in the setting of dermal filler-induced ischemia, and describe the facial anatomy danger zones in order to avoid vascular injury.

METHODS A literature review was conducted to examine the mechanism of action of nitroglycerin, and a treatment algorithm was proposed from clinical observations to define strategies for impending facial necrosis after filler injection.

RESULTS AND CONCLUSIONS Our experience with nitroglycerin paste and our review of the medical literature supports the use of nitroglycerin paste on the skin to help improve flow in the dermal vasculature because of its vasodilatory effect on small-caliber arterioles.

The authors have indicated no significant interest with commercial supporters.

The use of nitroglycerin paste has become an important intervention for suspected dermal ischemia, a rare but nevertheless encountered complication of dermal fillers used in cosmetic surgery. There is little evidence-based medicine supporting its use in this aesthetic setting. Nitroglycerin paste is an organic nitrate that belongs to a class of anti-anginal drugs or vasodilators that are active on arteries and veins.[1] Nitroglycerin is also being marketed and used for off-label use in a paste formulary for the management of rare but significant ischemic complications resulting from soft tissue augmentation with fillers in aesthetic practice, but its utility in dilating potentially compromised small-caliber dermal vessels is unclear.

The number of filler procedures performed has rapidly increased in the past decade. According to the 2010 American Society for Dermatologic Surgery (ASDS) procedure survey, soft tissue filler injections ranked among the top five procedures performed by dermasurgeons, and the number of soft tissue augmentation procedures increased 130% between 2005 and 2007.[2] As with any medical intervention, complications occur, and adverse events may be unforeseen. Although the majority of adverse filler events are mild (erythema, edema, and bruising), granuloma formation and other local reactions such as tissue necrosis and ischemia can occur. In the event of such circumstances, it is imperative for the trained dermatologic surgeon to follow some type of guidelines to try to reverse these sequelae.[3–7]

To better understand the role of nitroglycerin in cosmetic surgery, this article will review five topics:

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off-label uses of nitroglycerin paste, various commercial nitroglycerin formulations, adverse effects, precautions, and pharmacokinetics. Finally, after familiarizing ourselves with the mechanism of action of nitroglycerin, we will examine its utility in the dermal vasculature in the setting of dermal filler–induced ischemia and the spectrum of cutaneous necrosis.

Nitroglycerin in Dermatology (All Off-Label Uses)

Soft tissue augmentation with dermal fillers is performed to achieve a more-youthful appearance and has become an integral part of aesthetic physician practices. When performing these procedures, physicians must be mindful of the rare, but clinically important, complications associated with dermal fillers. Ischemic complications from injection necrosis can be partly attributed to several factors. For instance, anatomic variation from scars, trauma, or prior surgery may be an inciting event leading to focal necrosis. Patients who have undergone previous surgery such as cosmetic rhinoplasty or skin cancer reconstruction may be at higher risk of such complications because of the altered blood supply secondary to scarring and anatomic alteration. Grunebaum and colleagues[8] reported necrosis of the left ala after injecting nasolabial folds with hyaluronic acid in a woman who had previously undergone rhinoplasty. The choice of a filler product and knowledge of proper injection techniques also plays a significant role in minimizing potential complications. In particular, deep injections with thick dermal products into high-risk areas should be avoided. Injecting superficially and medially, aspirating before injecting by drawing back on the plunger, ensuring that the needle tip is not in the vessel, and using low volumes of product in several treatment sessions will improve the cosmetic outcome.[4] Glaich and colleagues note that overcorrection with high filler volumes, particularly into small areas, can cause compression of adjacent vessels by exceeding the intravascular pressure.[6] Compromise of vascular supply itself is believed to occur by direct injury to the vessel, compression of the area around the vessel, or obstruction of the vessel by the filler material.[9] Arterial injury or occlusion is sometimes immediately apparent, with localized blanching of the area being injected. Necrosis is suspected when a bluish or violaceous and reticulated discoloration develops over subsequent days.[10] Resulting arterial occlusion presents with prolonged pain, swelling, and dark discoloration[11] (Figure 1). Left untreated, significant necrosis can ensues so it is imperative to identify the proper management of these adverse reactions.

