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CASE REPORT
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Nitrous Oxide Improves Tissue Perfusion in Vascular Occlusion Management

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Summary: Filler-related vascular occlusion (VO) treatment remains challenging despite established protocols, including high-dose pulsed hyaluronidase injections and ultrasound-guided targeted injections. Managing patients' pain and anxiety during treatment presents additional difficulties. Nitrous oxide (N_2O) has been found to be effective for analgesia and anxiolysis in minor procedures, with a 55% reduction in photodynamic therapy pain, and a visual analog scale reduction from 6.6 to 2.9 for aesthetic laser treatment pain. Use of N_2O for analgesia, anxiolysis, or improvement of perfusion in VO has not been previously reported. We present two cases of filler-related VO management with high-dose hourly hyaluronidase injections and adjunctive use of self-administered 50% N_2O. Pain and anxiety of the treatment were self-reported by the patients. Capillary refill and livedo reticularis were monitored for establishing VO diagnosis and treatment outcome. In both cases, self-administration of N_2O led to contemporaneous improvement in skin perfusion. Patients reported decreased anxiety and pain during treatment. Hyaluronidase treatment led to permanent resolution of occlusion symptoms. N_2O presents a promising adjunctive treatment option for relief of pain and anxiety, and potentially additional perfusion improvement. Further investigation is necessary to better define N_2O's role in treating VO. *(Plast Reconstr Surg Glob Open 2023; 11:e5154; doi: 10.1097/GOX.0000000000005154; Published online 25 July 2023.)*

USE OF NITROUS OXIDE FOR ADJUNCTIVE MANAGEMENT OF VO: A CASE REPORT

Vascular occlusion (VO) is a challenging complication of filler injections, with potentially devastating sequalae, including skin necrosis and blindness. A recent study found that among 370 dermatologists, 106 (28.6%) experienced at least one occlusion in the previous 10 years.[1] Hyaluronidase injections are the primary therapy, either with high-dose pulse injections[2] or using ultrasound guidance.[3] However, treatments may require hours or days of repeated injections with uncertain prognosis, creating additional challenges in managing patients' pain and anxiety.

Nitrous oxide (N_2O) has analgesic and anxiolytic properties, mediated by its action on opioid and γ-aminobutyric acid receptor pathways, respectively,[4] and is widely used in aesthetic medicine,[5] typically as a self-administered mixture with oxygen via a demand-valve device. (**See Video [online],** which shows the self-administration of N_2O/oxygen mixture by the patient with simultaneous hyaluronidase injections.) It has been reported to reduce photodynamic therapy pain by 55%, and reduce aesthetic laser treatment pain from 6.6 to 2.9 on a visual analog scale.[5] Its ease of administration, rapid onset of action, and minimal side effects[5] make it an attractive adjunctive treatment. However, its use in VO management has not been previously reported. We present two cases of VO treated with self-administered N_2O in addition to hyaluronidase. The decision to use N_2O as an adjunctive treatment was guided by its potential to alleviate patients' pain and anxiety.[4] Additionally, we observed temporary improvement in livedo reticularis and capillary refill. Our findings suggest the potential of N_2O as an adjunctive treatment option for VO.

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Received for publication November 22, 2022; accepted June 15, 2023.

Presented at Vegas Cosmetic Surgery (VCS), June 2021, Vegas, Nev., and at the IMCAS World Congress, June 2022, Paris, France.

DOI: 10.1097/GOX.0000000000005154

Disclosure statements are at the end of this article, following the correspondence information.

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CASE 1

A 32-year-old woman presented for filler injection of nasolabial folds. After the injection of 24 mg/mL Hylacross hyaluronic acid (HA) filler, the HA patient developed livedo reticularis across her right medial cheek and right lateral nasal wall, along with capillary refill of 4 seconds (Fig. 1), indicating VO. Self-administered 50% N_2O was offered to alleviate the patient's anxiety and concerns about pain during hyaluronidase treatment. The patient consented to N_2O and reported lessened anxiety after starting self-administration and minimal pain during subsequent injection treatment. Surprisingly, her cutaneous symptoms also improved after 3 minutes of N_2O use, with the disappearance of livedo, hyperemia in the affected area, and a decrease in capillary refill to 1 second (Fig. 1). However, this improvement was temporary, diminishing within 2 minutes after N_2O discontinuation, and returning after N_2O was restarted. The patient then received five vials of hyaluronidase, 150 U/mL (totally 750 units), injecting every hour per protocol,[2] with concurrent self-administration of N_2O (**See Video [online]**). Permanent resolution of livedo and capillary refill of 1 second were achieved. The patient had no residual symptoms on follow-up the next day and in 12 days.

