Recurrent venous thrombosis following free flap surgery: The role of heparin-induced thrombocytopenia

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Complications following free tissue transfer have been well established in the literature. Common and rare causes of free flap failure must be addressed by the treating surgeon when microvascular patency is threatened. With the evolution and prevalence of microsurgery, 'rare' causes of free flap failure will become increasingly frequent. A high index of suspicion must be established in patients with multiple failed operative interventions. A case of recurrent free flap failure secondary to heparin-induced thrombocytopenia is presented in a patient with a history of squamous cell carcinoma of the floor of the mouth, and a long-standing history of alcohol and tobacco consumption.

Key Words: *Free flap failure; Heparin; Heparin induced thrombocytopenia; Leeches; Venous thrombosis*

Free flap failure occurs in 4% to 10% of cases (1) and is the result of a variety of intraoperative and postoperative vascular complications (2). Venous thrombosis, either intra- or postoperative, is frequent (found in 8.3% of cases) (2) and re-exploration surgery is often warranted for free flap salvage. The use of local and systemic heparin is effective in reducing flap failure through its antithrombotic effects and its protective effect on the microvascular endothelium (1,3). Nevertheless, a major complication of heparin treatment is an immune-mediated heparin-induced thrombocytopenia syndrome (HIT), which occurs in 5% to 10% of patients receiving heparin (4-6). This syndrome can cause a hypercoagulable state and therefore can paradoxically lead to thrombosis (HIT-T syndrome).

A case of recurrent free flap failure caused by repetitive multifocal venous thrombosis associated with thrombocytopenia following local and systemic heparin administration is presented. The role of hypercoagulable states and more precisely HIT-T syndrome in free flap failure, as well as the beneficial effects of leech therapy in this case, will be addressed.

CASE PRESENTATION

A 65-year-old man with a history of heavy alcohol and tobacco use was admitted for the treatment of a squamous cell carcinoma of the lower lip with mandibular invasion. The patient reported pain and paraesthesias in the lower lip area, with an

Thrombose veineuse récurrente après la pose d'un lambeau libre : Le rôle de la thrombocytopenie sous héparine.

Les complications fréquentes et rares des lambeaux libres sont bien décrites dans la littérature. Le chirurgien se doit d'être vigilant afin de préserver l'intégrité microvasculaire du lambeau. Les complications «rares» deviendront fréquentes suite de la prévalence croissante de la microchirurgie vasculaire. Par la lumière d'échecs chirurgicaux répétés, la cause devrait être recherchée par une investigation plus poussée. Voici un cas de thrombose récurrente de lambeau libre secondaire à une thrombocytopenie à l'héparine chez un patient traité pour un carcinome épidermoïde du plancher buccal et ayant des antécédents anciens de tabagisme et de consommation d'alcool.

induration progressing for six months before admission. Biopsy of the lesion confirmed an infiltrating squamous cell carcinoma with mandibular involvement, with evidence of cervical adenopathy present on the computed tomography scan. Preoperative blood tests demonstrated a normal coagulation profile and a mild pancytopenia, which was attributed to chronic alcohol use. A commando procedure was performed, followed by reconstructive surgery of the mandible, lower lip and floor of the mouth with an osteocutaneous right radial forearm free flap.

The intraoperative anastomosis of the free flap to the recipient vessels was uneventful. Heparin 5000 U subcutaneously twice daily and acetylsalicylic acid 80 mg daily were prescribed following surgery, and the patient was closely monitored for flap viability. Although postoperative management included close surveillance of neurological status and prophylactic medication for alcohol withdrawal, the patient developed an episode of confusion and combativeness eight hours following surgery. On examination flap viability was excellent at this time. On the second postoperative day, approximately 30 h following the completion of surgery, the patient once again became increasingly combative. After assessment by the on-call physician, the patient received low dose benzodiazepines and chlorpromazine for sedation. Two hours following sedation, the patient developed an episode of respiratory depres-

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Figure 1) Radial forearm free flap transfer for the reconstruction of the floor of the smooth, anterior mandible and overlying skin. Evidence of repeated vascular insults is present

sion leading to hemodynamic collapse. Once reanimated, the patient was transferred to the surgical intensive care unit (ICU) for closer monitoring of the hemodynamic parameters.

Subsequent to the patient's cardiovascular collapse the cutaneous portion of the free flap developed signs of venous congestion. Immediate surgical exploration following cardiovascular stabilization demonstrated a proximal thrombosis involving the right jugular vein. A thrombectomy was performed on the right jugular vein and the anastomosis was revised. The patient was placed on a continuous heparin infusion following the establishment of vascular patency. Seven hours following this second intervention, the patient's flap became increasingly congested and required a second re-exploration (Figure 1). A second thrombectomy was performed, followed by a reanastomosis of the flap after revision of the anastomosis. This led to immediate decongestion of the flap. A total of 6000 U of heparin was given during the procedure and systemic heparin was resumed. The platelet count following the second intervention was 98,000 U, demonstrating no remarkable variation from the preoperative values.

On the seventh postoperative day, a third re-exploration procedure was necessary following a further episode of flap congestion. Despite adequate anticoagulation, intraoperative findings demonstrated a right jugular vein that was completely thrombosed. The thrombosed venous segment of the free flap was revised and anastomosed to the contralateral jugular vein. An 8 cm venous deficit was overcome with a left saphenous interposition vein graft. Venous outflow from the free flap was re-established. Three heparin boluses of 2000 U each were administered intraoperatively. Within 12 h of the last revision,

Figure 2) Leech therapy for venous drainage of recurrent venous thromboses

the flap became congested and leech therapy was initiated and continued for 10 days (Figure 2).

