Clinical Case Report

Medicine®

OPEN

Anterograde injection of low-dose urokinase salvages free anterolateral thigh flap

A case report of safe and effective treatment

Shao-Yun Hsu, MD, Hsu-Tang Cheng, MD, Oscar Manrique, MD, Yung-Chang Hsu, MD*

Abstract

Rationale: A 54-year-old Taiwanese male came to our hospital presented with right retromolar mucoepidermoid carcinoma. Composite resection and right modified radical neck dissection were performed. We then use free anteral lateral thigh flap to reconstruct the defect. However, venous congestion was found 32 h after the surgery.

Patient concerns: The main concerns of the patient is complete salvage of the free flap, and avoiding the secondary free flap harvesting and reconstruction surgeries.

Diagnoses: Right retromolar mucoepidermoid carcinoma.

Interventions: We report the case of a patient with an anterolateral thigh flap with venous perianastomosis thrombosis and intraflap microvascular thrombosis successfully salvaged using anterograde intra-arterial injection of low-dose urokinase (60,000 U), without administering intravenous anticoagulation heparin during the postoperative period.

Outcomes: The flap was completely salvaged 3 days after treatment. No other flap-associated or bleeding complications were noted. The intra-oral wounds around the flap completely healed without any post-ischemic complications.

Lessons subsections: Although the ideal urokinase doses and delivery procedures for free flap salvage have not been developed thus far, our method maximizes the urokinase gradient in the flap, minimizes the total dose required for flap salvage, and ensures no systemic spread. Thus, compared with other thrombolytic agents, urokinase may be more effective and safe for free flap salvage. With more experience, a standardized dosage and procedure can be developed.

Keywords: free tissue transfer, salvage therapy, tissue plasminogen activator

1. Introduction

Free tissue transfer has become a standard procedure for repairing complex soft tissue defects, with a high success rate (95–99%).[1] Thrombosis of the perianastomotic or intraflap microvasculature often causes flap failure. Urokinase and other thrombolytic agents can be used to successfully salvage flaps with thrombosis.[2] However, the systemic spread of urokinase can cause major health concerns.[3] Urokinase is derived from kidney cells and directly convert plasminogen into plasmin to achieve thrombolysis. Its half-life is short (only about 15 min).[4] In clinical practice, urokinase has been used to vessel and catheter clotting. However, the systemic spread of urokinase can cause major health concerns.[3,5] While antibody induction of urokinase has not been reported, doses larger than 250,000 IU will induce tachycardia and shaking chillness.[3] Therefore, microsurgeons are dedicated to developing the most effective delivery procedure to reduce the dosage. The lowest dosage which has been reported is 100,000 IU.[4] Effectiveness of low-dose urokinase on dialysis catheter had been proved.[5] Yet few relevant cases have been reported thus far, safe and effective urokinase doses and delivery procedures for free flap salvage remain unclear.[3]

2. Presenting concerns

A 54-year-old Taiwanese male patient presented at our hospital for right retromolar mucoepidermoid carcinoma, for which we performed composite resection of the right posterior lower alveolar ridge and retromolar trigone, followed by right modified radical neck dissection and free anterolateral thigh flap reconstruction. The flap was elevated using a skin paddle measuring 7×15 cm, and 2 perforators were included. The recipient artery was anastomosed in an end-to-end manner to a well-matched right superior thyroid artery. The vein was anastomosed in an end-to-end manner to a branch of the right internal jugular vein. The warm ischemia time was approximately 1.5 h. After microanastomoses, the flap appeared pink and warm with adequate venous return. The patient was then transferred to the surgical intensive care unit for postoperative care and flap monitoring, with dextran used as the only anticoagulant.

3. Clinical findings

At 32 h after surgery, we noted congestion of the skin paddle (Fig. 1). The patient was immediately retransferred to the

Editor: Satyabrata Pany.

The authors have no funding and conflicts of interest to disclose.

Department of Plastic Surgery, China Medical University Hospital, Taichung, Taiwan.

* Correspondence: Yung-Chang Hsu, Department of Plastic Surgery, China Medical University Hospital, No. 2, Yu-Der Road, Taichung, Taiwan 40449 (e-mail: D23644@mail.cmuh.org.tw).

