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PRS GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Nontopical Nitrates in Flap Perfusion and Delay Phenomenon

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Background: Topical nitrates have demonstrated efficacy in improving flap perfusion. However, evidence for nontopical nitrates in modulation of flap perfusion dynamics has yet to be consolidated. Here, we review evidence regarding the use of intravascular, sublingual, and oral nitrates in modulating flap perfusion.
Methods: We performed a review of the literature for evidence linking nontopical nitrates and flap perfusion, and included clinical studies, animal studies, and in vitro studies.
Results: Evidence suggests that intravascular, sublingual, and oral nitrates exert vasodilatory properties, which may be harnessed for identification of perforators and improved flap perfusion. We also found evidence suggesting nitrates may facilitate ischemic preconditioning while reducing ischemia–reperfusion injury.
Conclusions: Nitrates delivered intravascularly, sublingually, or orally may increase flap perfusion and serve as a method for ischemic preconditioning, particularly in the intraoperative setting. *(Plast Reconstr Surg Glob Open 2024; 12:e5918; doi: 10.1097/GOX.0000000000005918; Published online 17 June 2024.)*

INTRODUCTION

Insufficient vascular perfusion and lack of control of flow dynamics are challenges in flap reconstruction. Pharmacological modulation of flap perfusion dynamics may provide surgeons means to mitigate ischemia and direct flap perfusion. Nitric oxide (NO) stimulates guanylyl cyclase in smooth muscle, present in vascular wall, resulting in an increase in cyclic GMP that induces vascular vasodilation. NO precursors, such as nitroglycerin, have shown clinical utility in reconstructive surgery. Two recent meta analyses found that topical nitroglycerin reduced rates of mastectomy flap necrosis and debridement.[1,2] Consistently, a systematic review found that in neonatal peripheral tissue ischemia, topical nitroglycerin ointment promoted recovery in 76% of cases, whereas glyceryl trinitrate provided recovery in 53.8% of cases.[3]

However, limited clinical evidence exists regarding the use of nontopical nitrates in modulation of flap perfusion. Here, we review evidence regarding the use of intravascular, sublingual, and oral nitrates in modulating flap perfusion. We chose not to include topical or transdermal nitrate formulations because there is extensive literature that has been analyzed recently.[1,2] We highlight key findings regarding the potential role of nitrates in ischemic preconditioning, identification and utilization of sizeable perforators, and flap blood flow (Tables 1–3). Finally, we synthesize these findings into a novel strategy for use of nitrates to control flap perfusion dynamics.

VASODILATORY PROPERTIES OF NITRATES IN FLAPS

Several studies highlight the ability of nitroglycerin to promote vasodilation in flaps, particularly under prevasoconstricted conditions. These studies were done on free flaps. In the case of ex vivo flaps, sizeable vessels were cannulated for perfusion studies and thus mimicked free flaps (Table 1). Nitroglycerin promoted vasodilation in norepinephrine preconstricted ex vivo human skin flaps derived from dermolipectomy.[5] Similarly, nitroglycerin induced vasodilation in a norepinephrine preconstricted isolated perfused porcine skin flap.[6] The preconstricted conditions enabled the study of the maximal vasodilatory effects of nitroglycerin and also enabled proper titration of pressure within the flaps under ex vivo conditions. Additionally, during surgery, flaps may experience a vasoconstriction in response to transection of sympathetic nerves accompanying vessels, which release norepinephrine. The preconstricted conditions in the ex vivo studies, therefore, may

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Received for publication January 28, 2024; accepted April 30, 2024.

