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CASE REPORT

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Simultaneous Pancreas-Kidney Transplantation in a Patient with Heparin-Induced Thrombocytopenia on Dabigatran Therapy

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Background: New oral anticoagulants like direct thrombin inhibitors are an attractive alternative to vitamin K antagonists as anticoagulation therapy and can be used in heparin-induced thrombocytopenia. They are convenient in low-risk surgery, as there is no need for bridging with heparins. Patients who need urgent major surgery are at similar risk as on warfarin therapy, which, however, is much higher than in elective procedures. Due to their elimination profiles, these drugs are generally contraindicated in patients with severe renal insufficiency. On the other hand, pancreas transplantation is associated with high risk of bleeding and substantial risk of graft thrombosis. There are no recommendations on anticoagulation therapy in high-risk patients on kidney-pancreas waiting lists who cannot be given heparins.

Case Report: We describe a case of simultaneous pancreas-kidney transplantation in a patient with heparin-induced thrombocytopenia on dabigatran treatment.

Conclusions: We conclude that, despite the high risk, pancreas transplantation in a patient with HIT can be safely done while on NOAC therapy, but an access to idarucizumab should be assured.

MeSH Keywords: **Anticoagulants • Pancreas Transplantation • Renal Insufficiency • Thrombocytopenia**

Abbreviations: **DTI** – direct thrombin inhibitor; **HIT** – heparin-induced thrombocytopenia; **LMWH** – low molecular weight heparin; **NOAC** – new oral anticoagulants; **SPKT** – simultaneous pancreas-kidney transplantation

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Background

Oral direct thrombin inhibitors (DTI) and direct-acting oral anticoagulants inhibiting factor Xa (new oral anticoagulants, NOAC) are attractive alternatives to vitamin K antagonists as anticoagulation therapy, and their use is increasing in prevention of atrial fibrillation complications and venous thromboembolism. They were shown to be as effective as warfarin (INR 2-3) in secondary prevention of venous thromboembolism. In heparin-induced thrombocytopenia (HIT), vitamin K inhibitors may result in microthrombosis, and parenteral NOACs are useful option, as is fondaparinux, in non-critically ill patients. Although potentially practical, dabigatran and other oral agents have not been approved for this indication.

The mechanism of action is a reversible, direct free and fibrin-bound thrombin inhibition, which prevents conversion of fibrinogen into fibrin and excludes the thrombin-dependent pathway of factor V, VIII, XI, and XIII activation. Dabigatran etexilate is quickly metabolized to dabigatran after ingestion, reaches peak concentration within 2 h, and has a half-life of 12 h. Most of the drug is excreted in urine and the half-life can exceed 27 h in stage 4 chronic renal failure, so the dosage should be reduced in renal insufficiency, and the discontinuation time needs to be adjusted accordingly before surgery, but hemodialysis used to be recommended to remove the drug from the bloodstream in severe bleeding before introduction of idarucizumab, although dialyzable and dabigatran are contraindicated in patients with end-stage renal disease. Tests to assess dabigatran-induced anticoagulation are activated PTT, thrombin time, and ecarin clotting time. Ecarin clotting time is not routinely available and only aPTT and TT were available in our patient.

NOACs are convenient in low-risk surgery, as there is no need for bridging with heparins, and discontinuation of the drug 24 h prior to surgery and restart 24 h after surgery is considered sufficient. In procedures with moderate risk of bleeding, discontinuation for 48 h is recommended to be extended to 5 days when other risk factors (e.g., moderate renal failure) are present [1]. Patients who need urgent major surgery while on NOAC are at similar risk of bleeding complications as patients on effective warfarin therapy [2], although the risk of bleeding and death is much higher than in elective procedures and is not dose-dependent [3]. In patients requiring major orthopedic surgery, the risk of major, intracranial, or fatal bleeding was found to be similar to NOACs and low molecular weight heparins (LMWH) [4]. In a group of 100 orthopedic patients with moderate renal impairment (eGFR 42.5 mL/min) who were given dabigatran 1–4 h after major surgery, only 4 major bleeding events occurred [5].

Simultaneous pancreas-kidney transplantation (SPKT) is associated with high risk of venous and arterial thrombosis in the pancreatic graft, so anticoagulants are quickly implemented postoperatively, but risk of bleeding remains substantial at the same time, so DTIs are not the first-choice option.

We were unable to find any reports on the risk of surgical bleeding in a pancreas graft recipient who was on heparins, warfarin, or NOACs while on a waiting list, nor on results of pancreas transplantation in a patient with HIT.

Case Report

A 36-year-old woman with a 25-year history of type 1 diabetes, complicated by diabetic retinopathy and nephropathy, was qualified to SPKT. She was on hemodialysis therapy for 16 months. When her hemodialysis program was started, she was diagnosed with HIT. The patient was admitted to the hospital 10 days after her first hemodialysis with LMWH. She had thrombocytopenia (PLT 16 000/µl) and deep-vein thrombosis in her right leg. Because HIT was clinically suspected, she was treated with steroids and fondaparinux, but after a few days fondaparinux was converted to dabigatran. After conversion, her platelet count returned to normal. Her hemodialysis program was continued without heparins and she was administered 150 mg of dabigatran 4 times a week. The patient was treated with dabigatran despite the fact that according to product characteristics, this agent is contraindicated in patients with severe renal function impairment (CrCL <30 mL/min). When she had an initial episode of HIT, no confirmatory test was attempted to detect antibodies against heparin-PF4 complexes (HIT antibodies). When the same test was run 1 year later, no HIT antibodies were found, but such a result proved nothing because of quick elimination of the antibodies, which can be detected only within 2–3 months after heparin treatment [6].