CASE 2

A 35-year-old woman was treated with 17 mg/mL Vycross HA filler injection in her nasolabial folds. 30 minutes after the injection, livedoid discoloration was noted over the right medial cheek, nasolabial fold, nasal sidewall, and nasal tip, with a capillary refill of 5 seconds at the nasolabial fold, indicating VO. The diagnosis of VO and treatment with hyaluronidase were discussed with the patient. Self-administered 50% N_2O was offered to alleviate her pain and anxiety, and the patient consented to its use. Three minutes after starting N_2O self-administration, livedo disappeared, and capillary refill improved to 2 seconds. Improvement was again transient, with symptoms returning within 2 minutes after N_2O discontinuation. The patient reported a decrease in her anxiety and minimal pain during the treatment. The patient received three vials of hyaluronidase over 2 hours, 150 U/mL (totally 450 units), with concurrent self-administration of N_2O, until permanent resolution of livedo and capillary refill of 1 second were achieved. On follow-up the next day and in 6 months, she had a complete recovery.

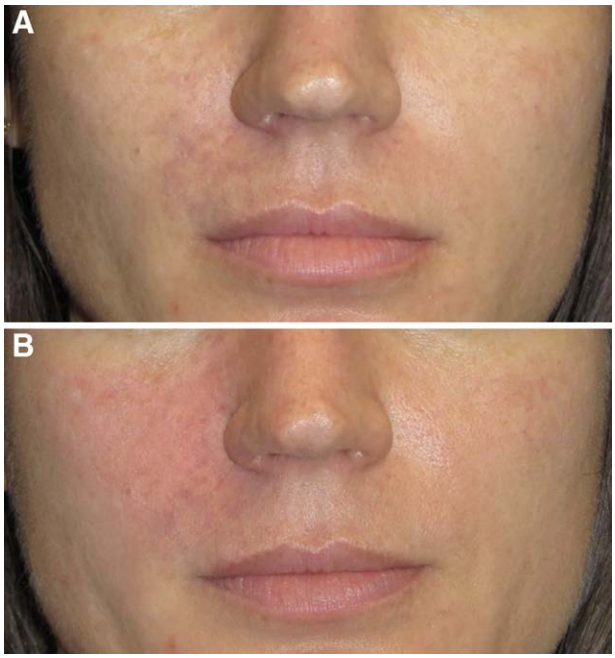

Fig. 1. Changes observed in cutaneous circulation, case 1, right cheek and nasolabial fold. A, After filler injection, livedoid discoloration due to VO. B, After nitrous oxide self-administration and hyaluronidase injection, hyperemia and improvement in livedoid discoloration.

DISCUSSION

In the cases presented, N_2O was used to mitigate pain and anxiety while also resulting in a temporary improvement in livedo reticularis and capillary refill. The observed perfusion change occurred before hyaluronidase administration, raising questions about the underlying mechanism. Various pathophysiology mechanisms have been proposed for filler-related VO, such as intraluminal blockage with HA, extraluminal compression, thrombosis, and vasospasm in the affected artery or choke anastomotic vessels.[6,7] Consequently, the improved tissue perfusion could be attributed to alleviating any of these factors or an increase in blood oxygen partial pressure related to oxygen in the mixture.