DOI: 10.1097/GOX.0000000000005918

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

potentially recapitulate certain aspects of this in vivo phenomenon. In ex vivo transverse paraumbilical human skin flaps, nitroglycerin was able to induce vasodilation before and after damaging of the endothelium with saponin, suggesting that nitroglycerin exerts its vasodilatory properties in an endothelium-independent manner.[4]

Nitroglycerin has also demonstrated utility in preoperative assessment of flap perforators (Table 2). Preoperative assessment of anterolateral thigh flap perforators by computed tomography (CT) angiography was performed 4 minutes after administration of 0.3 mg sublingual nitroglycerin.[8] Nitroglycerin resulted in successful identification and selection of sizeable perforators with accurate localization intraoperatively. CT angiography performed after nitroglycerin administration showed increased dilation of small peripheral arteries, dilation of small peripheral arteries, and increased number of assessable branches, compared with CT angiography without nitroglycerin.[8] Perforators were selected based on distance from intermuscular septum and size.[8] In another study assessing anterolateral thigh flap vascularization by CT angiography, sublingual glyceryl trinitrate resulted in increased lumen diameters of deep femoral artery, lateral circumflex femoral artery (LCFA), descending branch of LCFA and its perforators ($P < 0.01$) and increased number and qualitative grade of visible perforators.[9] These findings suggest the preoperative utility of nitrates to increase vascular caliber for identification of perforators and surgical planning.

In a series of human free tissue transfers for head and neck reconstruction, all of which were free flaps, a verapamil-nitroglycerin solution applied topically to the vessels prior and after anastomosis resulted in a 48% increase in vascular caliber measured at 30 minutes after administration, with elimination of vasospasm[7] (Table 2). These findings suggest that vasodilatory properties of nitrates can be extended to intraoperative applications, with the goal of rapidly increasing vascular caliber, which may be useful in establishment of robust perfusion while decreasing vasospasm. It is important to note, however, that the effects observed cannot be solely attributed to nitrates, because a combination verapamil-nitroglycerin was used. In this study, utilization of verapamil-nitroglycerin solution did not change flap survival rate (~99%), and changes in perfusion were not explicitly measured. Given the adventitial administration of the verapamil-nitroglycerin solution, the results may reflect localized changes in the vessel, leading to vasodilation and potentially increased distal flow. Because intraluminal administration was not performed, direct effect of verapamil-nitroglycerin on distal flap vasculature is less likely. The increased vessel diameter observed after 30 minutes may be useful in anastomoses of small-caliber vessels. Although the long-term maintenance of perfusion was not assessed explicitly in this study, the lack of adverse effects combined with the relatively quick onset and no change in the 99% flap survival rate suggest utility in adventitial administration of verapamil-nitroglycerin. The rate of vasospasm during microvascular anastomosis is highest during the initial dissection and handling of the vessels, in response to mechanical manipulation and potential thermal injury from electrocautery, and therefore, the use of verapamil-nitroglycerin intraoperatively is likely to be most useful. However, vasospasm can occur at any time intraoperatively and postoperatively. Future investigations are required to evaluate the utility of verapamil-nitroglycerin or nitroglycerin alone for postoperative vasospasm.

Takeaways

Question: What is the role of nontopical nitrates in modulation of flap perfusion?

Findings: Evidence suggests that intravascular, sublingual, and oral nitrates exert vasodilatory properties, which may be harnessed for identification of perforators and improved flap perfusion. Nitrates may also facilitate ischemic preconditioning while reducing ischemia–reperfusion injury.

Meaning: Nontopical nitrates may increase flap perfusion and serve as a method for ischemic preconditioning, particularly in the intraoperative setting.

NITRATES IN MITIGATION OF ISCHEMIA

A series of experimental studies performed on rats demonstrated the utility of nitrates in mitigation of adverse ischemic effects on flaps (Table 3). In rat epigastric adipocutaneous flap, preischemic intravenous administration of