Today, 2% nitroglycerin paste (NitroBid, Fougera, Melville, NY) is used increasingly for management of vascular compromise after filler injection. Schonberger and colleagues used laser Doppler flowmetry (LDF) to assess the true nature of the local vasodilatory effects of nitroglycerin on the downstream low-caliber, "resistance" arterioles (Figure 2). Mean blood flow readings of forehead perfusion were 365% higher at sites of transdermal nitroglycerin patch application than with placebo ($p = .005$) (Figure 3).[12,13] This ability of topical nitroglycerin to induce a local vasodilatory response in small- or medium-caliber dermal vessels supports its use by physicians in the setting of filler-induced ischemia.

Formulations

Different commercial formulations of nitroglycerin are available: Nitrobid (Fougera, Melville, NY)

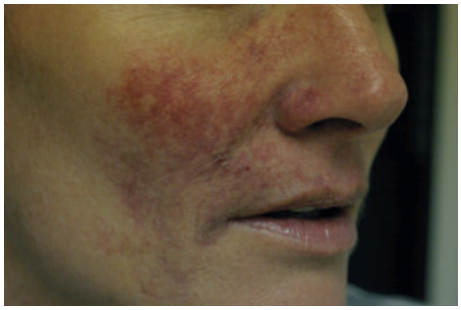

Figure 1. Vascular compromise appearance of reticulated pattern after injection with calcium hydroxylapatite in the nasolabial fold and oral commissure.

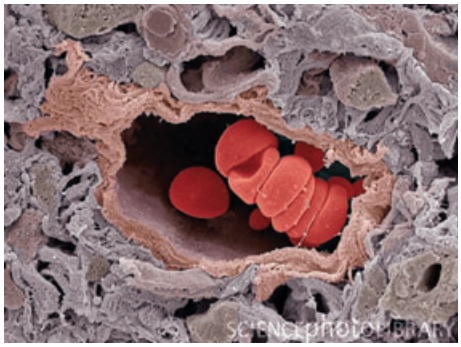

Figure 2. Colored scanning electron micrograph of a cross-section of an arteriole. The inner wall (*tunica intima*) of the lumen is composed of a thin endothelial lining and elastic layer. Magnification ×4000. Reprinted with permission from ref.12.

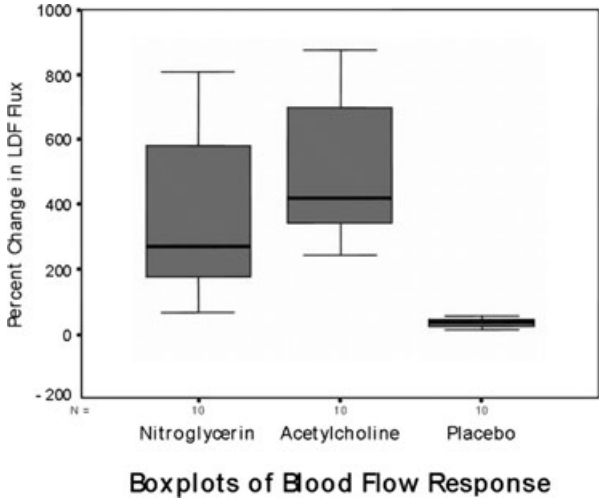

Figure 3. Boxplots of percentage change in blood flow at sites of nitroglycerin and placebo patches. Reprinted with permission from ref. 13.

Minitran, Nitrolingual Pumpspray (First Horizon Pharmaceuticals, Alpharetta, GA), Nitrek (Bertek Pharmaceuticals, Sugar Land, TX), Nitro TD Patch-A (Mylan Pharmaceuticals, Morgantown, WV), Nitro-Dur (Key Pharmaceuticals, Miami, FL), Nitrol (Savage Pharmaceuticals, Melville, NY), and Nitrogard (Forest Pharmaceuticals, St. Louis, MO) (Table 1). These commercial nitroglycerin formulations come in sprays, ointments, transdermal patches, and capsules and as a solution for intravenous use.[14,15]

Pharmacokinetics

Generally, the volume of distribution of nitroglycerin is approximately 3 L/kg. It is normally cleared from this volume at a rapid rate (~1 L/kg per minute), with a serum half-life of 3 minutes. The initial products of metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less potent as vasodilators but have a longer plasma half-life than the parent compound.[15] They are further metabolized into nonvasoactive mononitrates and ultimately to glycerol and carbon dioxide.