On the morning of the day of the procedure, she took another 150 mg of dabigatran and had an extra 3-h hemodialysis. Because it was the day after her regular hemodialysis, she had received her regular dose of dabigatran on the previous day. When the patient was admitted to the Department of Surgery, her thrombin time was undetectable. Having already explanted the organs for transplant, with ongoing ischemia time and no option for quick arrival of a substitute patient, after checking availability of idarucizumab in a hospital pharmacy, we decided to perform the procedure.

The operation was begun 9 h after the last dose of dabigatran and 6 h after dialysis. First, the right kidney of the donor with elongated renal vein was transplanted extraperitoneally to the left iliac fossa. Renal vessels were sutured to external iliac vessels of the recipient and stented urinary anastomosis

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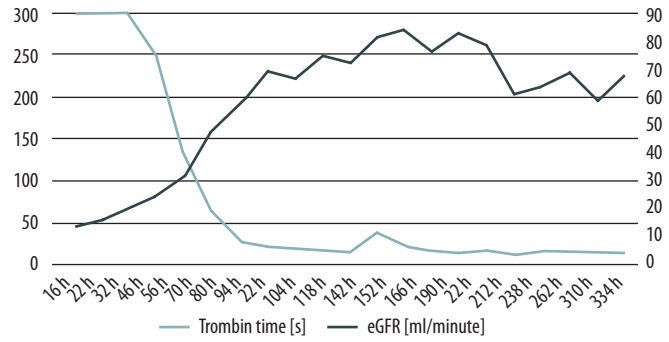

Figure 1. Thrombin time and estimated glomerular filtration rate according to Cocroft-Gault formula.

was accomplished with Lich-Gregoire technique. There was notable tissue bleeding during the surgery, but it did not impede the procedure, and meticulous hemostasis was assured. There was no leakage from the anastomosis site. Suction drainage was placed in the proximity of the anastomoses, and Gibson's incision was closed. As blood loss at this stage was estimated at less than 100 mL, and back-table preparation of the pancreas graft had been finished, we decided to proceed with pancreas transplantation. Midline laparotomy was performed, the portal vein of the graft was anastomosed to the inferior vena cava, and an artery reconstructed with iliac vessels of the donor was sutured to the external iliac artery of the recipient. Enteric drainage of the pancreatic juice was performed with anastomosis of the duodenum of the graft with the jejunum of the recipient. Immediate renal function was observed with increasing glomerular filtration rate (eGFR). Thrombin time decreased accordingly and had returned to normal by about 120 h after the last dose of dabigatran (Figure 1). Surgery was finished at 10 pm. With continuous glucose infusion, her blood glucose levels at 1 h and 2 h later were 175 mg/dL and 95 mg/dL, respectively, with no need for insulin substitution. At 24 h after the procedure, her hemoglobin dropped to 8.2 g/dL and she received a transfusion of 2 packs of red blood cells. When her thrombin time became measurable at 72 h after the operation, she was administered a prophylactic dose (2.5 mg) of fondaparinux qd. On day 17, warfarin was started and fondaparinux was discontinued when the therapeutic level of INR=2 was achieved. She was discharged home 30 days after admission, but 1 week later was re-admitted for benign graft pancreatitis, which resolved spontaneously with NPO diet. Two months after transplantation, she is at home with HBA1c of 5.4% and C-peptide of 8.17 ng/mL and perfect renal function.

Discussion

SPKT is a procedure with high risk of bleeding, with approximately 7% of recipients requiring early re-laparotomy. Operating while the patient is on chronic anticoagulation therapy may increase this risk substantially. Patients with thrombophilia who received kidney transplants while on heparin or argatroban (a short-acting iv direct thrombin inhibitor) had 35% risk of postoperative hemorrhage compared to 5% in patients with no need for anticoagulants [7]. The risk is long-term and can be as high as 33%. Of 13 kidney or SPKT patients who received enoxaparin and aspirin within 10 days after the operation, 9 (69%) suffered from major bleeding and 6 of them had transplanted kidney function impairment [8].

Organ transplantation is an urgent situation with a major risk of bleeding; therefore, quick reversal of the inhibitory action of DTI may be required, although usually a few hours pass between drug administration and surgical incision. On the other hand, renal failure patients have a significant problem with eliminating the drug in urine, which increases the risk of bleeding and makes the need for drug reversal more likely. When there is an urgent need for surgery or when life-threatening hemorrhage occurs, idarucizumab can be used, although more than 1 dose may be needed and it must remember that its efficacy has only recently been confirmed, with evidence that was not of high quality [9].

Conclusions

We conclude, that despite high risk, pancreas transplantation in a patient with HIT can be safely done while on NOAC therapy, but an access to idarucizumab should be assured.

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