Table 1. Ex Vivo Studies Utilizing Nitrates for Modulation of Flap Perfusion

Author, Year	Model	Type of Flap	Intervention	Drug	Dosage	Duration of Treatment	Result
Kreidstein et al, 1992[4]	Human: in vitro human dermolipectomy derived skin flap model	Free flap (in vitro): paraumbilical artery and vein	Intra-arterial nitroglycerin perfusion	Nitroglycerin	1×10^{-6} M	10 min	Induction of vascular dilation
Black et al, 2001[5]	Human: in vitro human paraumbilical skin flap model	Free flap (in vitro): paraumbilical artery and vein	Intra-arterial nitroglycerin perfusion	Nitroglycerin	1×10^{-8} to 1×10^{-5} M	Not explicitly reported	Dose-dependent induction of vascular dilation in setting of preconstriction by norepinephrine
Rogers and Riviere, 1994[6]	Pig: isolated perfused porcine skin flap	Single pedicle, axially patterned ventral abdominal skin flap (in vitro)	Intra-arterial nitroglycerin perfusion	Nitroglycerin	5×10^{-8} to 5×10^{-5} M	1 h	Nitroglycerin lowered vascular resistance in a dose-dependent manner in norepinephrine preconstricted flaps

Table 2. Human Studies Utilizing Nitrates for Modulation of Flap Perfusion

Author, Year	Model	Type of Flap	Intervention	Drug	Dosage	Duration of Treatment	Result
Seth et al, 2021[7]	Human free tissue transfer for head and neck defect reconstruction	Free flaps; anterolateral thigh, fibula, radial forearm, latissimus, iliac, gracilis	Nitroglycerin + verapamil solution applied topically to the arterial adventitia of recipient and donor vessels prior to and following anastomosis	Nitroglycerin	Nitroglycerin 8.3 µg/mL; verapamil 16.7 µg/mL	Postadministration measurement: 30 min after administration	48% increase in recipient vessel ($P < 0.01$), elimination of vasospasm
Watanabe et al, 2020[8]	Preoperative assessment of anterolateral thigh flap perforators by CT angiography following sublingual nitroglycerin	Free flap: ALT	Sublingual nitroglycerin administration before CT angiography	Nitroglycerin	0.3 mg	CT angiography performed 4 min after nitroglycerin administration	Sizeable perforators identified and accurately located intraoperatively without any error; dilation of small peripheral arteries, dilation of small peripheral arteries, and increased number of assessable branches
Lu et al, 2023[9]	Preoperative assessment of anterolateral thigh flap perforators by CT angiography after glyceryl trinitrate	Free flap: ALT	Sublingual glyceryl trinitrate before CT angiography	Sublingual glyceryl trinitrate	Not explicitly reported	Not explicitly reported	Increased lumen diameters of deep femoral artery, LCFA, descending branch of LCFA and its perforators ($P < 0.01$); increased number and qualitative grade of visible perforators

ALT, anterolateral thigh.

Table 3. Animal Studies Utilizing Nitrates for Modulation of Flap Perfusion

Author, Year	Model	Type of Flap	Intervention	Drug	Dosage	Duration of Treatment	Result
Gatti et al, 1986[10]	Rat skin flap model, with intravenous nitroglycerin given 30 min before or after flap elevation	Dorsal pedicle skin flap	Systemic intravenous nitroglycerin given before or after flap surgery	Nitroglycerin	50 µg/kg/min	Preoperative nitroglycerin: 30 min; Postoperative nitroglycerin: 48 h	Improved flap blood flow as evidenced by perfusion fluorometry
Kuntscher et al, 2002[11]	Rat epigastric adipocutaneous flap	Left epigastric adipocutaneous flap based on left epigastric artery	Preischemic IV spermine/nitric oxide; postischemic IV spermine/nitric oxide; ischemia (3 h) induced by Yasargil clip compressing pedicle	Spermine/NO	500 nmol/kg	Preischemic spermine/NO: 30 min; Postischemic nitroglycerin: 5 min before reperfusion	Preischemic application of spermine/NO showed a significantly lower area of flap necrosis than either of the control groups or the group receiving spermine/NO just before reperfusion ($P < 0.05$)
Cui et al, 2020[12]	Rat dorsal skin flap with ischemia/reperfusion injury	Dorsal skin flap based on deep circumflex artery	Per oral sodium nitrate given before flap surgery and ischemia (10 h) induced by clamping deep circumflex iliac	Sodium nitrate	5 mmol/L	From 7 d preoperatively	Administration of per oral sodium nitrate before flap surgery and ischemic-reperfusion injury reduced flap necrosis and tissue edema

