Thromboprophylaxis Challenge after Pancreas Transplantation: A Literature Review

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ABSTRACT

Background: Pancreas thrombosis is a significant complication after pancreas transplantation. Most centers use pharmacologic thromboprophylaxis with anticoagulants and antiplatelet drugs during and/or immediately after transplantation. Currently, there is no consensus on the best thromboprophylaxis in these patients.

Methods: A literature review of MEDLINE, SCOPUS, and Google Scholar was done. Studies administered pharmacologic thromboprophylaxis after pancreas transplantation and reported thrombosis and/or bleeding complications were recruited.

Results: Aspirin, unfractionated or low-molecular-weight heparin (LMWH) were the most utilized options. Dextran, antithrombin III, and warfarin have been occasionally used. The reported rates of thrombosis and bleeding ranged from 4-43% and 0.3-58%, respectively.

Conclusion: Best regimen and duration of pharmacologic thromboprophylaxis in pancreas transplantation remain to be determined. Low-dose aspirin is a common part of antithrombotic regimens that usually continue after discharge. Intraoperative heparin has been administered in some centers and appears to decrease the risk of thrombosis without increasing the risk of bleeding. Adding post-operative, prophylactic doses of intravenous or subcutaneous heparin, starting while the patient is homeostatically stable, forms a part of the current thromboprophylaxis regimen. LMWH has sometimes been substituted for heparin; however, the dose adjustment according to renal function is challenging. Warfarin should be reserved only for patients with hypercoagulability or for thrombosis treatment.

KEYWORDS: Anticoagulant; Antiplatelet; Antithrombotic; Pancreas transplantation; Thrombosis

INTRODUCTION

Pancreas transplantation is a treatment option for uncontrolled diabetic patients [1]. As diabetes mellitus is a leading cause of end-stage kidney disease, simultaneous pancreas and kidney (SPK) transplantation is the most common type of pancreas transplantation. Patient and graft survival after pancreas transplantation is excellent. SPK transplantation improves the patients' quality of life and decreases morbidities and mortality associated with diabetes and secondary complications [2, 3].

Due to the complexity of the pancreas transplantation procedure, technical failure of the pancreas graft, especially early after the transplant surgery, is a challenging problem. Pancreas allograft thrombosis is the expected result of technical failure following pancreas transplantation [4-6]. The incidence of pancreas graft thrombosis has been reported to be between 1 to 40% in different studies [7-9]. A recent systematic review reported a graft loss

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rate of 83.3% in pancreas transplant recipients who experience graft thrombosis [10].

The etiology of pancreas graft thrombosis is multifactorial. It is mainly due to inherently low microcirculatory blood flow through collateral circulation. This circulation, which drains splenic and mesenteric veins, has high capacity, leading to venous stasis. Other thrombogenic factors could be vascular injury during transplant procedure [11], reperfusion injury [12], or inherited hypercoagulability and decreased fibrinolysis in diabetic patients [13]. Histological studies revealed that up to 33% of thrombosis after pancreas transplantation, might result from vascular injury due to immunological failure (acute and hyperacute rejections) early after transplantation [10, 14].

Several risk factors have been associated with increased risk of pancreas allograft thrombosis in different studies, including donor and recipient age, donor and recipient obesity (body mass index (BMI) of more than 30 kg/m^2), baseline hypercoagulability state, nontraumatic especially cardio-cerebrovascular causes of donor death, cold ischemic time and preservation time of more than 12-24 hours, hypotension and vasopressor use during transplantation, and post-reperfusion pancreatitis [4, 10].

Optimizing donor and recipient selection and surgical factors modification are effective strategies for reducing the risk of thrombosis after pancreas transplantation. Most transplant centers routinely use pharmacologic thromboprophylaxis with various combinations of anticoagulant and antiplatelet agents during or immediately after transplant surgery [15]. Different retrospective and cohort studies have evaluated the effectiveness and safety of different thromboprophylaxis protocols for preventing graft thrombosis in pancreas transplantation [16, 17]. Although the efficacy of pharmacologic prophylaxis has been shown in different studies, bleeding risk early after transplantation is a significant concern [18]. Currently, there is no guideline or consensus on the best thromboprophylaxis protocol for pancreas transplantation and any evidence to support either selective or universal anticoagulation after pancreas transplantation is lacking [19]. Herein, we reviewed the literature regarding different thromboprophylaxis regimens that have been applied after pancreas transplantation by different centers or researchers.