Seventy-two hours following the last intervention the patient developed right lower limb edema strongly suggestive of deep venous thrombosis. A right femoral deep vein thrombosis was confirmed by Doppler ultrasound. At this point, platelet levels decreased to 26,000 to 30,000 U. Heparin was immediately discontinued and a hematology consultation was requested. HIT was diagnosed and confirmed by positive anti-heparin antibodies. Danaparoid sodium (Orgaran, Orgaran Inc, USA), a specific inhibitor at the Xa level of the coagulation cascade, was initiated immediately and continued for two weeks. Platelet levels rose steadily to values above 150,000 U within 48 h following heparin cessation (Figure 3). Two weeks after the HIT-T diagnosis, the patient was discharged fully anticoagulated while receiving warfarin (Figure 4).

DISCUSSION

Free flap failure can result from numerous causes, including hematoma, infection, tissue trauma or hypovolemia (7), but is most frequently associated with vascular complications (2). Venous insufficiency is the most common and most dreadful cause of vascular flap failure, leading to quick vascular compromise secondary to stasis and eventual tissue ischemia. Monitoring should include continuous clinical flap examination for signs of decreased capillary refill, congestion, discoloration and dark blood after pin prick (8). In this case, experienced ICU nurses, surgical residents and staff surgeons monitored the flap hourly as a team. A Cook-Swartz intracorporeal Doppler catheter was placed on the outgoing vein during the initial pro-

Figure 3) Platelet count distribution over time (hours following initial surgery). Note the acute increase in platelet count following heparin cessation (hour 285)

cedure, but was removed by the patient during the initial episode of confusion without any sequelae. In our experience, we believe this device could have helped to detect early venous outflow impairment and therefore led to quicker intervention.

This patient had numerous risk factors for free flap failure: the baseline neoplasm contributing to hypercoagulability, alcohol abuse and the potential for alcohol withdrawal in the postoperative phase, an iatrogenically induced hemodynamic compromise on postoperative day 2 and a HIT-T syndrome following heparin administration. In addition, the patient presented with a mild pancytopenia on admission most likely due to alcohol abuse, which made red blood cell and platelet monitoring difficult.

Heparin has been proved to be very efficient in reducing the risk of vascular complications and consequent free flap failure following surgery. Heparin administration has been proved to be more effective in venous than arterial thrombosis prevention whether by local or systemic delivery (1,3). Intraoperative and postoperative unfractionated heparin was given to the patient during his hospitalization. The comorbid states mentioned earlier and the many surgical re-explorations could have explained the recurrent episodes of venous thrombosis. Nevertheless, if anticoagulant therapy seems inefficient and further events occur, HIT-T syndrome should be strongly considered.

HIT is defined as an immune-mediated thrombocytopenia following anticoagulant treatment with heparin (5). Typically, platelet count drops four to 14 days following initial treatment and is not dose dependant. In our case, the nadir of the platelet count was on postoperative day 12. HIT should be considered in any patient who develops a 50% drop in platelet count while on heparin (4). Frequent complete blood counts while the patient was in the ICU helped prompt diagnosis. Many immune assays have been developed in hematology for HIT syndrome detection that are useful but not necessary for diagnosis (5). Furthermore, HIT is more frequent with unfractionated heparins, but all heparins must be discontinued and avoided in the future in a patient in whom HIT has been diagnosed. Treatment includes heparin cessation and addition of another anticoagulant such as danaparoid sodium or lepirudin

Figure 4) Follow up picture four weeks following surgery

(Refludan, Aventis Pharmaceuticals Inc, USA), a highly specific inhibitor of thrombin (4).

Danaparoid can be monitored by measuring anti-Xa activity. Once heparin use has been discontinued, platelet count recovers in 90% of patients with a significant reduction in thrombosis-related mortality (5). Platelet levels recovered within two days of heparin cessation in this case. Although the patient did not develop any new episodes of venous thrombosis after heparin cessation, vascular return of the flap had been compromised by the previous thrombosis of bilateral jugular veins, requiring continuous leech application until new venous channels could be established.

Medicinal leeches (*Hirudo medicinalis*) are effective in the salvage of a congested flap with venous compromise (7,9-11). The leech attaches onto the congested tissue and may suck up to 790% of its body weight within 2 h. Furthermore, after the leech has detached from the skin, its teeth leave an opening permitting a slow ooze for one to two days (7). The salivary complex of the leech produces many active substances, including proteolytic inhibitors such as hirudin (among others) that are very useful for the prevention of thromboses (12). Coincidentally, recombinant hirudin is also used to treat patients with HIT-T syndrome (4). Complications associated with leech therapy include infection and significant blood loss (12).

CONCLUSION

Venous thrombosis and free flap congestion are devastating complications of free flap surgery. Heparin has been used to prevent thrombotic complications in reconstructive surgery. Nevertheless, when confronted with recurrent venous thrombosis in a patient receiving anticoagulation therapy, the surgeon should eliminate a hypercoagulable state as a contributing factor. HIT-T should be suspected and the diagnosis should be made or ruled out with the aid of anti-platelet antibody assays. When HIT is suspected, cessation of all heparin derivatives is warranted and treatment with a different class of anticoagulant should be instituted to prevent further thrombotic events. Finally, the medicinal leech was proved useful once again in relieving flap congestion efficiently. This permitted the formation of vascular venous channels, which consequently led to free flap survival.

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