spermine/NO complex, which is an NO donor, was shown to significantly decrease flap necrosis compared with postischemic administration.[11] It is important to note, however, that the effects observed cannot be solely attributed to NO because the spermine/NO complex was used. In a rat skin flap model, intravenous administration of nitroglycerin improved flap blood flow and flap survival.[10] These findings suggest that preischemic administration of nitrates have protective effects against subsequent ischemia. Consistently, in rats, dietary nitrate was shown to reduce skin flap ischemia–reperfusion (IR) injury.[12] Pretreatment with nitroglycerin has been shown to mitigate IR injury in rat intestine.[13] It is important to note that rat skin is different from human skin, particularly because it includes the muscular panniculus carnosus. When applying principles from rat studies to human flaps, the different structure and possibly different metabolic demand due to the presence of muscle should be considered.

Ischemic preconditioning refers to the intentional induction of a state of controlled ischemia to tissue, which

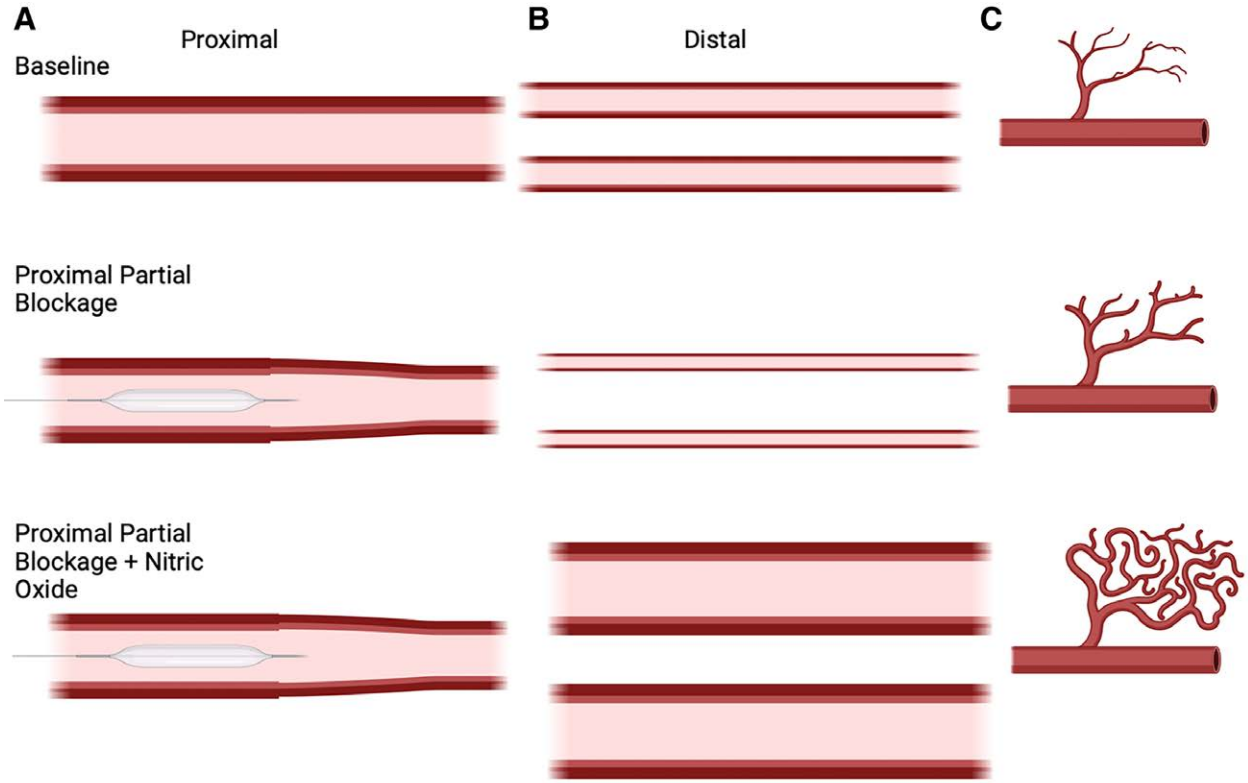

Fig. 1. Proposed model of nitrates in ischemic preconditioning of flaps. A, At baseline, a proximal pedicle branches into distal perforators and terminates as microcirculation in the flap. B, Partial occlusion of the proximal pedicle reduces blood flow to the distal circulation. If the ischemia remains sublethal, the hypoxic microcirculation will undergo microvascular growth. C, Combined partial occlusion of the proximal pedicle and nitrate administration will improve distal blood flow through vasodilation, counter vasoconstriction, and enhance angiogenesis through induction of VEGF. Created with BioRender.com.

then stimulates the tissue's vascular network to adapt and increase collateral circulation. In reconstructive surgery, the delay phenomenon applies principles of ischemic preconditioning to flaps.[14] The utility of the delay phenomenon includes increased length-to-width ratio in random-pattern flaps and extension of axial flaps beyond their typical range. Delaying flaps involves flap isolation on its axial blood supply, which will dilate and reorient choke vessels to anastomose, thereby strengthening blood supply. Additionally, it has been proposed that vasoconstriction occurring during flap dissection is due to the transection of sympathetic nerves accompanying the vessels, leading to norepinephrine release. By delaying the flap, the release of norepinephrine is cleared from tissues, and flap harvesting after the delay prevents this vasoconstriction.[15] On the molecular level, the delay procedure leads to hypoxia which induces hypoxia inducible factor 1 alpha that subsequently leads to the production of vascular endothelial growth factor (VEGF), which drives vascularization,[16] including choke zone vascularization.[17]

