Anterograde Injection of Alteplase Salvages Deep Inferior Epigastric Perforator Flap in Reconstructive Breast Surgery

Julia M. Wimbauer, MD
Klemens M. Heinrich, MD
Karl Schwaiger, MD
Peter Pumberger, MD
Fabian Koeninger, MD
Gottfried Wechselberger, MD, MSc
Elisabeth Russe, MD

Summary: The DIEP flap is currently considered the gold standard for autologous reconstructive breast surgery. Postoperative flap failure due to microvascular post-anastomotic thrombotic occlusion is a rare but severe complication. Alteplase, a thrombolytic agent typically used in the setting of an ischemic stroke, myocardial infarction, or pulmonary embolism, has also been injected into the microcirculation of flaps as a rescue procedure due to imminent flap loss. The purpose of this article is to provide an overview and detailed guidance for such a thrombolytic procedure due to suspected thrombotic microsurgical failure in free flap surgery. We report the case of a 43-year-old woman who underwent unilateral breast reconstruction with a DIEP flap at our department. Approximately 12 hours postoperatively, an arterial inflow problem was suspected and revision surgery was performed. Peripheral flap perfusion remained absent without an obvious cause and distal thrombosis was assumed to be present. Therefore, alteplase was gradually injected into the arterial pedicle in the anterograde direction just distal to the anastomosis while clamping the artery proximally. About 3 hours after selective flap thrombolysis, microcirculation of the flap was successfully restored without complications. Anterograde injection of alteplase can successfully salvage a free flap. To our knowledge, evidence for optimal dosing and delivery of alteplase for the treatment of thrombosed DIEP flaps has not been published to date. Our approach presents a therapeutic option that both maximizes alteplase concentration in the flap and minimizes the dosage required for flap salvage to significantly reduce systemic adverse effects. (Plast Reconstr Surg Glob Open 2022;10:e4415; doi: 10.1097/GOX.0000000000004415; Published online 20 June 2022.)

CASE REPORT

A 43-year-old woman with a history of breast cancer of the left breast presented at our hospital and asked for autologous breast reconstruction. The decision was made to perform a DIEP flap 1 year after uneventful follow-up. A single venous anastomosis was performed with a 2.0-mm coupler between the inferior epigastric vein and the internal mammary vein at the level of the fourth rib. Microvascular anastomosis between the deep inferior epigastric artery and the internal mammary artery with a...
noticeable difference in the caliber was performed with 8-0 nylon. Intraoperatively, 40mg intravenous bolus of heparin was given. Postoperatively, our thrombosis prophylaxis regimen included subcutaneous heparin, 20mg in the morning and 40mg in the evening.

Clinical Findings

Approximately 12 hours postoperatively, an arterial inflow problem was suspected and revision surgery was performed. Despite a patent arterial anastomosis was confirmed by Doppler sonography and probing, peripheral flap perfusion remained absent without an obvious cause.

Inspection of the vascular pedicles revealed no twisting, kinking, and external compression of the pedicle could be excluded. Both Doppler sonography and milking test were performed to confirm patency of the donor artery and vein, anastomosis, and the recipient artery and vein. Distal thrombosis was assumed to be present, when peripheral flap perfusion remained absent without an obvious cause.

Therapeutic Focus and Assessment

Therefore, in an attempt to salvage the flap, a 2-ml bolus of alteplase was gradually injected into the arterial pedicle in anterograde direction just distal to the anastomosis without removing stiches to prevent loss of solution. Additionally, the artery and vein were clamped proximally for about 8 minutes (Fig. 1). This allowed the solution to stand for that period in the flap, before reestablishment of arterial blood flow. Also, a small area of the flap was deepithelialized for monitoring purposes (Fig. 2).

Follow-up and Outcomes

About 3 hours after selective flap thrombolysis, microcirculation of the flap was successfully restored. Postoperatively, normal wound healing was noticed. At a 3-month follow-up, the salvaged flap was soft throughout; no other complications including fat necrosis or hemorrhage occurred (Fig. 3).

DISCUSSION

Although thrombolytic agents have been used in a few clinical studies and most authors recommend the local use of thrombolytic agents, pharmacological thrombolysis has been overlooked by many reconstructive microsurgeons. However, there often exists the fear of systemic complications such as bleeding tendency and hypertension.
The use of thrombolytic agents such as alteplase, urokinase, streptokinase, and acylated-plasminogen-streptokinase-activator-complex are the most commonly used thrombolytic drugs which have been shown to be effective for flap salvage in animal studies. However, there have also been a few clinical studies of thrombolytic therapy in free-tissue transfer for flap salvage in clinical setting reported. There are only some differences between the individual thrombolytic agents.

Alteplase has been widely used in the treatment of myocardial infarction, pulmonary embolism, or ischemic stroke and is also the most clinically used thrombolytic agent to salvage compromised flaps.

In our case, alteplase was used because of its clinical availability and our familiarity with its actions. Establishing the optimal rt-PA doses for treating microvascular thrombosis in free flaps is difficult, as ideal doses and delivery procedures have not been reported so far. In our case the bolus of 2 ml of alteplase was based on the weight of the flap (1950 g), as we followed the guidelines for the acute stroke therapy which recommend 0.9 mg/kg for optimal lysis of thrombi when infusing systemically. Higher concentrations may increase the risk of hemorrhage without increasing the efficacy. Baumer et al reported in their in vitro thrombolysis study a dose dependent decrease in thrombus weight induced by rt-PA. Based on these findings, it is recommended to administer no more than 1 mg/kg rt-PA for optimal lysis of thrombi when infusing systemically.