MATERIALS AND METHODS

A literature review of the medical databases, including MEDLINE, SCOPUS, and Google Scholar, was performed up to April 2021 using the keywords ("pancreas transplantation" or "pancreatic transplantation" or "pancreas after kidney" or "pancreas transplant alone" or "solitary pancreas transplant" or "simultaneous pancreas kidney" or "simultaneous kidney pancreas" or" simultaneous kidney and pancreas" or "simultaneous pancreas and kidney" or "kidney and pancreas" or "pancreas and kidney" or "kidney pancreas" or "pancreas kidney" or "primary combined pancreas and kidney" or "pancreas-kidney" or "kidney-pancreas" or SPK) AND ("thrombosis" or "anticoagulant" or "antiplatelet" or "heparin" or "enoxaparin" or "low molecular weight heparin" or "aspirin"). In the relevant studies, a manual review of the reference lists was also performed. No data or language filters were applied. Studies that had administered pharmacological thromboprophylaxis after pancreas transplantation and reported thrombosis and/or bleeding complications were included.

RESULTS

After the exclusion of duplications and unrelated studies, 30 articles were evaluated. Table 1 summarizes the characteristics of the included studies, the applied pharmacologic thromboprophylaxis regimen in each study, and the rates of graft thrombosis, graft loss, and bleeding, if reported. Most pancreas transplant centers administered some form of pharmacologic prophylaxis intraoperatively, postoperatively, or both to prevent pancreas graft thrombosis. As seen in Table 1, anticoagulants and antiplatelet drugs have been widely used for prophylaxis of graft thrombosis in pan-

creas transplant recipients. Low-dose aspirin, unfractionated heparin or low-molecular-weight heparin (LMWH) are the most utilized options for thromboprophylaxis following pancreas transplantation [16-18, 20-22]. Intravenous (IV) dextran, antithrombin III, and warfarin have been used occasionally [23-28]. Among the included studies, the rates of thrombosis, bleeding complications, and pancreas allograft loss ranged from 4-43% [27, 29], 0.3-58% [11, 30], and 0-21.6% [28, 30], respectively. Some selected studies are discussed below, while all articles have been summarized in Table 1

Intraoperative Anticoagulation

One component of thromboprophylaxis regimen used in some centers is an intraoperative bolus of IV heparin [7, 17, 31-35]. Arjona-Sánchez *et al.* performed a retrospective analysis among 198 SPK transplantation patients from 1989 to 2017. In that study, pancreas graft thrombosis and bleeding complications were compared between SPK transplant recipients who had undergone intraoperative heparinization with those who had not. One day after surgery, all patients were administered a daily prophylactic dose of LMWH 40 mg. Aspirin 100 mg daily was started on the third postoperative day for all patients. The rates of pancreas graft thrombosis were 4.9% and 14.6% among patients who received and did not receive intraoperative heparin, respectively (P= 0.119). The incidences of hemoperitoneum (17.1% vs. 12.2%; P= 0.53) and upper gastrointestinal bleeding (9.8% vs. 4.9%; P= 0.67) were higher in patients who received intraoperative heparin, but the differences were not statistically significant. The authors concluded that intraoperative heparinization during SPK transplantation surgery was not helpful, so they stopped using intraoperative systemic heparin [17]; However, observing their data shows that pancreas graft thrombosis was approximately threefold more common among patients who did not receive intraoperative heparin. This difference may be clinically remarkable, although it was not statistically significant. Walter *et al.* [27] and Fertmann *et al.* [24] administered 1500-3000 international units (IU) of antithrombin III intraoperatively and then started IV heparin infusion 4-6 hours after transplantation. Both of them reported thrombosis rates of 16% at the end of their studies. Prospective comparative studies with more patients are needed to clarify intraoperative anticoagulantation's effectiveness in thrombosis prevention in pancreas transplantation.