Critically, the sequential dilation of choke vessels during delay occurs between 48 and 72 hours,[18] and represents the manifestation of the proangiogenic response. Jung et al[19] demonstrated that the renoprotective effects of remote ischemic preconditioning of rat hindlimb were mitigated by administration of N-nitro-L-arginine methyl ester, an NO synthase inhibitor, suggesting that ischemic preconditioning is mediated, at least in part, by NO. At a molecular level, a study done on rat vascular smooth muscle cells showed that inducible NO synthase (the enzyme that makes NO) induces VEGF.[20] This may suggest that early introduction of NO may accelerate production of VEGF and enhance choke vessel function, thereby achieving ischemic preconditioning in less time. Importantly, VEGF also increases NO,[21,22] which suggests a positive feedback loop between VEGF and NO.

PROPOSED UTILIZATION OF NITRATES

Based on the principles gleaned from the literature, we propose an innovative method that combines the principles of ischemic preconditioning with the rapid vasodilatory and proangiogenic effects of nitroglycerin. This approach aims to mediate hemodynamic changes in perforator branches and distal vessels, significantly enhancing microvascular proliferative capacity and angiogenesis in the distal areas of the flap (Fig. 1). Importantly, this is relevant to axial, perforator, and free flaps. The approach may be combined with the standard delay procedure, with the goal that the nitrate administration, due to the ischemic preconditioning, vasodilatory, and proangiogenic properties, may reduce the time necessary for the beneficial effects of delay to be gained.

After dissection, the axial vessels or primary vessels for free flaps are identified. For axial flaps, because the vessels will not be ligated, it is important to consider cannulation of the primary vein before nitrate administration arterially, to siphon off the nitrate solution to prevent systemic nitrate entry. For free flaps, the cannulation of the primary vein can be considered if an additional delay period will be performed. If no additional delay period will be performed, then the vein can be ligated to allow drainage of the nitrate solution.