Current evidence supports use of hyaluronidase as the standard treatment of VO, reporting no skin loss when using high-dose pulsed injections within 2 days of the ischemic event,[2] and reporting similar success rate for ultrasound-guided reversal.[3] Hyaluronidase has been shown to dissolve HA filler[2] and diminish myocardial necrosis in canine models.[8] It produced endothelium-dependent relaxation in canine coronary arteries, blocked by nitric oxide (NO) synthase inhibitors,[8] demonstrating a possible pathway via release of endogenous NO, a potent vasodilator that prevents vasospasm, inhibits platelet aggregation, and protects against reperfusion injury.[8]

N_2O has been shown to improve random flap survival in animal models, decreasing necrotic areas from 46% to 13% and increasing capillary formation from 1.3 to 6.3 units.[9] Additionally, its analgesic and anxiolytic effects were found to be blocked by NO synthase inhibitors.[4] We hypothesize that N_2O temporarily improves perfusion in VO cases, potentially via NO release. We propose a synergistic or additive effect on endogenous NO production and release when using N_2O and hyaluronidase together (Fig. 2).

We suggest that adjunctive use of N_2O for VO treatment may benefit patients by relieving pain and anxiety and temporarily alleviating tissue ischemia (Fig. 3).

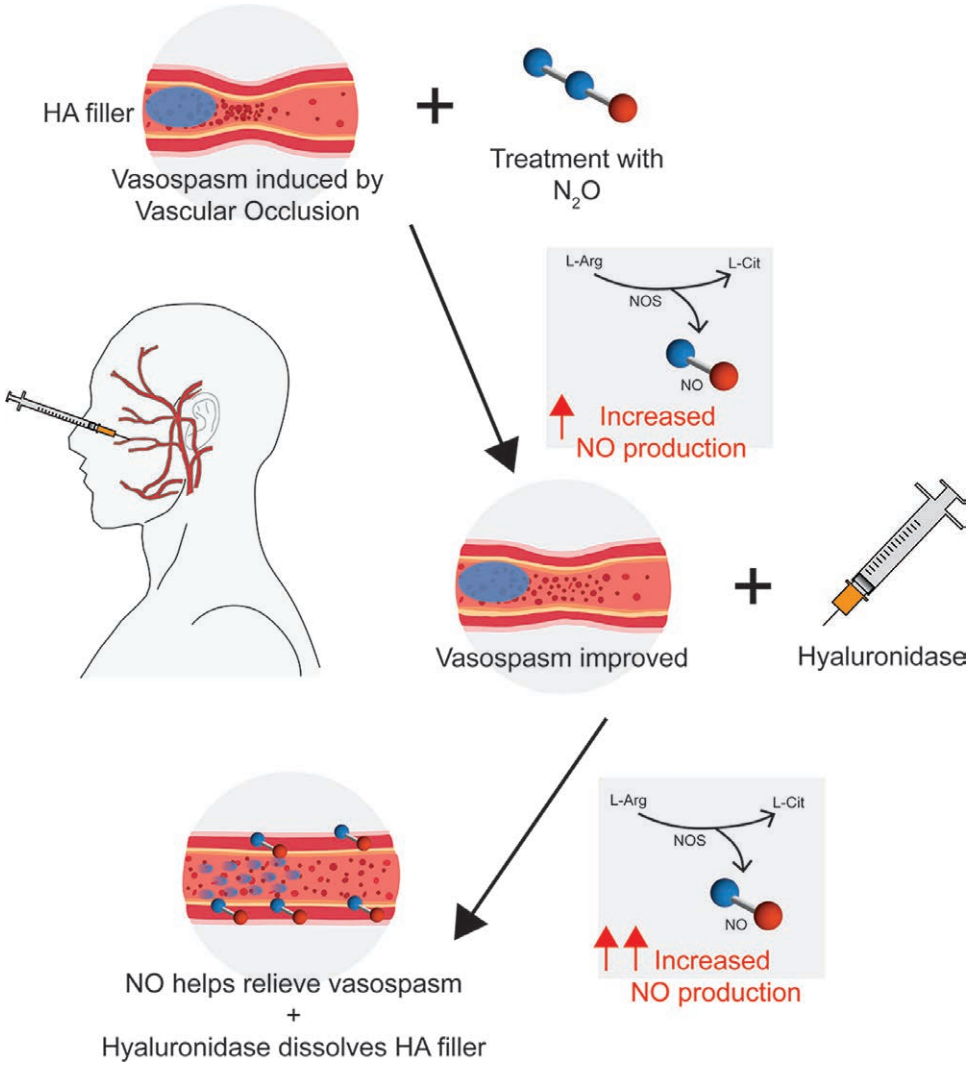

Fig. 2. Proposed mechanisms of action for N_2O in mitigating the effects of HA filler induced vascular occlusion with associated vascular blockage and vasospasm. Treatment with self-administered N_2O leads to activating NOS and increased vascular endothelial NO via conversion of L-Arg. NO leads to