The nitroglycerin transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is directly related to the area of the compound or patch applied. Thus, each cm^2 of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Nitroglycerin paste can also be

TABLE 1. Commercial Formulations of Nitroglycerin

Route of Administration	*Brand Name*	*Manufacturer or Distributor*
Transdermal	Nitro TD Patch	Mylan Pharm. Ltd., Melville, NY
	Minitran	Douglas Pharm. Ltd., New Zealand
	Nitrek	Bertek Pharm., Ltd., Sugar Land, TX
	Nito-Dur	KeyPharm Ltd., Miami, FL
Ointment	Nitrol*	Savage Pharm. Ltd., Melville, NY
Oral, buccal, or sublingual	Nitrogard	Forest Pharm. Ltd., St. Louis, MO
	Nitrolingual Pump Spray	First Horizon Pharm. Ltd., Alpharetta, GA
Intravenous	Nitrobid	Fuegera, Melville, NY

*Also manufactured as a patch (Nitrol TD).

an effective way to provide a patient with nitroglycerin administration in the event of angina symptoms.

The onset of action of the transdermal system and the ointment form of nitroglycerin is within 30 minutes.[16] The patch is usually worn for 12 to 14 hours and then removed. A new patch is placed after a "patch free" period of 10 to 12 hours. The undistributed nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered 10% of its original content of nitroglycerin. In healthy volunteers, the steady-state plasma concentrations of nitroglycerin are reached approximately 2 hours after application of a patch. Nitroglycerin must be protected from light, or it can be de-activated and lose efficacy. Nitroglycerin loses potency quickly once the paste or patch is exposed to air, so the tube or container should be tightly sealed immediately after each use. A properly sealed tube can be reused.[1]

Adverse Events

Application-site irritation is rarely severe.[14] In one study, erythema, edema, scales, papules, and dermal thickening was observed in rabbits treated for 26 weeks with daily treatment with 10% nitroglycerin ointment at doses of 15, 60, and 240 mg/kg. These effects were reversible after the end of exposure.[17]

Nitroglycerin should not be used if one is allergic to nitroglycerin, isosorbide mononitrate, or isosorbide dinitrate.[1]

Facial Anatomy and Danger Zones

Skin necrosis is more likely to occur in certain potential "danger zones" than other areas. These higher risk areas include the glabella, nasal skin, temple, alar groove, and lip.[8,10] With many years of clinical use, the glabellar area has been found to be the most common area of vascular compromise and necrosis in reports on the use of bovine collagen.[8,10,18,19] Although the most common site of tissue necrosis after filler injection is the glabella, caution should be taken in many other regions of the face. Cohen and colleagues[20] reported vascular compromise after hyaluronic acid cheek augmentation.

To avoid vascular compromise and eventual eschar formation or scar, the injector should not only have a thorough knowledge of the facial anatomy, including common aberrations, but should also be mindful of each patient's history. For example, older patients may have more empty space to fill and thus empirically a lower risk of ischemia. Younger patients, especially those with a history of dental or facial surgery, may be at a higher risk because of aberrant neovascularization after the trauma of a procedure in combination with less tissue laxity overall. Patients with a history of face lifts, rhinoplasty, parotid surgery, or liposuction may have altered anatomy, vascular supply, or soft tissue thickness.

