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Successful free flap salvage surgery with off-label use of Alteplase: A case report, review of the literature and our free flap salvage algorithm

Fatima Barhoum^a, Klaus Tschaikowsky^b, Michael Koch^a, Markus Kapsreiter^a,
Matti Sievert^a, Sarina Müller^a, Miguel Goncalves^a, Maximilian Traxdorf^a,
Claudia Scherl^{a,*}

^a Department of Otorhinolaryngology, Head and Neck Surgery, Waldstrasse 1, 91054, Erlangen, University of Erlangen-Nuremberg, Germany

^b Department of Anesthesiology, Krankenhausstrasse 12, 91054, Erlangen, University of Erlangen-Nuremberg, Germany

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ABSTRACT

INTRODUCTION: Microvascular free tissue transfer is a technique for reconstruction of large defects in head and neck surgery. Failure due to microvascular thrombosis can lead to microvascular damage or flap loss. Recombinant tissue-type plasminogen activator (Alteplase) is still an off-label use but it can help to rescue free flaps when embedded in a salvage algorithm.

PRESENTATION OF CASE: A 39-year-old patient with received a tumor resection and reconstruction by a radial forearm flap of the left palate. Postoperatively a venous flap thrombosis occurred and immediate surgical revision was done. Initially eperfusion of the flap could not be achieved even after mechanical removal of the thrombus. Then a thrombolysis with Alteplase, which was applied directly into the radial artery, was done. The flap was salvaged and is now completely integrated into the mucosa. Flap salvage procedure was performed according to our free flap salvage algorithm.

DISCUSSION: Thrombolysis with Alteplase for free flap salvage is not a common method. Pedicle thrombosis cannot be predicted. Important procedures during surgical intervention when thrombosis occurs are careful reopening, removal of thrombus, flushing with heparin. Since these procedures failed, surgeons decided to employ Alteplase to optimally rescue the flap.

CONCLUSION: The present case shows that pharmacological thrombolysis with Alteplase is an effective ultima ratio in free flap salvage with venous thrombosis, although it is still considered offlabel use. Early detection of flap failure and a clear salvage algorithm are important for successful surgical revisions.

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1. Introduction

Microvascular free tissue transfer is an essential and reliable technique for reconstruction of large defects in head and neck surgery with overall success rates of about 90–95%. Nevertheless, in up to 10% failure due to microvascular thrombosis is a major problem that complicates the issue of reconstructive surgery [1–4]. When recognized late anastomotic thrombosis leads to local endothelial injury, free radicals and inflammatory mediators. These can cause intimal edema with no-reflow-phenomenon and reduced thrombolytic activity [5]. Salvage rates are reported to be 50%–70% [1,2]. Fast re-exploration, thrombectomy, and revision of the anastomosis are crucial for successful salvage. In cases with difficult vascular conditions or recurrence of venous thrombosis throm-

bolytic agents such as Streptokinase and Urokinase have been described as promising [6]. A modern agent is Alteplase, a recombinant tissue-type plasminogen activator (rt-PA). It is a well-known fibrinolytic drug for standard treatment of ischemic stroke, lung embolism and myocardial infarction, but it is still considered offlabel use in the treatment of thrombotic free flaps. We present a case of a successful thrombolysis with Alteplase as a final attempt to radial forearm free flap salvage. The patient was treated at a tertiary referral center. The work has been reported in line with the SCARE criteria [7]. The checklist is available as supplemental material (Supplemental file).

2. Presentation of case

We present a case of a 39-year-old male patient. The investigators have obtained written informed consent from the patient. He had a local recurrent carcinoma of the left soft palate 2.5 years before he was treated alio loco for a squamous cell carcinoma of the same region and was reconstructed with a left radial forearm flap. The patient received no adjuvant treatment then. The patients'

* Corresponding author at: Department of Otorhinolaryngology, Head and Neck Surgery, University of Mannheim, Theodor-Kutzer-Ufer 1-3, D-68167, Mannheim, Germany.