Postoperative Anticoagulation

Postoperative anticoagulation consisted of the following parts:

Unfractionated heparin

A component of antithrombotic regimens that have been widely administered in different thrombosis prevention protocols among pancreas transplant recipients is IV heparin infusion shortly after surgery while the patient is homeostatically stable [11, 16, 18, 20, 21, 23, 24, 27, 28, 30, 32, 33, 36, 37]. Aboalsamh *et al.* compared two thromboprophylaxis protocols after SPK transplantation during a retrospective cohort study. The first group was administered oral aspirin 81 mg daily, starting on postoperative day 1. The second group received IV heparin infusion starting at a dose of 500 IU/hour (hr) from the recovery room until 24 hours. Heparin infusion was de-escalated by 100 IU/hr daily to be stopped on day five post-transplantation and followed by oral aspirin 81 mg daily afterward. Pancreas graft thrombosis and the resultant graft failure rate was 21.2% in the first group, while no pancreas graft thrombosis happened in the second group (P= 0.008). The postoperative hemorrhage rate was not significantly different between the two groups [16].

Adrogue' *et al.* retrospectively evaluated the role of hypercoagulable states in thrombotic events after SPK transplantation. They administered 70 IU/Kg of bolus IV heparin intraoperatively followed by 7-10 IU/Kg/hr for 5-7 days postoperatively to patients who were transplanted between 1994 to 2003. In addition, all recipients started taking 325 mg/day of oral aspirin from day 3-5 after the operation, which was continued for three months. The authors detected that using IV heparin plus aspirin as a thromboprophylaxis regimen

Table 1: Graft thrombosis, bleeding and graft loss rates following different antithrombotic regimens

Author	Country/ published date	Study type/time	N of patients	Follow up	Anticoagulant/ Antiplatelet	Thrombosis rate	Bleeding rate	Graft loss due to thrombosis
Kajosen et al. [33*]	Norway/ 2021	Open-label, observational study (2015-2016)	34	5 (1-13) days	- Before clamping the iliac artery: 30 IU/kg IV UFH - Six hrs postoperatively: 2500 IU LMWH SC - Thereafter, LMWH 2500–7500 IU SC daily depending on the patient weight, uremic status, and type of transplant - ASA 75 mg daily from POD7	26.47%	17.64%	11.76%
Shahrestani et al. [34*]	Australia/ 2021	Retrospective (2008-2017)	235	> 2 months	- In the operating room:5000 IU UFH SC - UFH 5000 IU SC BD started on POD2, unless there was increased risk of bleeding. If concerns of an increased risk of thrombosis existed, UFH 5000 IU SC TDS from POD1	17.4%	___	6.8%
Innes et al. [29*]	England/ 2021	Retrospective (2009-2018)	63	1 month	Group1: IV UFH or SC tinzaparin according to surgeon preference (n=26) Group 2: 30 mL/hr Dextran40 from reperfusion to 72 hrs, IV UFH was also started 48 to 72 hours post-transplantation (n=37)	group1:11% group2 : 23% (P= 0.294)	group1: 58% group2: 22% (P =0 .003)	group1: 3% group2 :19% (P= 0.039)
Gopal et al. [17**]	England/ 2020	Retrospective (2008-2019)	68	1 year	UFH 100 IU/hr IV once the patient was clinically stable postoperation up to a max of 500 IU/hr directed by TEG (n= 17) or CCT (n=51). Then UFH 2500 - 5000 IU BD SC, followed by changes to LMWH 20 mg SC once daily at hospital discharge until 6 weeks post-transplant. After 6 weeks, LMWH was stopped and ASA 75 mg/ day was continued indefinitely	partial thrombosis: TEG: 41.18% CCT:25.50% (P=0.23)	TEG: 17.65% CCT: 45.10% (P=0.05)	TEG: 0 CCT: 10.78% (P=0.06)
Raveh et al. [22]	USA/ 2019	Retrospective (2015-2018)	95	1 month	four anticoagulation regimens for early (<24 hrs) postoperative: Group 1: none (n=10) Group 2: UFH 5000 IU BD SC + ASA 81 mg daily (n=25) Group 3: Dextran 40 IV 20 mL/hr plus UFH SC and oral ASA (n=28) Group 4: UFH infusion targeting aPTT of 45-50 sec (n=32)	group 1: 70% group 2: 36% group 3: 45% group 2: 19% (P=0.01)	___	4.2%
Robbins et al. [36]	USA/ 2019	Retrospective (2001–2018)	183	1 year	Group 1: Enoxaparin 40 mg SC BD for 7 days (n=71) Group 2: UFH as a continuous infusion (~5 IU/kg/hr) until days 3 - 5 and SC enoxaparin up to day 7 (n=112)	group 1: 8% group 2: 5% (P=0.5)	___	___
Kopp Wouter et al. [21]	Netherland/ 2019	Retrospective (2004–2015)	230	3 months	LMWH BD based on weight: nadroparin 5700 IU BD for those over 100 kg and 2850 IU BD for weight below 100 kg. The first dose was administered at the recovery room	34 %	9.6%	7.8%
Wallace et al. [1]	England/ 2019	Retrospective (2009–2016)	198	3 months	Postoperative UFH 5000 IU SC BD during the inpatient stay, with ASA 75 mg once daily for life.	___	___	3.5%
Hakeem et al. [7]	England/ 2018	Retrospective (2009-2014)	103	53.7 months	Epoprostenol 4 ng/kg/min immediately after reperfusion until day 5. ASA 75 mg/day started at hospital discharge	23.3%	19.4%	2.9%
Arjona-Sánchez et al. [16]	Spain/ 2018	Retrospective (1989-2017)	82	2 months	LMWH 40 mg daily from POD 1+ ASA 100 mg daily from POD 3. Group 1: Intraoperative UFH(n=41) Group 2: No UFH(n=41)	group 1: 4.9% group 2: 14.6% (P=0.26)	group 1: 17% group 2: 26% (P>0.05)	___
Harbell et al. [41]	USA/ 2017	Retrospective (5 years)	112	4 years	ASA 325 mg prior to surgery then ASA 325 mg daily and dipyridamole 75 mg four times daily post-operatively	27%	___	3.5%