Nevertheless, our current procedure maximizes the rt-PA gradient in the flap, minimizes the total dose required and ensures prevention of systemic spread or systemic side effects.

We applied a vessel clamp on the artery, as well as on the vein distal to the anastomosis, to allow the solution to stand for that period in the flap, before reestablishment of arterial blood flow. Without clamping the artery, increased pressure in the flap and recipient artery may cause backflow, potentially causing systemic spread of alteplase. Even the blood continually flowing into the flap may reduce the alteplase gradient in the flap and thus additional doses of alteplase might be required without clamping.

CONCLUSIONS

Our approach presents a therapeutic option that both maximizes alteplase concentration in the flap and minimizes the dosage required for flap salvage. Therefore, it has the potential to significantly reduce adverse effects associated with systemic administration of thrombolytic agents.

For the treatment of thrombosis in free flap surgery, guidelines on optimal dosing regimens or application periods of thrombolytic agents are still not available. To our knowledge, evidence for optimal dosing and delivery of alteplase for the treatment of thrombosed DIEP flaps has not been published to date. We can only follow existing hospital guidelines and protocols on thrombolytic therapy when choosing a thrombolytic agent. There are prospective randomized studies needed concerning their indications, dosages, and methods of administration, as well as their efficacy and safety.

ETHICAL APPROVAL STATEMENT

The study was performed in accordance with the principles outlined in the Declaration of Helsinki, and informed consent for participation was obtained and registered.

Julia M. Wimbauer, MD
Hospital of St. John of God (Barmherzige Brüder) Salzburg
Department of Plastic, Aesthetic and Reconstructive Surgery
Paracelsus Medical University (PMU) Salzburg
Kajetanerplatz 1, 5020 Salzburg, Austria
E-mail: julia_wimbauer@hotmail.com

REFERENCES

1. Chang EI, Chang EI, Soto-Miranda MA, et al. Comprehensive evaluation of risk factors and management of impending flap loss in 2138 breast free flaps. Ann Plast Surg 2016;77:67–71.
2. Khansa I, Chao AH, Taghizadeh M, et al. A systematic approach to emergent breast free flap takeback: clinical outcomes, algorithm, and review of the literature. Microsurgery. 2013;33:505–513.
3. Schubert W, Hunter DW, Guzman-Stein G, et al. Use of streptokinase for the salvage of a free flap: case report and review of the use of thrombolytic therapy. Microsurgery. 1987;8:117–121.
4. Lipton HA, Jupiter JB. Streptokinase salvage of a free-tissue transfer: case report and review of the literature. Plast Reconstr Surg. 1987;79:977–981.
5. Yiu NW, Evans GR, Miller MJ, et al. Thrombolytic therapy: what is its role in free flap salvage? Ann Plast Surg. 2001;46:601–604.
6. Atiyeh BS, Fuleihan NS, Musharafieh RS. Pharmacologic partial salvage of a failing free flap with recombinant tissue plasminogen activator (rt-PA). J Reconstr Microsurg. 1999;15:585–590.
7. Nelson JA, Kim EM, Efekhari K, et al. Late venous thrombosis in free flap breast reconstruction: strategies for salvage after this real entity. Plast Reconstr Surg. 2012;129:86e–15e.
8. Chang EI, Mehrara BJ, Festeckjian JH, et al. Vascular complications and microvascular free flap salvage: the role of thrombolytic agents. Microsurgery. 2011;31:505–509.
9. Serletti JM, Moran SL, Orlando GS, et al. Urokinase protocol for free-flap salvage following prolonged venous thrombosis. Plast Reconstr Surg. 1998;102:1947–1953.
10. Rohrich RJ, Handren J, Kersh R, et al. Prevention of microvascular thrombosis with short-term infusion of human tissue-type plasminogen activator. Plast Reconstr Surg. 1996;98:118–128.
11. Hergrueter CA, Handren J, Kersh R, et al. Human recombinant tissue type plasminogen activator and its effect on microvascular thrombosis in the rabbit. Plast Reconstr Surg. 1988;81:418–424.
12. Cooley BC, Jones MM, Dellow AL. Comparison of efficacy of thrombolysis, streptokinase, and urokinase in a femoral vein clot model in rats. Microsurgery. 1983;4:1–4.
13. Hoffmeister HM. Bewertung alter und neuer Thrombolytika beim akuten Myokardinfarkt: Indikation, Caveats und Erwartungen. Journa für Kardiologie. 2002;9 (Supplementum C):3–5. Available at: https://www.kup.at/kup/pdf/2307.pdf#search='Hoffmeister%20HM'. Accessed May 30, 2022.
14. Madhani J, Mowsowitz H, Kotler MN. Tissue plasminogen activator (t-PA). Ther Drug Monit. 1993;15:546–551.
15. Brouwers K, Kruit AS, Hummelink S, et al. Management of free flap salvage using thrombolytic drugs: a systematic review. J Plast Reconstr Aesthet Surg. 2020;73:1806–1814.
16. Bäumer W, Herrling GM, Feige K. Pharmacokinetics and thrombolytic effects of the recombinant tissue-type plasminogen activator in horses. BMC Vet Res. 2013;9:158.
17. Seifried E, Tanswell P, Rijken DC, et al. Pharmacokinetics of antigen and activity of recombinant tissue-type plasminogen activator after infusion in healthy volunteers. Arzneimittelforschung. 1988;38:418–422.