Next, clamping the proximal arterial pedicle will reduce flow in distal portions of the vascular network. The drop in pressure and flow, combined with the transection of sympathetic nerves, may trigger a neurovascular vasoconstrictive response that may further decrease blood flow. Over time, the tissue subsequently undergoes metabolic adaptation in response to hypoxia, resulting in increased concentrations vasodilatory substances, including CO_2, adenosine, lactate, potassium, and H^+ ions, which counteract the initial vasoconstriction. This response may be insufficient and manifests as peripheral flap edge necrosis. Partial clamping is likely to be more beneficial due to reduced IR injury, compared with intermittent complete clamping, and can be achieved using an internal catheter or external partial clamp to partially occlude the proximal vessel. For the internal catheter approach, a small cannula can be used, rather than an occlusive catheter, to modulate the decreased blood flow, and also allows for intravascular access and administration of nitroglycerin. The size of the cannula depends on the caliber of the perforator or axial vessel. For example, for smaller caliber vessels, including those with diameters around 1 mm, fine microcannula can be used, such as 20 gauge (0.908 mm outer diameter) to 27 gauge (0.413 mm outer diameter) sizes. For perforator flaps, administration within the perforator is preferred compared with the source vessel due to increased localization of nitrates to the flap. Potential risks include damage to the proximal part of the artery, distal ischemia, bleeding, thromboembolic events, arterial tears, and infection. In free flaps not undergoing delay, the vessel can be cannulated proximally and ligated just proximal to the point of cannulation to avoid risk of arterial compromise. Proper insertion technique should be utilized to avoid damaging the vessel and nearby structures. Careful and thorough dissection during initial flap lifting should identify vessels and structures which should be preserved. Careful monitoring, careful manipulation, and proper removal of the cannula should be performed to ensure vascular integrity. Furthermore, there is potential for morbidity from this invasive intervention, including flap ischemia and foreign body infection.

Next, intra-arterial nitroglycerin is injected in titrated dosages in the arterial vessel supplying the flap. The NO will induce vasodilation distal to the site of partially clamped vessel. The immediate vasodilatory response (within minutes) mitigates the adverse effects of neuroreflexive vasoconstriction, and decreased blood flow and, crucially, initiates angiogenesis pathways.[20] The decreased blood flow from the initial clamping will enable a longer circuit perfusion time and enable the nitrate to take effect within minutes. To reduce systemic entry of nitrates and potential hypotension, cannulation of the dissected flap vein can allow siphoning of the nitrate containing perfusate. This approach stimulates angiogenesis immediately, bypassing the delays associated with vasodilatory substance buildup. Indeed, proangiogenic growth factors, such as VEGF, increase angiogenesis in part through increase in NO.[21] Moreover, the critical role of nitrates in inducing angiogenesis under ischemic conditions is well established, particularly in the cardiac literature.[23,24] Introducing nitrates intraoperatively after flap dissection, but before harvesting, may accelerate adaptive angiogenic processes quicker than the typical delay period, which usually takes days to a few weeks. For flaps undergoing delay, after the administration of nitrates, the arterial and venous cannulas can be removed with caution, and the flap can be delayed in a standard manner. For free flaps not undergoing delay, after the administration of nitrates, the vessels can be ligated in a standard manner. Therefore, the vessel would be partially clamped for a duration of up to about 5 minutes, whereas the nitrate solution is being circulated.

We propose that in this model, although baseline ischemia exists due to decreased flow proximally, vasodilation of distal vessels provides an optimal redistribution of perfusion, particularly to areas that would otherwise be constricted. Combined with the proangiogenic properties of nitrates, this approach may enhance flap vascularization, perfusion dynamics, and flap survival.

DISCUSSION

Currently, the use of nitrates in flaps is primarily as a topical agent. Although this may be useful in the postoperative setting, our literature review provides evidence that nitrates may be used in the intraoperative setting due to the rapid onset of action. The vasodilatory effects of intravascular nitroglycerin occur within 1–3 minutes, with maximal activity occurring at 5 minutes of administration. This is much quicker than topical nitroglycerin, which takes 9–11 minutes.[25] The concentration of nitroglycerin or NO donors must be optimized and titrated based on systemic blood pressure, flap weight, flap dimensions, and microvascular risk factors, such as smoking, hypertension, and diabetes mellitus. Optimally, the NO should be dosed such that the limited amount is consumed in the local vascular network and converted to excretable nitrites or nitrates. It is also possible to generate a closed loop flap circulation whereby the nitroglycerin is administered through the arterial perforator and siphoned through the dominant venous perforator, to reduce systemic side effects.