Major facial vessels of concern during soft tissue augmentation are the superior (Figure 4) and inferior labial arteries, both branching off the facial artery at the angle of the mouth; the angular artery, the terminal branch of the facial artery; the lateral nasal artery, the branch of the angular artery (Figure 5); the dorsal nasal artery, which

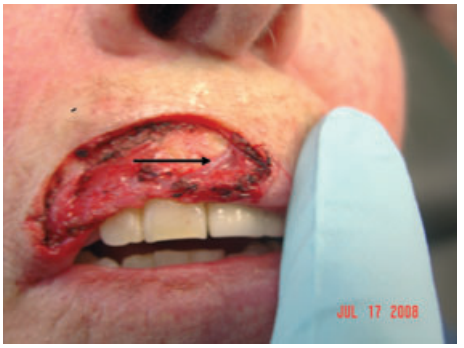

Figure 4. Mohs surgical defect exposing the right superior labial artery (courtesy of Joel L. Cohen, MD).

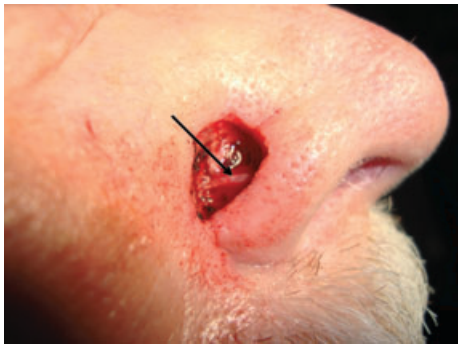

Figure 5. Mohs surgical defect exposing the right lateral nasal artery (courtesy of Joel L. Cohen, MD).

anastomosis with the angular artery; the supratrochlear artery, one of the terminal branches of the ophthalmic artery; and the superficial temporal artery, arising from the external carotid artery (Figure 6).[21]

Diagnosis of which vessel is affected requires knowledge of which zones the vessel perfuses. Treatment of the vessel with nitroglycerin paste should begin proximal to the ischemia and over the entire zone. For example, impending necrosis of the nasal ala and septum may be due to compromise of the superior labial artery (Figure 4). Necrosis of the lower lip and a portion of the superior chin may result from compromise of the inferior labial artery. The angular artery follows a tortuous course along the alar groove and ends with its anastamose with the dorsal nasal branch of the ophthalmic artery. It has an important role in the facial vasculature, supplying the nasal ala, sidewall, and dorsum of the medial canthus.[5,22] When injecting the high nasolabial fold or alar groove, one should be mindful of necrosis from occlusion of the lateral nasal artery, which is critical to the arterial supply of the nasal alar area. Its superior nasal branch separates into small branches, supplying the nasal dorsum and superior rim of the nostril.[8] Kang and colleagues and Inoue and colleagues[23,24] reported necrosis with significant scabbing and eschar changes of the entire nasal alar region after compromising the lateral nasal artery with hyaluronic acid injections. Damage to the superficial temporal artery may affect the temporal fossa.[5,22] Finally, the nasal root and inferior central forehead may become ischemic when the glabellar area is injected because of compromise of the supratrochlear artery (Figure 6). As we all venture to try to avoid botulinum toxin above the immediate lateral brow, many injectors are instead turning to filler products to reduce the folds produced by dynamic movement—which can put the supraorbital artery at risk as well.

Treatment Algorithms for Ischemic Events

Several treatment algorithms for impending facial necrosis after filler injection have been.[3–7] The utility of topical nitroglycerin in the case of vascular compromise has been explored in various arenas of medicine.

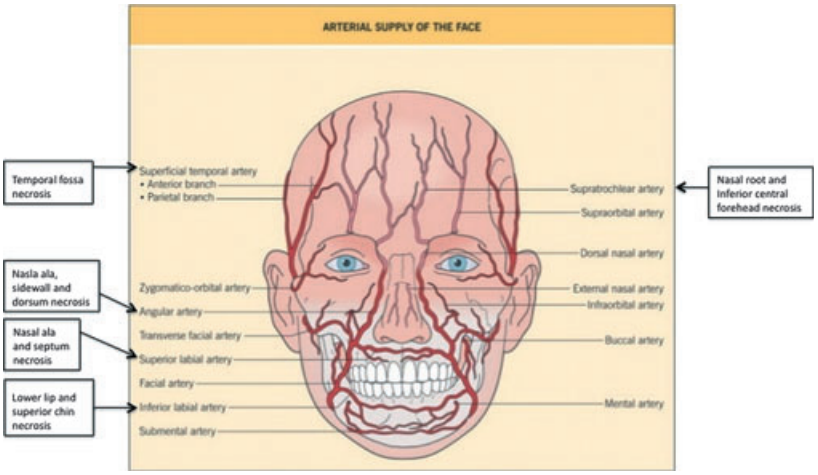

Figure 6. Arterial supply of the face. Reprinted with permission from ref. 21.