Table 1: Continued ...

Author	Country/ published date	Study type/time	N of patients	Follow up	Anticoagulant/ Antiplatelet	Thrombosis rate	Bleeding rate	Graft loss due to thrombosis
Aboalsamh et al. [15]	Canada/ 2016	Retrospective (2004-2014)	62	5 years	Group 1: ASA 80 mg/day from day 1 (n=33) Group 2: UFH 500IU/hr for first 24 hrs, reduced by 100IU/hr(n=29) every day to stop on day 5; then ASA 80mg/day afterwards	group 1: 21.2% group 2: 0% (P<0.01)	group 1: <5% group 2: <5%	group 1:21% group 2: 0%
Han et al. [27]	Korea/ 2016	Retrospective (2013–2015)	110	9.4 months	SPK patients: UFH 3000-5000 IU SC TDS then warfarin for 3 months PAK and PTA patents: UFH 400-1000 IU/hr, target aPTT= 45 sec then oral warfarin for 3 months.	33%	2.7%	___
Moiz et al. [38]	USA/ 2015	Retrospective (2007-2013)	83	1 year	ASA 325 mg/day.	21.69%	___	4.8%
Scheffert et al. [20]	USA/ 2014	Retrospective (2001-2009)	152	1 month	Group 1: UFH 300 (200-400) IU/hr, or 5 (3.4-6) IU/kg/hr for 48 (33-69) hours + ASA 300- 325 mg daily from day 1 (n=52) Group 2: ASA 300- 325 mg daily from day 1 (n=100)	partial thrombosis: group 1: 10% group 2: 3% (p=0.123) complete thrombosis: group 1: 10% group 2: 15% (P=0.452)	group 1: 12% group 2: 12%	group 1: 10% group 2: 15% (P=0.452)
Walter et al. [26]	Germany/ 2014	Retrospective (2000-2012)	241	59 months	- 1500 IU dose of AT III intraoperatively. - UFH 400–600 IU/hrwas started 4–6 hrs after the operation for 7–10 days and after that was switched to a LMWH (enoxaparin or fraxiparin). - All patients received 100 mg ASA starting from day 7. Type of transplantation: group 1: DD (n=125)/ group 2: DJ (n=116)	group 1: 4% group 2: 16% (P=0.002)	group 1: 11% group 2: 3% (P=0.026)	group 1: 4% group 2: 15% (P=0.002)
Grabowska Derlatka et al. [28]	Poland/ 2014	Retrospective (2003-2013)	60	6-8 days	Enoxaparin 40 mg daily after surgery.	43%	___	21.6%
Finger et al. [32]	USA/ 2013	Retrospective (1998-2011)	1115	3 months	- UFH bolus (70 IU/kg) prior to vascular clamping. - UFH infusion was started 4 hrs postoperatively (3 IU/kg/hr) and was increased 8 hrs postoperatively to 7 IU/kg/hr for five days. - ASA 81mg/day was started within 48 hrs after surgery and was increased to 325 mg/day when UFH was discontinued.	5.6%	___	___
Ramessur et al. [42]	Australia/ 2013	Retrospective (1992-2010)	118	1 month	UFH 5000 IU BD or enoxaparin 40 mg/day in the perioperative period.34 patients recieved100–300 mg ASA pre-operatively.	10.2%	0.8%	10.2%
Montiel-Casado et al. [35]	Spain/ 2012	Retrospective (2007-2011)	58	2 weeks	Until 2010: 200 IU/hr UFH in the first day and 400 IU/hr over the following 4 days Then enoxaparin 40 mg SC per day until discharge. After 2010: LMWH 2 hours prior to transplantation and during 4 weeks after discharge. All patients received 100 mg daily ASA after discharge	13%	___	12%
Kim et al. [25]	Korea/ 2012	Retrospective (1992-2009)	119	group 1: 95.6 months group 2: 24.3 months	Group 1: 3500 IU UFH/day SC then ASA during admission (n=28) Group 2: UFH 3000-5000 IU SC TDS then oral warfarin for 3 months. Target INR 1.5 to 2 (n=39)	group 1: 7.8% group 2: 27.9%	group 1: 7% group 2: 25%	group1: 5.8% group 2: 1.4%