E-mail address: claudia.scherl@umm.de (C. Scherl).

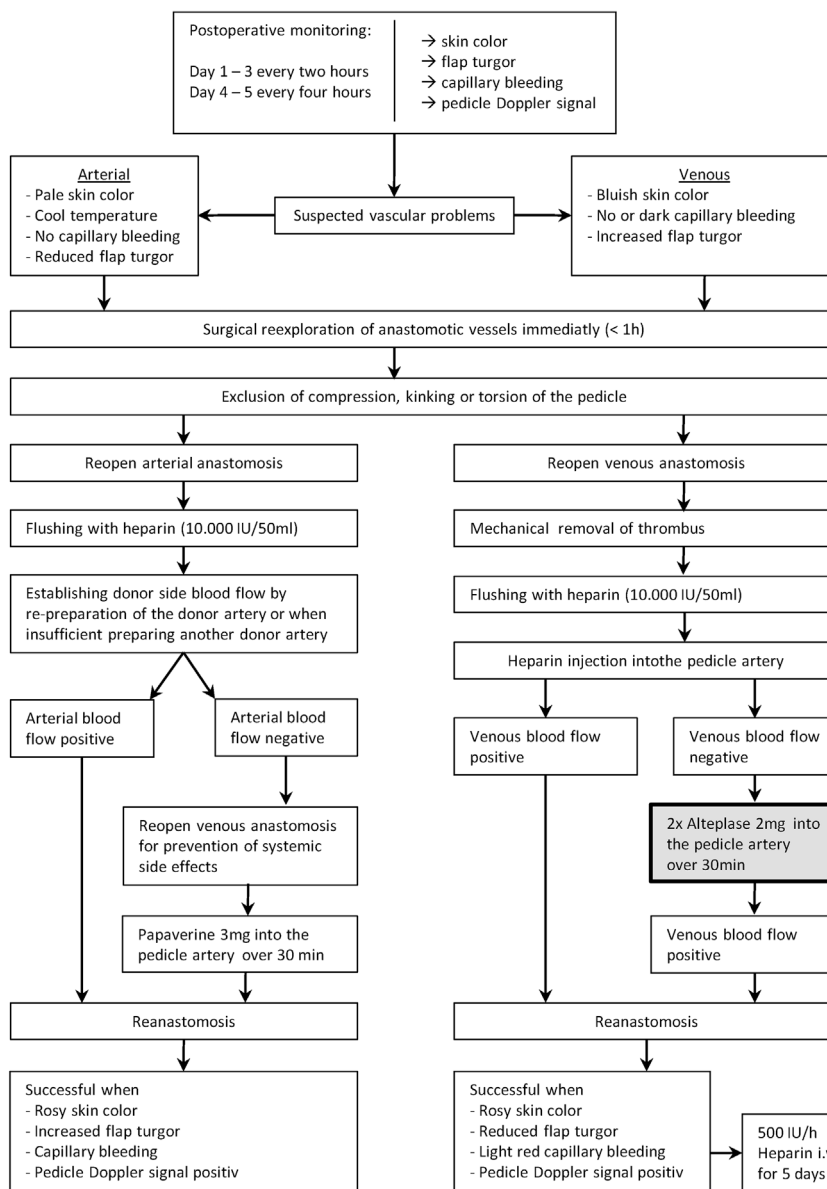


Fig. 1. Free flap salvage algorithm.

ASA (American Society of Anesthesiologists) physical status was 2 due to former alcohol abuse. Blood results including coagulation parameters were normal. He underwent transoral salvage surgery and reconstruction by a radial forearm flap from the right arm. The flap size was 16 × 8 cm. Arterial anastomosis was performed with 8.0 polyamide suture to the left pharyngeal ascending artery. Due to revision surgery of the neck only one venous anastomosis was possible to a branch of the internal jugular vein by usage of a 2.0 mm coupler. The surgery was done by senior experienced surgeons. No complications occurred intraoperatively. After surgery the flap was monitored every 2 h by visual inspection according to our monitoring scheme (Fig. 1).