Injection should be stopped immediately after blanching is seen. Warm gauze (to facilitate vasodilation) and tapping (to break up product) are then recommended. Nitroglycerin paste should be applied immediately to facilitate vascular dilatation and blood flow to the area.[11,25] This regimen should be used for the treatment of arterial and venous occlusion. In the case of hyaluronic acid use, the area can be injected with hyaluronidase enzyme.[26–28] Grunebaum and colleagues reported treating a 25-year-old woman for necrosis after she had received hyaluronic acid filler injection to the nasal tip. The patient experienced a full recovery after using daily topical nitroglycerin paste on the nose over the reticulated area with concomitant use of hyaluronidase injections and oral antibiotics for 1 week.[8] Glaich, Goldberg, and Cohen recommend treatment with topical nitroglycerin paste at the first sign of blanching until improvement is noted. One suggested protocol for glabellar ischemia is the application of 0.5 to 1.0 inch of ointment with overlying cellophane wrap occlusion within 3 cm of the affected area. An applicator may be used to spread the ointment into a thin uniform layer. After 12 hours, the nitroglycerin ointment is removed, although in one author's experience, short application for 5 minutes may be sufficient because the known pharmacokinetics of the drug. The treatment cycle should be continued and repeated until clinical improvement is seen or as the patient tolerates.[6] Hirsch, Cohen, and Carruthers note that the application of nitroglycerin paste may be tried not only in the office, but also at home by the patient to further promote vasodilation. The above algorithm is of particular importance in cases in which hyaluronic acid filler is not used and hyaluronidase cannot be used.[26] Physicians and patients should be comfortable with topical application of nitroglycerin at home. If there are cardiovascular risk factors such as arrhythmia or history of angina, daily treatment in the office may be implemented, or the patient may be followed at the physician's discretion. Warm compresses and nitroglycerin ointment may also be used in the case of impending lip necrosis after hyaluronic acid gel injection to try to facilitate reperfusion.[29] Some physicians are concerned that warm soaks may speed up damage to tissue that is oxygen deprived by accelerating cell metabolism, but it is our experience that introduction of heat causes vascular vasodilation and increases oxygen flow to damaged tissue without any signs of reperfusion injury.

Medications with an anticoagulant effect, such as aspirin and nonsteroidal antiinflammatory agents, and vitamins that inhibit platelet aggregation should be encouraged in any protocol to treat cutaneous tissue ischemia. For instance, platelet adhesion is significantly lower in patients taking 200 to 400 IU of vitamin E for 2 weeks.[30] Platelet aggregation is also inhibited, and vasodilation may be induced with the use of intravenous prostaglandin E1 (PGE1). Kim and colleagues reported the use of intravenous infusion of 10 mg/d of PGE1 to relieve venous occlusion and reverse venous compromise of the nose after hyaluronic acid filler injection. Forty-eight hours after treatment, a change to pink color was observed, with evidence of full recovery in 5 months.[31]

Hyperbaric oxygen has been used successfully for nasal tip grafting in cases of cancer or trauma reconstruction.[32,33] In cases of vascular complications secondary to cosmetic filler injections, we suggest administrating oxygen through a nasal cannula or face mask or using hyperbaric oxygen. For cases with severe, unremitting swelling, oral antihistamines may be used.