Table 1: Continued ...

Author	Country/ published date	Study type/time	N of patients	Follow up	Anticoagulant/ Antiplatelet	Thrombosis rate	Bleeding rate	Graft loss due to thrombosis
Schenker et al.[19]	Germany/ 2009	Retrospective (2000-2006)	187	1 year	Group 1: IV UFH 400–600 IU/hr started 4 hrs after surgery for 9.0 ± 4.9 days then SC prophylactic LMWH therapy was applied (n=129) Group 2: 3000–3800 IU LMWH daily SC was started 12 hrs after surgery (n=58)	group 1: 17% group 2: 7% (P=0.047)	group 1: 7.8% group 2: 6.9% (P=NS)	group 1: 17% group 2: 5.1% (P=0.047)
Adrogue et al. [31]	USA/ 2007	Retrospective (1994-2003)	1028	——	Bolus of 70 IU/kg IV UFH in the operating room followed by 7–10 IU/kg/h IV 5-7 day + ASA 325 mg daily starting POD 3-5 and continuing for 3months	12.7% (6.5% pancreas graft thrombosis)	——	17.5%
Vaidya et al. [24]	England/ 2007	Retrospective (2004-2006)	74	Until dicharge	All patients received dextran-40, prophylaxis UFH SC and low-dose ASA	8.1%	——	0
Sudhindran et al. [43]	India/ 2006	Retrospective (1985-2000)	57	1 year	ASA 75 mg/day postoperative	——	——	——
Fertmann et al. [23]	Germany/ 2006	Retrospective (2001-2004)	53	4 days postop-eration	Group 1: At the time of the renal vein anastomosis: 3000 IU of AT III (n=24) Group 2: when AT activity postoperatively decreased to <70%, but ≥60%, 1000 IU of AT and when AT activities<60%, 2000 IU AT were administered (n=29) -In both groups:6hrs after operation:UFH2–4 IU/kg/hr until POD5.	Group 1: 16% Group 2: 24% (P<0.05)	——	——
Humar et al. [10]	USA/ 2004	Retrospective (1994-2003)	937	45.1 months	UFH 300–500 IU/hr POD0-POD5 and ASA 325 mg/day for 3 months	——	0.3%	6.8%
Burke et al. [6]	USA/ 2003	Retrospective (1998-2002)	85	1 week	- At the clamp off: 0-5000 IU UFH; based on the degree of hypercoagulabilityby TEG, typically 2–3000 IU. - Prior to discharge from the hospital: ASA 325 mg/d was started	——	2%	1%
Gilabert et al. [44]	Spain/ 2002	Retrospective (1986-2000)	196	——	during the first 10 days after transplantation: LMWH (Fragmin 2500 IU) SC, BD - Then ASA until discharge from hospital.	12.75%	——	8.1%
Ciancio et al. [30]	USA/ 2000	Retrospective (1994-1999)	126	36.4 month	3000– 5000 IU heparin IV before vascular clamps + ASA 325mg/day beginning on post-operative day 2	11%	0.7.9%	0