vasodilation and improvement of vasospasm. Subsequent treatment with hyaluronidase dissolves filler and may further increase NO production, improving vasospasm and restoring cutaneous perfusion. L-Arg, L-arginine; L-cit, L-citrulline; NOS, nitric oxide synthase.

These findings merit further research, and may prove beneficial for treatment of filler-related blindness, which is often irreversible due to the brief viability window of retinal cells.[10] Extending this window, even temporarily, may improve the success rate of definitive treatment.

Drawbacks of this approach include the need for a specialized device and additional cost; however, these devices are usually affordable, priced around $5000–$7000. Limitations of our study include a small patient sample, the absence of an objective cutaneous perfusion test, a brief follow-up period, and the absence of a control group. Further research is required to evaluate the efficacy, safety, and cost–benefit of adjunctive N_2O in managing filler-related VO.

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DISCLOSURES

Dr. Stella Desyatnikova is a consultant for GE Health and receives speaker fees for Clarius and Revance. Dr. Leandra Mangieri has no financial interest to declare in relation to the content of this article.

ACKNOWLEDGMENTS

Pronox is the device for self-administration of nitrous oxide and oxygen mixture discussed in the article. It is distributed by

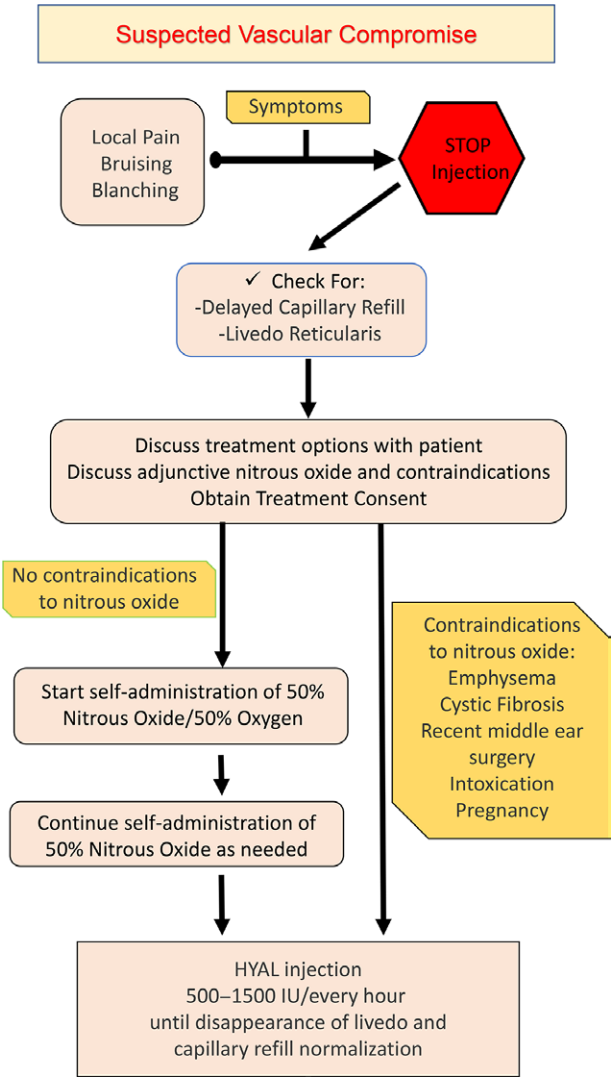

Fig. 3. Algorithm for filler-related VO management.

CAREstream America. The study was conducted in accordance with the principles of Declaration of Helsinki.

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