Patients may report pain and stinging upon application of the nitroglycerin paste. Reperfusion may also be painful. Postischemic erosion, sterile pustules, and granulation tissue should be treated with gentle wound care until re-epithelization is complete. This process may take 1 to 3 weeks, followed by erythema that may last for 6 to 24 months or change in texture of the skin of the affected area. Some dermatologists use light-emitting diode treat-

ments to expedite the healing process. Once the area has re-epithelialized, laser modalities are helpful. Pulsed dye laser or intense pulsed light may ameliorate the erythema and may help the irregular skin texture after cutaneous necrosis. Fractional lasers are helpful in facilitating improvement in textural changes and hypopigmented scarring of cutaneous necrosis as well (Table 2). Finally, treatment with low-molecular-weight heparin (5000 IE/d) has been reported to be effective in the treatment of impending necrosis after using hyaluronic acid to treat frown lines. Sanchz and colleagues[9] witnessed fading of the reticular pattern after 1 week, appearance of an ulcer after 10 days, and complete resolution with no residual cosmetic defect after 5 weeks of treatment.

Conclusion

Nitroglycerin paste is now gaining popularity for the management of adverse effects of soft tissue fillers, specifically impending necrosis of soft tissue. Nitroglycerin paste is now gaining popularity for the

TABLE 2. Management of Ischemic Events with Topical Nitroglycerin

Immediate evaluation of the cause of ischemia based on:
Technique the injector used (e.g., microdroplet, linear, bolus)
Evaluation of the property of the injectable used
Reversible (hyaluronic acid)
Irreversible (poly-L-lactic acid, calcium hydroxylapatite, silicone, polymethylmethacrylate)
Immediate risk assessment of the localized area
Anatomic danger zones (Figure 6)
If do not know whether vascular occlusion vs compression, suspect both
Immediate massage-technique
Massage area with firm, rapid, circular motions, moving to different areas and making sure to allow for circulation and not to further compress the area
Apply topical nitroglycerin and continue massage
5–15 minutes
Area may sting
May occlude nitroglycerin using a non-stick Telfa in lieu of massage
Stop and re-evaluate
Review any allergies to medications (hyaluronidase, aspirin, antihistamines, methylprednisolone).
Inject hyaluronidase
Indicated for adverse events after injection of hyaluronic acid
May inject hyaluronidase after adverse events from calcium hydroxylapatite and other fillers
Starting dose: 16–50 U of hyaluronidase
Inject same volume of diluted hyaluronidase as volume of hyaluronic acid you want to dissolve (if you injected 0.3 mL of hyaluronic acid in the target area, inject 0.3 mL of diluted hyaluronidase)
Inject hyaluronidase in setting of nonhyaluronic acid adverse events
May aid in debulking any prior hyaluronic acid in the region
May aid to diminish native hyaluronic acid
Massage hyaluronidase gently, moving away from area so as not to worsen occlusion
Administer aspirin
Consider administering oxygen through nasal cannula, face mask, or hyperbaric oxygen
Consider administering antihistamine or methylprednisolone to decrease swelling
Observe patient for 30–60 minutes or until symptoms have stabilized (topical nitroglycerin should remain on skin during this time)
If stable, discharge patient with instructions
Be explicit—no compression, may take ibuprofen, give telephone number to call for immediate help if any changes, moisturize with bland ointment, follow up in morning
May repeat all steps as deemed necessary by operator; may continue wound care and close observation
May use light-emitting diode, intense pulsed light, pulsed dye lasers for residual erythema after skin has re-epithelialized

management of adverse effects of soft tissue fillers. Although impending necrosis of soft tissue is a rare occurrence, millions of filler injections are performed worldwide each year, and intra-arterial injection and vascular compromise should be recognized when using fillers for soft tissue facial augmentation. The use of nitroglycerin paste should be implemented in medical practice as an early intervention to prevent progression of long-term ischemic complication. Further studies are needed, but our experience with the product and our review of the medical literature supports the use of nitroglycerin paste on the skin to improve blood flow in the dermal vasculature due to its vasodilatory effect on small-caliber arterioles. All aesthetic physicians should become familiar with nitroglycerin topical formulations. Although evidence of the use of nitroglycerin may be regarded as anecdotal and may not be definitive, every avenue should be pursued to avoid the sequelae of necrosis. We propose that nitroglycerin paste be used for the management of impending necrosis after the use of dermal filler agents.

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