The delay phenomenon promotes flap vascularity and success. However, there are challenges with delay phenomenon, including the duration which typically ranges from days to a few weeks. Furthermore, there is limited control on the level of ischemia that can result in reduced flap survival. Furthermore, lifting a flap on a particular perforator or pedicle most likely induces peripheral ischemia and subsequent ischemia-driven microvascular angiogenesis that is not central. Often, however, the angiogenesis is insufficient, as evidenced by flap edge necrosis. Because

Table 4. Risks, Localization, and Advantages of Topical, Adventitial, Intra-arterial, and Systemic Administration of Nitrates for Modulating Flap Perfusion

	Topical	Adventitial	Intra-arterial	Systemic (Intravenous)
Risks	Variable absorption	Potential to diffuse intraluminally leading to systemic side effects;	Potential to travel systemically if not titrated correctly or if not siphoned off via vein (closed circulation)	Systemic side effects; headaches, dizziness, nitrate-induced hypotension, syncope, nitrate tolerance, nitrate rebound, nitrate-induced coronary steal phenomenon, potential drug–drug interactions with PDE5 inhibitors and antihypertensives
Localization	Localized	Localized	Localized	Nonlocalized
Advantages	Noninvasive; can be administered easily postoperatively	Direct vasodilation of proximal flap circulation	Direct vasodilation of proximal and distal flap circulation	Improved flap perfusion via intravenous access

the central vascular supply remains intact during the lifting process, the central portions of the flap remain relatively normoxic and not stimulated to induce angiogenesis, with only peripheral areas experiencing relative hypoxia.

Because we found that nitrates have both proangiogenic and ischemic preconditioning properties, administration of nitrates during a period of immediate preconditioning is likely to accelerate angiogenic pathways, leading to increased flap perfusion and survival, and decreasing the need for delay. Furthermore, the central delivery of nitrates ensures that both central and peripheral flap circulation undergo the proangiogenic effects.

The use of topical nitroglycerin is an alternative approach that may have similar effects but remains limited in duration of onset, locoregional targeting, and variability of absorption.

Precise control of the perforator, afforded by an intravascular catheter or external clamp, offers advantages over topical nitroglycerin. Partial occlusion of the proximal perforator also maintains a lower baseline flow rate, thus mitigating rapid changes in flow and associated IR injury.

However, there are many risks associated with intravascular nitrate administration for flap surgery (Table 4). Intra-arterial administration of nitrates has a high risk of entering systemic circulation, even if the corresponding flap vein is cannulated to siphon off the perfusate. Systemic side effects of nitrates include headaches, dizziness, nitrate-induced hypotension and potential syncope, development of nitrate tolerance, nitrate rebound, and nitrate-induced coronary steal phenomenon. Therefore, based on the patient's comorbidities, medications, and cardiovascular status during the operation, the use of nitrates should be considered carefully and may be contraindicated.

CONCLUSIONS

Our findings suggest that intravascular, sublingual, and oral nitrates exert vasodilatory properties, which may be harnessed for identification of perforators and improved flap perfusion. We also found evidence suggesting nitrates may facilitate ischemic preconditioning while reducing IR injury. Future studies should investigate the duration and dosage of nitrate necessary for clinically meaningful changes in vascularity and survival. Future studies, inclusive of both animal studies and human flap studies, should also further characterize the utility of this study and potential side effects. Although intraoperative application of this method would save a second operation, compared with the delay procedure, a formal cost analysis is also necessary to evaluate the feasibility of this procedure.

These beneficial impacts of nitrates could possibly be combined into a strategy to accelerate the process of ischemic preconditioning while increasing flap perfusion, especially during the intraoperative setting. Further studies are necessary to further understand the effect of intravascular nitrates on perfusion dynamics, particularly as it relates to venous congestion and thrombosis. The studies we found focused on free flaps and axial flaps; future studies should investigate the vasomodulatory effects of nitrates on random flaps. It is also necessary to further evaluate the effect of preoperative systemic and local nitrates on perforator identification and flap perfusion.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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