

# Exploring the efficacy of nitroglycerin in filler-induced facial skin ischemia: a narrative review

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**Background:** Filler-induced facial skin ischemia is a potential complication of dermal filler injections that can result in tissue damage and necrosis. Due to its vasodilatory properties, nitroglycerin has been proposed as a treatment option; however, its effectiveness in this context remains uncertain.

**Method:** A narrative review was conducted to investigate the existing evidence on the effectiveness of nitroglycerin in treating filler-induced facial skin ischemia. Relevant studies were identified through searches of electronic databases and manual screening of reference lists.

**Results:** findings demonstrated limited evidence supporting the efficacy of the nitroglycerin in this context. Although there are case studies indicate that the combination of nitroglycerin and hyaluronidase effectively treats filler-induced facial skin ischemia, only one case report demonstrates the efficacy of nitroglycerin alone. Furthermore, a rat model showed no benefits from nitroglycerin and revealed harmful results.

**Conclusion:** The evidence regarding the efficacy of nitroglycerin in treating filler-induced facial skin ischemia is inconclusive, which calls into question its routine use. Further studies are needed to ascertain the efficacy of nitroglycerin both as a standalone treatment and in combination with other therapies for this condition. Clinicians should consider the limited available data when selecting treatment options for individuals with filler-induced facial skin ischemia.

**Keywords:** nitroglycerin, facial, skin ischemia, dermal fillers, skin diseases, vascular

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## INTRODUCTION

Filling agents have been widely used in recent years to achieve aesthetic goals, providing sustained cosmetic benefits for up to one year <sup>1</sup>. Fillers are used for soft tissue augmentation and volumization in cosmetics procedures <sup>2</sup>. Moreover, dermal fillers

are utilized in various clinical conditions, including the treatment of tear trough deformity <sup>3</sup>, severe nasolabial folds <sup>4</sup>, osteoarthritis <sup>5</sup>, facial paralysis <sup>6</sup>, HIV-associated facial lipoatrophy <sup>7</sup>, among others. Achieving successful cosmetic and therapeutic outcomes depend on multiple factors, including

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the physician's technique and expertise, product characteristics, and patient-related variables<sup>8,9</sup>. However, adverse events and complications are inevitable<sup>10</sup>. Local or systemic reactions may lead to immune-mediated adverse effects<sup>11</sup>. FDA-approved filler products rarely cause hypersensitivity reactions<sup>12</sup>. These adverse responses have decreased due to improved physician education, standardized injection techniques, proper dilution, and avoidance injections into blood vessels<sup>13</sup>. Bacterial infections are rarely reported in pathological examinations of filler induced adverse events<sup>14</sup>. However, bacterial contamination during procedures can lead to bacterial cellulitis or abscess formation<sup>15</sup>. Certain fillers, such as injectable hyaluronic acids (HA), have short-term effects, and hyaluronidase can typically resolve their complications; in contrast, other fillers are permanent, making the management of their side effects more challenging<sup>16</sup>. The lack of evidence-based medicine in cosmetic practice has contributed to increased inexperience and incompetence in the diagnosis and management of side effects related to filler adverse events. Consequently, due to insufficient management protocols to prevent these side effects, there has been a rise in unwanted vascular or vascular-related complications. These complications are often referred for treatment at later stages and require more complex therapeutic approaches to achieve optimal recovery<sup>17</sup>. Because hyaluronic acid fillers can be injected at various tissue levels, there is a risk of unintended intravascular injection. If vascular occlusion is not promptly identified and treated, Tissue necrosis may develop. Unexpected intravascular filler injections are directly associated with more severe side effects and the formation of emboli, which can exacerbate life-threatening conditions, including cerebral embolism<sup>17</sup>. Intravascular injections are not uncommon; more than half of expert aesthetic clinicians with years of injection experience have reported such incidents<sup>18</sup>. Furthermore, these events can present with multiple symptoms, including sudden dermal changes indicative of ischemia<sup>19</sup>, nausea and vomiting, lateralized neurological symptoms, central nervous system manifestations, and even death<sup>20</sup>. Vision changes have also been reported in the literature<sup>21</sup> as a consequence of ophthalmic artery embolism<sup>22</sup>. A review of the literature does not support the sensitivity of aspiration prior to injection, despite its fundamental