10 h later the staff noticed an increased flap turgor, bluish discoloration and dark capillary bleeding. As recommended in our flap salvage algorithm (Fig. 1) the patient was taken back to the operation room within an hour for exploration of the anastomotic vessels. The salvage surgery was done by one of the senior experienced flap surgeons who also performed the initial flap surgery. The anesthesia was performed by an experienced anesthetist. The venous pedicle showed thrombosis while arterial blood flow was

still patent. Following our algorithm the venous anastomosis was reopened and a thrombus of the pedicle vein was removed. Heparinized saline (10.000 IU heparin/50 mL saline) was injected into the still pulsating radial artery and into the flap veins. All these procedures did not lead to any reperfusion of the flap tissue. Now Alteplase (Actilyse®, 2 mg) was injected directly into the arterial pedicle over a period of 10 min (Fig. 2A). The procedure was repeated after 30 min and a fresh venous blood return occurred. To prevent systemic side effects and to control reperfusion the venous anastomosis was open during the time of thrombolysis and was reanastomosed after successful intervention. At the end of the procedure the flap showed a rosier coloration, reduced turgor and bright capillary bleeding (Fig. 2B). The patient received systemic Heparin (500 IU/h) after revision for 5 days. The flap was salvaged but developed a slight superficial necrosis at the epidermis and a dehiscence at the cranial part. The deep layers of the dermis survived (Fig. 3A). Refixation was performed and necrotic skin areas had been removed after 18 days. The flap resisted 6 weeks of adjuvant chemoradiotherapy (Cisplatin, radiation dose 64 Gy) and is completely incorporated into the mucosa (Fig. 3B).

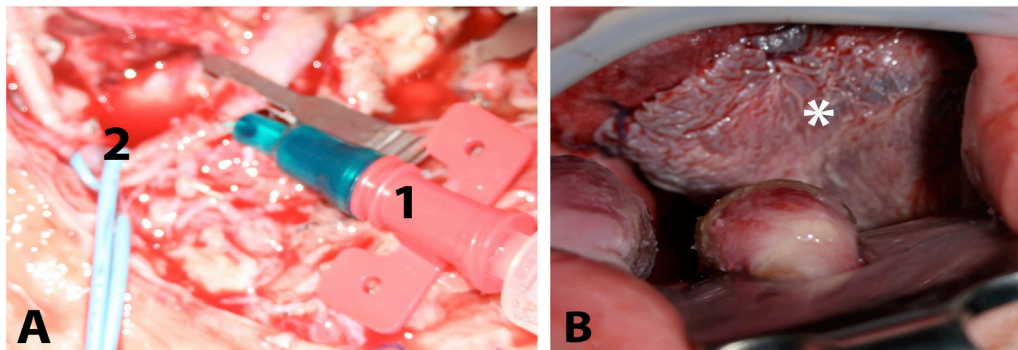


Fig. 2. Free flap salvage operation. (A) Intra-arterial vessel catheterization of 2 mg Alteplase (1) into the radial artery (2). (B) Flap (*) during salvage operation directly after thrombolysis. The bluish skin color declines and rosy skin coloring returns.