Medicine (2017) 96:41(e7932)

Received: 16 October 2016 / Received in final form: 29 July 2017 / Accepted: 6 August 2017

http://dx.doi.org/10.1097/MD.0000000000007932

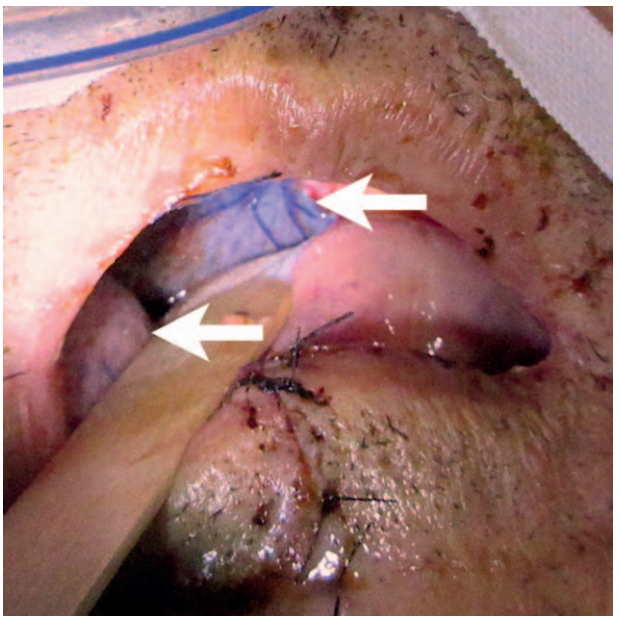

Figure 1. Flap (white arrow) became congested 32 h after primary reconstruction surgery.

operating room for emergent flap exploration. Institutional review board approval is inapplicable under the emergent condition, no twisting, kinking, or external compression of the pedicle was noted. The patency of the donor artery, anastomosis, and the recipient artery were confirmed using the milking test. No flow was noted on the recipient vein (Fig. 2); hence, we removed the vein. A 1.5-cm-long thrombus was observed at the micro-anastomosis site.

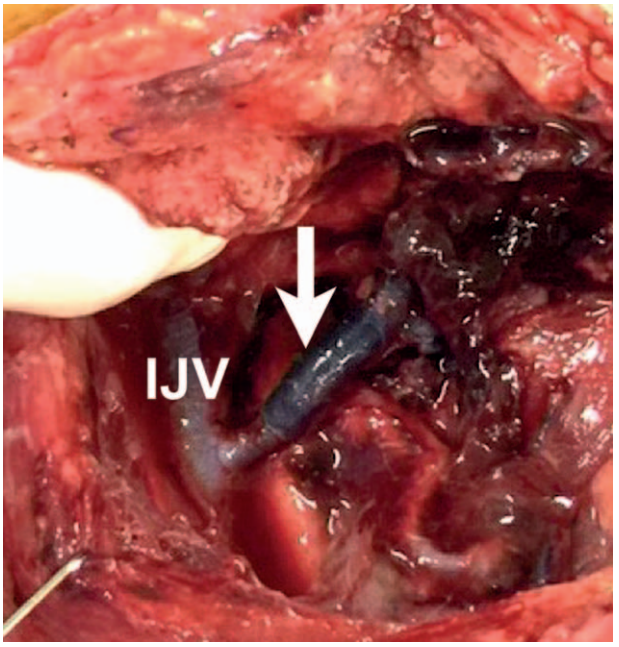

Figure 2. Thrombus (white arrow) inside the vein of the flap pedicle and anastomosis.

4. Timeline

4.1. Therapeutic focus and assessment

We performed thrombectomy; however, no blood flow appeared and the skin paddle remained congested. Therefore, we removed 2 stitches on the arterial anastomosis and injected a heparin solution. However, because the intravascular pressure was considerably high, no flow was apparent from the recipient vein. Next, we slowly injected 1 ampule of urokinase solution (60,000 U in 20 mL of saline) into the arterial pedicle with manual pressure. A vascular clamp was applied on the donor artery, immediately proximal to the anastomosis before injection, to ensure that urokinase was completely injected into the flap, without leakage to the system from the backflow (Fig. 3). Approximately 5 min after the injection, the urokinase solution flowed out of the recipient vein. We then performed arteriorrhaphy, and the recipient vein demonstrated satisfactory flow. To prevent systemic adverse effects, the vein was kept open for an additional 15 min to completely drain excess urokinase from the flap. We anastomosed the vein to another branch of the internal jugular vein at approximately 20 min after injection. Intravenous heparin was not administered during the postoperative period.