role<sup>23</sup>. Additionally, skin ischemia and necrosis may occur following filler injections<sup>24-26</sup>. Reduced blood flow to the skin, or skin ischemia, is a common side effect of filler injections that may result from blood vessel compression or embolization filler material into arterial vessels<sup>24-26</sup>. This is a significant concern in the field of aesthetic, as it can result in serious complications and poor patient outcomes, often accompanied co-injuries to nerves or vision<sup>24-26</sup>. However, there is currently limited information on this topic, and the available studies are often conflicting and difficult to interpret. Case reports with individualized treatment remain the only available evidence. For filler-induced facial skin ischemia, various techniques and dosages are used, including topical applications of hyaluronidase<sup>28</sup>, intra-arterial injections of hyaluronidase<sup>27</sup>, and as pulsed hyaluronidase injections. Additionally, the timing of hyaluronidase administration is a critical factor in the effective treatment of ischemia injection<sup>30</sup>. Although adverse reactions to hyaluronidase are rare, some authors recommend performing a skin test prior to application<sup>31</sup>. A potential issue with hyaluronidase is its capacity to cause endothelial injury<sup>32</sup>, which may increase the risk of scarring or tissue damage. Although no research has been conducted, some authors have suggested nitroglycerin as a possible alternative or supplemental therapy for filler-induced skin ischemia. To provide a comprehensive overview of this potential complication of dermal filler injections, this narrative review focuses on filler-induced facial skin ischemia. By evaluating the potential benefits and risks of nitroglycerin as a treatment option, this study aims to guide clinical practice and improve outcomes for patients experiencing filler-induced skin ischemia.

## METHODS

This narrative review was conducted by searching electronic databases, including PubMed, Scopus, and Web of Science, up to July 1<sup>st</sup> 2025, using a combination of keywords, and Medical Subject Headings (MeSH) terms. PubMed search syntax was as follows: (“Nitroglycerin”[Mesh] OR “Nitroglycerin”[tiab] OR “glyceryl trinitrate”[tiab]) AND (“Facial Dermatoses”[Mesh] OR “Skin Ischemia”[Mesh] OR “facial ischemia”[tiab] OR “skin necrosis”[tiab] OR “vascular occlusion”[tiab])

AND (“Dermal Fillers”[Mesh] OR “Hyaluronic Acid”[Mesh] OR “fillers”[tiab] OR “soft tissue fillers”[tiab]) AND (“Treatment Outcome”[Mesh] OR “therapeutics”[Mesh] OR “efficacy”[tiab] OR “management”[tiab])

Boolean operators (AND, OR) were used to refine the search. Additional searches were performed in Scopus and Web of Science using similar keyword combinations. Manual screening of reference lists from retrieved papers identified further relevant studies.

### Eligibility Criteria

This review, limited to English-language publications without date restrictions, included original research papers, case reports, and systematic reviews examining the use of nitroglycerin for filler-induced facial ischemia in both human and animal studies. Exclusion criteria eliminated irrelevant studies on ischemia unrelated to fillers, non-English publications without available translations, conference abstracts lacking sufficient data, and duplicate reports.

### Data synthesis

Regarding the heterogeneity of the available evidence, the findings from 31 studies<sup>33-64</sup> were synthesized narratively to evaluate efficacy, underlying mechanisms, and clinical implications.

## RESULTS

### Pathophysiology and co-injuries of filler-induced skin ischemia:

Soft tissue augmentation with dermal fillers is performed to achieve a more youthful appearance and has become an integral part of procedures conducted by aesthetic physicians. When performing these procedures, physicians should be aware of the rare but clinically significant complications associated with dermal fillers<sup>33</sup>. Tissue necrosis can be prevented through prompt diagnosis and rapid management of ischemic events. Vascular occlusion occurs when blood flow through an artery that is obstructed. This occlusion may be complete or partial, resulting in reduced or halted blood flow<sup>34</sup>. Vascular blockage can be caused by internal factors, such as a blood clots, external factors like fillers, or compression from external sources. If left untreated, vascular blockage of the blood vessels supplying the skin can lead to skin necrosis and tissue death<sup>35</sup>. Necrosis