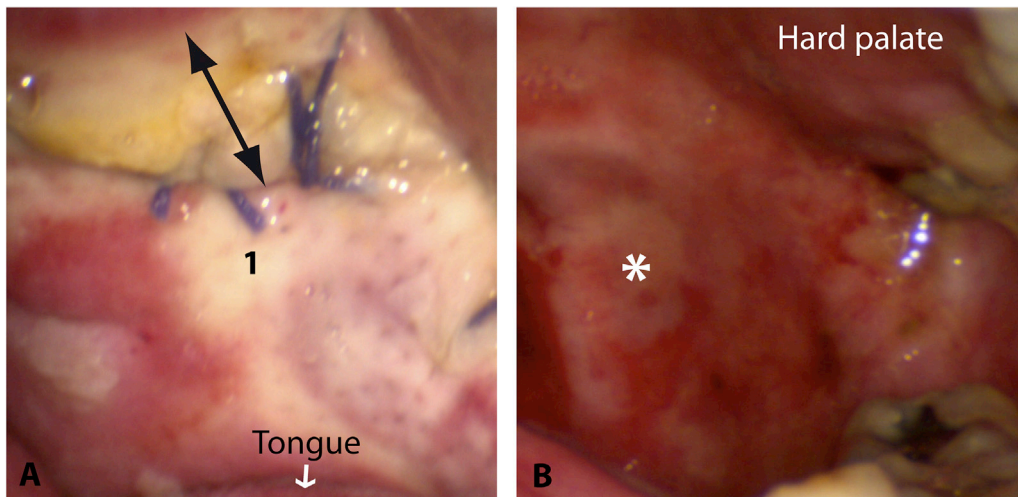


Fig. 3. Postoperative aspect. (A) 8 days after revision surgery the flap (*) developed a dehiscence (double arrow) at the cranial part and a partial superficial necrosis at the lateral edge (1). (B) 28 months after revision surgery the flap (*) is completely integrated into the mucosa of the left oropharynx.

3. Discussion

Microvascular free tissue transfer is a reliable, established technique in reconstructive surgery. Vascular complications of arterial and/or venous pedicle thrombosis can occur in up to 10% [1] and handling is still challenging even for experienced surgeons.

In the present case we found a venous thrombosis 10 h after surgery. Conventional methods of revision were not successful. Thus, we performed an off-label thrombolysis using the rt-PA Alteplase.

This drug is well-known and used systemically for ischemic stroke, lung emboli treatment and also locally in case of acute peripheral arterial occlusion. Contraindications are cerebral hemorrhage, renal insufficiency, coagulopathy, or allergy. These contraindications and other systemic side effects of the drug were not relevant because the flap was completely disconnected from the systemic circulation while applying the drug [4]. Literature shows that thrombolysis for free flap salvage is not a common method and only reported in single cases and small series. The first report about thrombolysis of a free tissue transfer with Streptokinase dates back to 1987 by Lipton and Jupiter [8]. Since then, the great benefit of thrombolytic agents such as Alteplase, Urokinase and Streptokinase has been shown in animal studies [9]. Serletti et al. performed an effective thrombolysis protocol in 5 patients. Anastomotic revision and intra-arterial instillation of Urokinase lead to a 100% flap survival [10]. Panchapakesan detected flap fail-

ure due to pedicle thrombosis in 7% out of 590 cases. Approximately half of them received revision and additional thrombolysis with Streptokinase or Urokinase based on availability. The salvage rate was 30% [6]. In single cases with recurrent venous thrombosis that received several revisions or when patients withdrew their consent for another surgery Ihler et al. injected Alteplase subcutaneously directly into the flap. According to them no further salvage surgery was necessary [11].

Risk factors of microvascular thrombosis are high blood viscosity, increased platelet function or activated thrombin. The patient's history, blood count and coagulation values should be checked preoperatively. A venous thromboembolism prophylaxis with low molecular weight heparins is recommended. The presented patient did not receive a perioperative venous thromboembolism prophylaxis which might have been a contributory factor to flap thrombosis. Apart from standard venous thromboembolism prophylaxis some patients might profit from additional anticoagulation even if it is not generally supported by literature [1,12,13]. In addition an “ex-vivo” irrigation of the transplant is recommended [14] and it was performed after raising the flap in the present case. “Hypercoagulable patients” whose thrombotic complication might be triggered by microvascular procedures have been described [14]. In these cases pedicle thrombosis cannot be predicted. Patients suffering from hypercoagulable history might be excluded from microvascular free tissue transfer or must at least be treated with systemic heparin [1,12,15]. Tumor type, grade, neck

dissection, flap-variety, irradiation, or smoking do not seem to be risk factors for causing thrombosis [6,16].