4.2. Follow-up and outcomes

At 3 days after surgery, the color of the skin paddle recovered to normal (Fig. 4). No other flap-associated or bleeding complications were noted. Intraoral wounds around the flap completely healed within 2 weeks after surgery, and the flap survived completely.

5. Discussion

Microsurgical free tissue transfer, a procedure used worldwide to reconstruct soft tissue defects after trauma or cancer resection, has a high success rate; however, failures have been noted in 1% to 5% of cases.[1] Free flap failure in the head and neck region causes more critical complications than that in other regions. Uncovered wounds in this region may cause meningitis, abscess formation, and exposure of vital structures, such as the major neck vessels. Marginal or partial necrosis of the flaps after

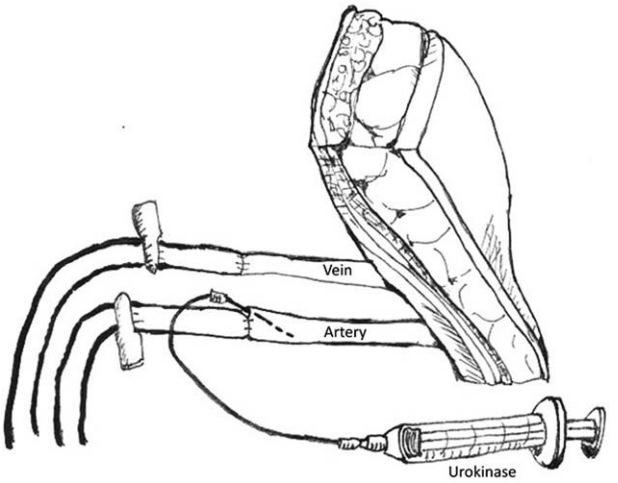

Figure 3. Schematic of anterograde injection of Urokinase.

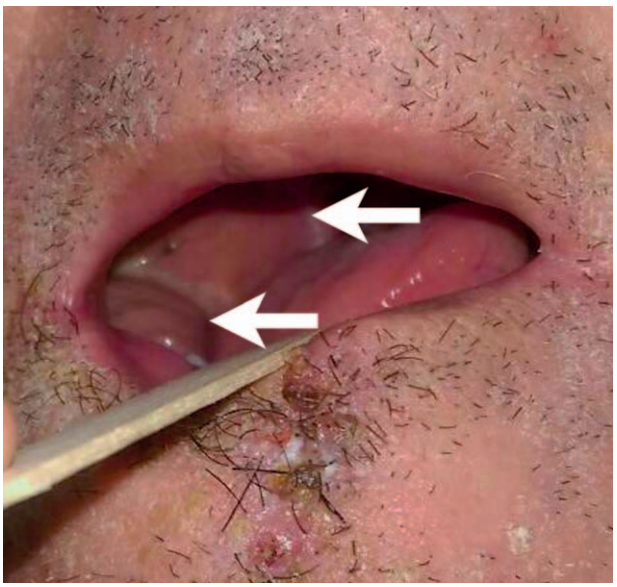

Figure 4. Flap recovered to the normal color and intraoral wounds completely healed 2 weeks after surgery.

incomplete salvage may lead to saliva leakage or oral cutaneous fistula, which can be life threatening. Therefore, flap monitoring and successful salvage in the head and neck region have become the major concerns for microsurgeons.[6] Most emphasis has been placed on flap monitoring, exploration, and anastomosis revision.[1] These procedures are effective for treating external compression, tension, twisting, or kinking of the pedicle vessels, but not for treating microvascular thrombosis.[4,7]

Pharmacological thrombolysis is a worldwide accepted procedure. The first reported case treated by this procedure is for pulmonary embolism in the 1960s, then it was applied to cases with coronary, peripheral, and artery thrombosis, even to solve dialysis graft or catheter occlusion in the following decades. There are 4 thrombolytic agents (streptokinase, urokinase, recombinant tissue plasminogen activator, and acylated plasminogen streptokinase activator complex) available in clinical practice, but urokinase has been seen as the most effective and safe one.[2,3] Urokinase showed the lowest rate of bleeding complication comparing with streptokinase or recombinant tissue plasminogen activator. [3] In previous large prospective randomized control trial for lower limb ischemia, urokinase is the most superior choice.[3]