is often associated with the injection of soft tissue fillers, although it may also occur as a consequence of various cosmetic procedures. Injection of several types of skin fillers- such as collagen, hyaluronic acid, polymethylmethacrylate beads (PMMA), calcium hydroxylapatite, and autologous fat- has been reported to cause skin necrosis<sup>36,37</sup>. Ischemic complications resulting from filler injections can be attributed to several factors. Anatomical changes and variations due to scarring, trauma, or previous surgery may be a primary cause of intravascular injection, contributing to focal ischemia and necrosis<sup>38,39</sup>. Because scarring and structural alterations affect blood flow, patients who have undergone prior surgeries, such as cosmetic rhinoplasty, may be more susceptible to these complications<sup>40</sup>. For example, Grunebaum *et al.* reported a case of left alar necrosis in a woman who had previously undergone rhinoplasty following a hyaluronic acid injection into the nasolabial folds. The choice of filler products and knowledge of proper injection techniques play a significant role in minimizing potential side effects. In particular, deep injections of concentrated skin products in high-risk areas should be avoided. Superficial and intradermal injection, aspiration before injection by retracting the piston to ensure the needle tip is not in a blood vessel, and using small volumes of product over multiple treatment sessions will improve the aesthetic upshot<sup>41</sup>.

Dermal fillers can cause vascular occlusion for several reasons, including direct injury to the artery, compression of the surrounding tissue, or embolism within the vessel caused by the fillers, all of which disrupt vascular blood flow<sup>42</sup>. Arterial damage or occlusion is sometimes immediately apparent, indicated by local blanching of the injected area. When a bluish or purple discoloration and reticulation appear at the procedure site in the following days, ischemia should be suspected. Arterial occlusion typically presents with prolonged pain, swelling, and dark discoloration. Prompt identification and appropriate treatment of these adverse reactions are crucial, as untreated occlusion may lead to significant necrosis<sup>43</sup>. When these conditions occur at the anastomotic connections between the internal and external carotid arteries, the consequences can be particularly severe. Irreversible outcomes such as blindness, stroke, or both may result. Animal studies

have shown that the retina can tolerate hypoxia for up to 97 minutes before sustaining irreparable damage. However, more recent studies indicate that vascular occlusion can cause retinal infarction within 12 to 15 minutes<sup>44</sup>. A 10-year retrospective analysis conducted by the U.S. Food and Drug Administration (FDA) from 2007 to 2017 reported 42 cases of visual impairment and 47 cases of blindness associated with filler injections<sup>45</sup>. Several superficial facial arteries -including the supraorbital, supratrochlear, dorsal nasal, and angular nasal arteries- are terminal branches of the ophthalmic artery. During soft tissue filler injections, the needle or cannula can inadvertently puncture the wall of one of these terminal branches and enter the arterial lumen. If the tip of the needle or cannula is within the arterial lumen, pushing the syringe plunger to expel the filler will inject the material directly into the artery. The filler displaces the arterial blood and moves as a column toward the origin of the retinal artery as pressure on the plunger increases<sup>46</sup>. Injection pressure ceases immediately when the surgeon stops applying force to the plunger, after which the arterial systolic pressure propels the filler into the branches of the ophthalmic artery. Even a small amount of filler entering the retinal artery can cause central retinal artery occlusion, potentially resulting in permanent blindness. Obviously, the same soft tissue filler can embolize the arterial supply to the mucosa, conjunctiva, or skin, leading to necrosis. Because these arteries are small, the volume of filler required to reach even the internal carotid artery is likely minimal. According to one study, blindness, stroke and skin necrosis were reported following the injection of only 0.5 ml of filler into the left side of the bridge of the nose<sup>46,47</sup>.

### **Nitroglycerin: Structure, and Mechanism of Action**

Nitroglycerin is an organic nitrate that belongs to a class of anti-anginal and vasodilator drugs active in both arteries and veins. It functions by dilating the coronary arteries of the heart, which is why it is classified as an anti-anginal medication<sup>48</sup>. These drugs act as anti-anginal, anti-ischemic, and antihypertensive agents by dilating peripheral and coronary arteries, thereby reducing both preload and afterload on the heart, as well as decreasing the myocardium's oxygen demand, ultimately lessening