aPTT: activated partial thromboplastin time; ASA: aspirin; AT III: antithrombin III; BD: twice daily; CCT: conventional coagulation test; DD: duodenoduodenostomy;DJ: duodenojejunostomy; hr: hour; IU: international unit; IV: intravenous; Max: maximum; POD: postoperative day; LMWH: low molecular weight heparin; SC: subcutaneous; Sec: second; TDS: three times daily; TEG: thromboelastogram; UFH: unfractionated heparin.

reduced the rate of pancreas graft thrombosis from 12% to 6% compared to their experience before 1994 when they did not apply perioperative heparin [32]. A comparison between patients who received IV heparin in the first 48 hours after transplantation plus aspirin and patients who received only aspirin 300-325 mg/day from the first day after pancreas transplantation found a statistically non-significant lower rate of complete thrombosis among patients who received IV heparin in combination with aspirin (10% vs. 15%; P=0.452) [21]. Raveh *et al.* retrospectively compared four different anticoagulation regimens early after pancreas transplantation. Anti-coagulation regimens included subcutaneous (SC) heparin plus oral aspirin, dextran plus SC heparin and oral aspirin, heparin infusion, and none. IV heparin infusion was the

most effective thromboprophylaxis regimen as the rate of pancreas allograft thrombosis in the heparin infusion group was 19% versus 48% in the rest of the groups (odds ratio (OR) 0.25, 95% confidence interval (CI): 0.09-0.70; P= 0.01). Among the anticoagulation regimens, heparin infusion was associated with increased bleeding complications compared to no anti-coagulation, but it depended on the partial thromboplastin time (PTT). Six percent of the patients with PTT value below 60 seconds versus 25%of the patients with PTT above 60 seconds needed re-exploration due to bleeding (OR 5.7; 95% CI 0.98-33.08; P= 0.048) [23]. In their review article, Farney et al. discussed the bleeding risk of IV heparin infusion. The thromboprophylaxis protocol in their center contained 1500–2000 IU heparin bolus intraoperatively followed by a heparin infusion of 100–200 IU/hr to a maximum rate of 500 IU/hr after transplantation when the patient was homeostatically stable. They did not intent to increase the PTT and reported increased risk of postoperative bleeding when PTT prolonged beyond 50 seconds [5].

As found, few studies administered therapeutic doses of heparin after pancreas transplantation to prevent thrombosis [22, 31], while most studies have used prophylactic IV heparin doses [10, 15, 17, 19, 20, 23, 26, 27, 29, 32, 35, 36] for this purpose. When IV heparin was administered in therapeutic doses, bleeding complications were reported in up to 17.5% of the cases [31]. The bleeding risk after IV heparin infusion seems to depend on the heparin dose and PTT values. More studies are needed to evaluate the optimal dose of heparin and PTT goal to balance most antithrombotic efficacy and least bleeding risk after pancreas transplantation. The other areas that need more research are comparisons between different routes of heparin administration (SC versus IV) and modes of heparin administration (bolus versus infusion administration) in the pancreas transplantation population.

