LETTER TO THE EDITORS

Anticoagulation practices in total pancreatectomy with autologous islet cell transplant patients: an international survey of clinical programs

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Dear Editor,

Total pancreatectomy with autologous islet cell transplant (TPAIT) is a treatment option for patients suffering from chronic or recurrent acute pancreatitis by providing benefits of pain relief, enhancing quality of life, and preventing brittle type 3c diabetes [1]. While surgical procedure requires extensive dissection and elevates the risk of bleeding [2,3], this operation also carries potential risk of portal venous thrombosis (0.9–3.4%) when impure or partially purified autologous islet preparations are infused into the portomesenteric circulation [4,5]. To mitigate the risk of thrombosis and to assist with islet engraftment by reducing Instant Blood-Mediated Inflammatory Reaction (IBMIR), anticoagulants are often utilized intra and postoperatively [6]. Through literature review and personal communications, it is clear that centers vary in their anticoagulation practices without any consensus guideline on the type, amount, or duration of anticoagulation, nor on the type and targets for postoperative monitoring [7]. The aim of this study is to gather information about the various anticoagulation strategies utilized by programs internationally.

We formulated an online survey [three questions regarding demographics, 46 questions assessing patient-related factors, hypercoagulability, intra and postoperative practices regarding the use of anticoagulants] via Google Form (Google LLC) with nine follow-up questions in a follow-up survey sent to programs who responded to the initial survey regarding their clinical outcomes and details of islet isolations between January 1, 2018 and January 1, 2020 (Appendix S1). An email list was generated from 45 distinct email domains of the personnel associated with autologous islet cell programs enrolled in the Collaborative Islet Transplant Registry with three reminder emails sent over the course of 6 weeks. We planned *a priori* to delete duplicate entries from the same program, prioritizing entries from a clinician or surgeon.

Fifteen responses were collected from 6 countries and 3 continents [surgeon (n = 8), physician (n = 5), and islet cell specialist (n = 2)]. Thirteen programs who responded to the follow-up survey performed a total of 122 TPAIT. Ten programs (66.7%) classified patients as high risk for thrombosis based on hypercoagulable disorder, prior deep vein thrombosis other than a segmental splenic vein thrombosis related to chronic pancreatitis (n = 7, 70%), and high portal pressure after

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islet infusion ($n = 8$, 80%). Five programs (33.3%) completed a hypercoagulability work-up prior to transplant and 2 (13.3%) used it to determine patient candidacy for TPAIT. Ten programs (66.7%) gave an intravenous heparin bolus before the infusion of islet cells with two giving a second intravenous heparin bolus prior to the clamping of the vessels before the pancreas is removed at doses between 0–50 units/kg. Four programs used variable weight-based heparin dosing ($n = 3$, 0–50 units/kg; $n = 1$, 51–100 units/kg). The other six programs used a set weight-based heparin dose ($n = 2$, 70 units/kg; $n = 1$, 15 units/kg; $n = 1$, 2,500 units). Fourteen programs (93.3%) added heparin to the final islet cell product.

In the immediate postoperative period, 10 programs (66.7%) used a continuous intravenous heparin drip, 2 used a fixed heparin dose regardless of patient weight, and the remaining 8 used weight-based dosing in unit/kg/h. Monitoring and adjustment of the heparin infusion was performed by activated partial thromboplastin time ($n = 5$, 62.5% used goal range of 45–50 s; $n = 3$, 37.5% with a goal of > 50 s) or heparin Xa level correlation checked every 2 h ($n = 1$, 11.1%), every 4 h ($n = 3$, 33.3%), or every 6 h ($n = 5$, 55.6%). These infusions were discontinued after 25–48 h ($n = 5$, 62.5%), 49–72 h ($n = 2$, 25%), or > 72 h ($n = 1$, 12.5%). None utilized portal pressure in deciding the rate of the drip. Of the programs that did not use a continuous intravenous heparin drip, 4 (26.7%) used a low molecular weight heparin (LMWH) subcutaneously and 1 (6.6%) used subcutaneous heparin at the prophylactic dose postoperatively.

Almost all programs ($n = 14$, 93.3%) used subcutaneous LMWH at some point postoperatively. The duration varied with 5 (38.5%) using LMWH for < 1 week, 1 (7.7%) until discharge, 4 (30.7%) around 2 weeks, 2 (15.4%) for 1 month, and 1 (7.7%) for 6 weeks. Five programs monitored anti-Xa levels with goal ranges: 0.4–0.6 IU/ml ($n = 3$, 60%), 0.6–1 IU/ml ($n = 1$, 20%), or 0.3–0.5 IU/ml ($n = 1$, 20%). Anti-Xa levels were monitored every week ($n = 2$, 50%), every 3 days ($n = 1$, 25%), or variably dependent upon clinical signs ($n = 1$, 25%). Five programs (33.3%) started aspirin postoperatively on either postoperative day 0 ($n = 1$, 20%), 1 ($n = 2$, 40%), or 3–7 ($n = 1$, 20%) with 3 using enteric coated 81 mg daily and others using 325 mg. The overall anticoagulation practices postoperatively are demonstrated in Fig. 1.

Of the 122 TPAITs performed by programs, the mean yield of isolates per patient was 3808 (SD 1451) IEQ/kg/infusion. In total, islet preparations were purified in 70 (57%) cases, partially purified in 23 (19%), or unpurified in 29 (24%) cases; three programs used routinely unpurified ($n = 30$), and two routinely purified ($n = 4$) islet preparations. The average tissue volumes were 8 (±4.3) ml. A routine splenectomy was performed at 8 of the 12 programs. The portal vein was accessed using the splenic vein stump ($n = 7$), direct transhepatic catheterization intraoperatively ($n = 2$), or postoperative ultrasound guided percutaneously by interventional radiology ($n = 3$). One center performed intramuscular ($n = 2$) injection. The number of bleeding episodes were 8 (6.6%) and portal vein thrombosis was *zero*. Insulin independence was reported in 39% of the cases.

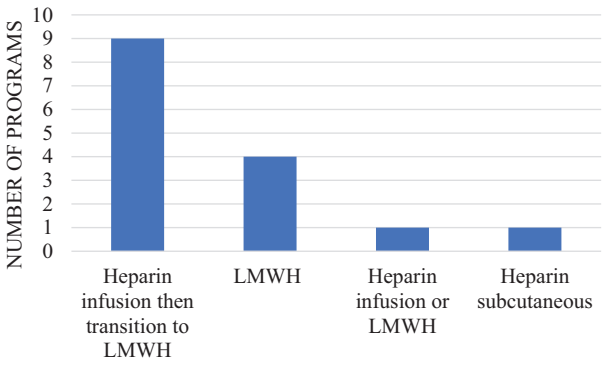

Figure 1 Overall anticoagulation practices postoperatively

The results point toward high variability of practice but some generalizations regarding the concern for hypercoagulable status, use of unfractionated heparin intraoperatively, and use of anticoagulation with LMWH in the postoperative period. The comparisons of complications from different centers would be more meaningful if a uniform protocol was established. If robust data could be collected in a prospective manner, it would assist in informing patients regarding surgical risks and postoperative expectations. Urgent efforts are required to create a consensus guideline on appropriate management either by forming a group that could use corroborative evidence to generate one or by conducting a prospective multicenter randomized trial comparing efficacy and risk.

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Conflict of interest

All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Survey questions.

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