cardiac workload. Nitroglycerin should not be used in individuals allergic to nitroglycerin, isosorbide mononitrate, or isosorbide dinitrate<sup>48</sup>. Additionally, nitroglycerin is employed in skin grafting procedures to enhance the likelihood of successful grafting. Its strong local vasodilation effect increases blood flow to skin flaps, potentially improving flap survival. Nitroglycerin induced vasodilation by generating nitric oxide, which relaxes vascular smooth muscle and enhances tissue perfusion, primarily affecting veins and thereby improving the skin flap salvage response. A notable beneficial effect of nitroglycerin is its antithrombotic property<sup>49</sup>. Several studies have demonstrated a reduction in tissue necrosis associated with nitroglycerin use. In the research conducted by Ghanbarzadeh *et al.*, the application of nitroglycerin ointment in an experimental group of rats reduced tissue flap necrosis from 24% to 16.1% compared to the control group<sup>50</sup>. Similarly, a 2022 study by Ellabban *et al.* reported therapeutic effects of nitroglycerin in cases of venous congestion, with a necrosis level of 19.2%<sup>51</sup>. This study showed that nitroglycerin helps restore epidermal thickness, keratinocyte characteristics, and dermal collagen and fibroblast integrity by mitigating necrosis in venous-blocked flaps. Additionally, a study by Aral *et al.* on rats found that the topical application of Nitroglycerin via a transdermal patch decreased the percentage of flap necrosis from 51.3% to 39.9%<sup>52</sup>.

Nitroglycerin, also known as glyceryl trinitrate (GTN), has the chemical formula of C<sub>3</sub>H<sub>5</sub>N<sub>3</sub>O<sub>9</sub>. Its molecular structure consists of a glycerol molecule with three hydroxyl (OH) groups, each esterified with a nitrate (NO<sub>3</sub>) group<sup>48</sup>.

### **Nitroglycerin for filler-induced skin ischemia:**

Some experts endorse the efficacy of nitroglycerin paste for treating filler-induced skin ischemia; nonetheless, this remains a contentious area with limited evidence. Multiple treatment methods have been proposed to mitigate the adverse effects of dermal fillers, including the use of nitroglycerin ointments and skin patches as viable options<sup>53</sup>. The idea of using nitroglycerin paste and skin patches for filler-induced ischemia likely originates from its application in improving ischemic flap survival. In a study by Glaich *et al.*, the authors recommended using warm compresses to dilate vessels when blanching

was observed, followed by nitroglycerin to further enhance vasodilation<sup>54</sup>. The vasodilatory properties of nitroglycerin were also discussed in a review by Kleydman *et al.* According to clinical research, nitropaste or nitroglycerin paste is not entirely free of risks or side-effects<sup>55</sup>. In an individual patient-level systematic review and meta-analysis study conducted by Sama *et al.* on the effect of nitroglycerin on tissue reperfusion and the improvement of necrosis following cosmetic filler injections, it was shown that, among the 66 case reports included in the study, only 7 involved the use of topical nitroglycerin. Of these, 6 cases successfully prevented tissue necrosis. Therefore, topical nitroglycerin may be considered a viable therapeutic option for tissue necrosis caused by dermal filler use<sup>56</sup>. However, Yuan's trial was the only one to employ nitroglycerin without hyaluronidase. In this case, cutaneous necrosis occurred after injection with poly-L-lactic acid. Nitroglycerin was applied alone for 30 minutes, accompanied by a warm compress to enhance its effect, which ultimately resolved the necrosis completely without causing scars or wounds<sup>57</sup>.

The study of Hwang *et al.* investigated whether topical nitroglycerin ointment could improve perfusion in filler-induced tissue ischemia using a rabbit ear model. Fillers were injected into the ears, and 30 minutes later, nitroglycerin ointment was applied topically. However, no statistically significant improvement in perfusion was observed, and the rabbit ear skin treated with nitroglycerin ointment appeared more congested than the controls. The authors caution against using topical nitroglycerin ointment in patients presenting with filler-associated ischemia and suggest that further studies are needed to establish the optimal treatment algorithm for such cases<sup>58</sup>. Some authors have reported successful outcomes using sublingual nitroglycerin in combination with standard hyaluronidase treatment<sup>59</sup>.

Nitroglycerin is applied in other medical conditions involving skin ischemia. The potential efficacy of topical nitroglycerin in managing symmetrical peripheral gangrene (SPG) in a pediatric patient is explored in a case report<sup>60</sup>. It has also been shown to be effective in the treatment of frostbite<sup>61</sup>. Its therapeutic effects on diabetic ulcers have been attributed to the treatment of ischemia caused by vascular disease<sup>62</sup> as shown by in-vivo research<sup>63</sup>.

Moreover, topical nitroglycerin ointment provides a safe therapeutic option for the salvage treatment of neonatal tissue ischemia, based on a review of 23 studies<sup>64</sup>.