Urokinase has become an option for flap salvage since 1989; however, only a few relevant clinical cases have been reported. Lee et al, Drijkoningen et al, and D'arpa et al have used urokinase for intraoperative flap salvage during reconstructive surgery,[2,4,7] and Agostini et al, Anavekar et al, D'arpa et al, and Serletti et al have used urokinase for salvaging flaps with delayed thrombosis.[3,2–9] Here, we present the first case of the use of urokinase in exploration surgery for salvaging an anterolateral thigh flap with delayed thrombosis, 32 h after primary reconstruction surgery.

The major concern of using urokinase for free flap salvage is the systemic spread, which may cause coagulopathic complications, chills, and tachycardia with large bolus doses of >250,000 U.[3] In previous reports, urokinase doses have ranged from 100,000[2] to 400,000 U,[8] administered using various delivery methods. In our case, only 60,000 U of urokinase resulted in successful flap salvage. We applied a vessel clamp on the donor artery and directly injected urokinase through a small window, created by removing 2 stitches from the arterial anastomosis. Serletti et al[3] reported a protocol for anterograde intra-arterial urokinase injection and indicated that manual pressure is required to infuse urokinase. Without clamping the donor artery, increased pressure in the flap and recipient artery may cause backflow through the donor artery, potentially causing systemic spread of urokinase; in addition, the blood continually flowing into the flap may reduce the urokinase gradient in the flap and thus additional doses of urokinase may be required. D'arpa et al used the same method to deliver urokinase. The authors first administered 50,000 U of urokinase, similar to our dose, but failed to salvage the flap. The authors then infused an additional 50,000 U of urokinase, successfully salvaging the flap. In this case, clamping of the donor artery during the first delivery could have led to effective results. After the infusion was completed, D'arpa et al drained the excess urokinase from the vein, thus indicating that urokinase remains within the flap, even after complete thrombolysis. Hence, during our procedure, we used a relatively lower dose of urokinase, which we synchronously adjusted according to the volume of urokinase drained from the vein.

The ideal urokinase doses and delivery procedures for free flap salvage have not been reported thus far.[3,4] Nevertheless, our current procedure maximizes the urokinase gradient in the flap and minimizes the total urokinase dose required; our procedure also ensures prevention of systemic spread. Thus, compared with other thrombolytic agents, the use of urokinase may be more effective and safe for free flap salvage. After gaining further experience, a standardized dosage and procedure can be developed.

References

[1] Salgado CJ, Moran SL, Mardini S. Flap monitoring and patient management. Plast Reconstr Surg 2009;124:e295–302.
[2] D'arpa S, Cordova A, Moschella F. Pharmacological thrombolysis: one more weapon for free-flap salvage. Microsurgery 2005;25:477–80.
[3] Serletti JM, Moran SL, Orlando GS, et al. Urokinase protocol for free-flap salvage following prolonged venous thrombosis. Plast Reconstr Surg 1998;102:1947–53.
[4] Lee D-S, Jung S-I, Kim D-W, et al. Anterograde intra-arterial urokinase injection for salvaging fibular free flap. Arch Plast Surg 2013;40:251–5.
[5] Seddon PA, Hrinya MK, Gaynord MA, et al. Effectiveness of low dose urokinase on dialysis catheter thrombolysis. ASAIO J 1998;44:M559–61.
[6] Wei F-C, Demirkan F, Chen H-C, et al. The outcome of failed free flaps in head and neck and extremity reconstruction: what is next in the reconstructive ladder? Plast Reconstr Surg 2001;108:1154–60.
[7] Drijkoningen T, van Weel V, Eberlin K, et al. Eptifibatide salvage of arterial anastomotic thrombosis in lower extremity free flap reconstruction: a case report. J Reconstr Microsurg 2015;31:544–6.
[8] Agostini T, Lazzeri D, Agostini V, et al. Delayed free flap salvage after venous thrombosis. J Craniofac Surg 2012;23:e260–1.
[9] Anavekar NS, Lim E, Johnston A, et al. Minimally invasive late free flap salvage: indications, efficacy and implications for reconstructive microsurgeons. J Plast Reconstr Aesthet Surg 2011;64:1517–20.