If free flap failure occurs surgical revision has to be done immediately. Yii et al. showed that early detection of imminent flap failure leads to better salvage rates and less need for thrombolysis [16]. With an average time of 1.5 h from suspicious examination to exploration Hidalgo et al. could reach a flap survival from over 90% [17]. First, external causes such as kinking, compression or torsion of the pedicle must be excluded or eliminated [2,18]. Internal problems such as vasospasm, technical failure of the anastomosis or thrombosis are also possible. If microvascular thrombosis is found opening of the anastomosis, mechanical thrombectomy by “milking” out clots or by use of a Fogarty catheter is essential [18–20]. Additional irrigation with heparin solution is a common and effective procedure [20]. Manipulation otherwise can also cause vessel injuries and repetitive venous stasis. Late or recurrent flap thrombosis may lead to extended flap damage or even loss which might be attributable to severe local ischemic effects on the endothelium [17]. We developed and extended an algorithm for the free flap salvage process postoperative and the postoperative flap monitoring (Fig. 1). It differentiates between arterial and venous complications and provides a step by step procedure in case of a suspicious flap failure. All aspects of flap salvage (time of revision, reopening of anastomosis, mechanical steps, pharmacological options) are addressed. Thrombolytic therapy has been described as an ultima ratio in flaps otherwise considered lost. The application of Alteplase lead to a successful flap salvage in the presented case. Thrombolysis with Alteplase is now a firm component of our salvage process even when still counting as an off-label use. Our close flap monitoring scheme and the clear salvage algorithm contributed to the positive outcome. It's essential to train and alert the staff in assessing signs of flap failure in order to start flap salvage surgery in a timely manner.

Factors to prevent venous thrombosis are careful patient selection, pharmacological prophylaxis, careful vessel selection, experienced surgical flap harvesting, precise vessel preparation, microsurgical anastomosis, close postoperative flap monitoring, and prevention of neck compression by hematoma or tight bandages.

4. Conclusion

Pharmacological thrombolysis with Alteplase is a useful weapon in flaps with venous thrombosis when all other attempts at flap salvage have failed. Early detection of flap failure is important and can be achieved by close monitoring after surgery. Flap revision surgery must be performed as soon as possible to avoid irreversible tissue damage. Clinicians should use a flap algorithm to make detailed decisions during the process of flap salvage surgery.

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Ethical approval

Ethics committee: University of Erlangen-Nuremberg, Germany.
reference number: 292_20B.

Consent

Our clinical investigation is in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration). The

authors have obtained written informed consent from the patient. The patient's anonymity is preserved. Patients' name, initials, or hospital number were not used. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Fatima Barhoum: Conception and design of the study acquisition, analysis and interpretation of data, writing the article and revising it critically for important intellectual content, review and editing of the manuscript, final approval of the version to be submitted.

Klaus Tschalkowsky: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, review and editing of the manuscript, final approval of the version to be submitted

Michael Koch: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be submitted.

Markus Kapsreiter: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be submitted.

Matti Sievert: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be submitted.

Sarina Müller: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, review and editing of the manuscript, final approval of the version to be submitted.

Miguel Goncalves: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be submitted.

Maximilian Traxdorf: Conception and design of the study, interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be submitted.

Claudia Scherl: Administrating the project, literature research, conception and design of the study, desing of the methodology, validation and supervision, acquisition, analysis and interpretation of data, writing the article and revising it critically for important intellectual content, final approval of the version to be submitted.

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Guarantor

Claudia Scherl.

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Declaration of Competing Interest

The authors report no declarations of interest.

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