## DISCUSSION

The use of nitroglycerin in treating filler-induced facial skin ischemia remains controversial due to inconsistent findings from clinical and experimental studies. This narrative review found limited evidence supporting nitroglycerin's efficacy, with only one case report demonstrating success when administered alone, and a rat model indicating no benefit and potential damage. These conflicting results have significant implications for clinical practice and future research. Regarding the potential for adverse effects- such as worsening ischemia or systemic side effects like hypotension and dizziness, as noted by Hwang *et al.*<sup>58</sup> the routine use of nitroglycerin as a standalone treatment for filler-induced facial skin ischemia cannot be recommended based on current evidence. Instead, clinicians should consider incorporating it into a comprehensive treatment strategy that includes hyaluronidase for hyaluronic acid fillers, as advised by the Management of Vascular Occlusion guidelines. The limited use of nitroglycerin reported by Carley *et al.* (10% of 66 cases) highlights the need for caution and the importance of combining it with other treatments<sup>56</sup>. To resolve these uncertainties, well-designed clinical trials are essential to establish standardized treatment protocols and clarify the role of nitroglycerin, whether used alone or in combination with other therapies. Until such evidence is available, practitioners must carefully weigh the potential benefits against the risks and consider alternative or adjunctive treatments to optimize patient outcomes.

## CONCLUSION

The review showed limited evidence supporting the efficacy of nitroglycerin in treating filler-induced facial skin ischemia. Although a combination of nitroglycerin and hyaluronidase has been shown to be effective in managing this condition, only one case report has documented the use of nitroglycerin alone. Furthermore, a rat model demonstrated no benefits from nitroglycerin and even suggested potential adverse effects. Current evidence regarding

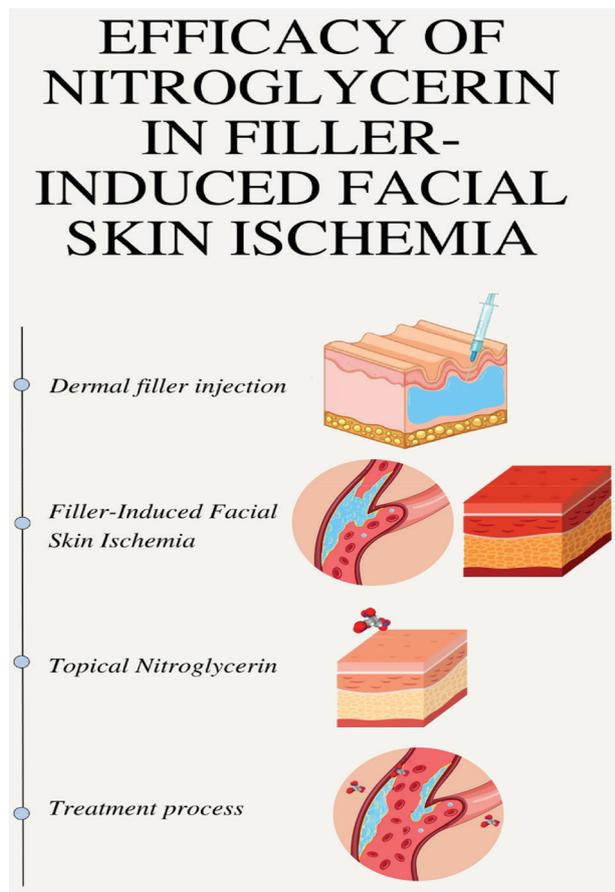


Figure 1. graphical abstract of review is demonstrated.

the efficacy of nitroglycerin for filler-induced facial skin ischemia remains inconclusive and indicates that its use may not be effective (summarized in Figure 1). Further research is necessary to evaluate the effectiveness of nitroglycerin both as a monotherapy and in combination with other treatments for this condition. Clinicians should be exercise caution and consider the limited evidence base when selecting treatment options for patients with filler-induced facial skin ischemia.

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### Authors contributions

MD conceived the idea for the review. NK, MD and ZKH contributed to the literature review. NK, MD and

ZKH provided critical input and expertise in the field of dermatology. NK, MD and ZKH contributed to the conceptualization of the manuscript and assisted in the organizing the content. MD supervised the entire process and ensured the coherence of the narrative. All authors critically reviewed and approved the final version of the manuscript.

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