Low-molecular-weight heparin

LMWH could be an attractive option for thrombosis prophylaxis after pancreas transplantation due to the ease of administration, once-daily dosing, and less need for laboratory monitoring. In a retrospective study, Schenker *et al.* compared IV heparin infusion adjusted to target aPTT within twice the normal range versus once daily LMWH after SPK transplantation. Patients did not receive an antiplatelet agent. Vascular graft thrombosis was 17% and 7% in the heparin and LMWH groups, respectively (P= 0.047). The frequency of major bleeding did not significantly differ between the two groups (7.8% vs. 6.9%) [20]. Also, Kopp *et al.* retrospectively evaluated LMWH efficacy for thrombosis prevention after SPK transplantation. Their protocol adjusted the LMWH dose according to the patient's weight. No other anticoagulant or antiplatelet agent was administered. According to computed tomography follow-up after transplantation, 34% of the patients had evidence of complete or partial thrombosis. Pancreas graft loss occurred in 7.8% of the patients due to thrombosis. This study required surgical intervention in 9.6% of the patients because of bleeding complications [22]. Estimation of appropriate dosing based on patient weight, dose adjustment in renal failure, cost, and reversibility of anti-coagulation effect are the main challenges for LMWH administration [5]. Although enoxaparin has been used safely in renal failure, dose adjustment is required [38]. Dose adjustment of LMWH is complicated due to unpredictable changes in renal function over time early after SPK transplantation. Because of this limitation, Gopal *et al.* administered LMWH at discharge, when renal function was stable, after the initial administration of heparin during hospitalization [18]. In solitary pancreas transplantation (pancreas transplant alone (PTA) and pancreas after kidney transplantation (PAK)) in which the transplant recipient is nonuremic, LMWH dose and safety could be more confident.

Aspirin

Antiplatelet drugs, especially aspirin, are components of most thromboprophylaxis protocols (Table 1). There is no randomized controlled trial or cohort study comparing different doses and duration of aspirin administration as thromboprophylaxis after pancreas transplantation. Raveh *et al.* retrospectively compared

four different anti-coagulation regimens early after pancreas transplantation. They developed a sonographic-based thrombosis severity score (TSS) system [TSS = (vessel grade) × (occlusion grade) × (diastolic flow grade)] in their study. There was no association between anti-coagulation regimens and venous TSS, but arterial TSS was higher in regimens without antiplatelet therapy on the first day after transplantation. This finding indicates the efficacy of antiplatelet therapy in thromboprophylaxis protocols [23]. In that study, platelet function analysis was done for patients on the day of surgery. Collagen-epinephrine (Col/Epi) closure time (normal 98-182 seconds) and collagen-ADP assay (Col/ADP) (normal 52-112 seconds) was measured. Isolated prolonged Col/Epi assay indicates a mild intrinsic or aspirin-induced platelet dysfunction, while prolongation of both Col/Epi and Col/ADP indicates a significant intrinsic or induced (other than aspirin) platelet dysfunction. Results should interpret in the absence of severe anemia or thrombocytopenia. Graft thrombosis rate was 20% in patients with normal platelet function, while thrombosis rates were 33% in patients with Col/Epi >182 seconds and Col/ADP <112 seconds and 61% in those with Col/Epi >182 seconds and Col/ ADP >112 seconds (P= 0.002). Moreover, worsening platelets' function was associated with higher venous TSS (P= 0.03). Col/Epi assay was normal in 29% of the patients on chronic low daily doses of 81 mg aspirin. This finding suggests a daily dose of 325 mg aspirin may be more effective for thromboprophylaxis after pancreas transplantation [23]. Some transplant centers have also used aspirin at a daily dose of 325 mg in their thrombosis prevention protocol [7, 11, 21, 31-33, 39]. Although daily doses of 75 to 325mg of aspirin are defined as low doses [39], there is a concern about the bleeding risk with higher doses of aspirin in this range. In a systematic review of studies for cardiovascular thrombosis prophylaxis, McQuaid et al. stated that a higher range of low-dose aspirin (162.5 to 325 mg daily) did not increase the relative risk of intracranial, gastrointestinal or any other forms of major bleedings comparing with lower range of low daily doses of aspirin (75 to 162.5 mg daily). In this systematic review, these doses ranges of aspirin were compared with placebo for bleeding risks [40]. Conversely, a systematic review that compared clinical outcomes and bleeding risk of aspirin daily doses of less than 160 mg versus 160 mg or higher in patients with the acute coronary syndrome who underwent coronary stent insertion or medical treatment found no improvement in the clinical outcomes with higher doses of aspirin. In contrast, major bleeding happened more commonly in the first month after acute coronary syndrome in medically treated patients, but not in coronary stent-inserted subjects, with higher than lower aspirin doses (4% versus 1.7%) [41]. Prospective comparative studies are needed to determine the most effective doses of aspirin with the least bleeding risk as thromboprophylaxis after pancreas transplantation.

Warfarin

Warfarin has been used as a part of the thromboprophylaxis regimen after pancreas transplantation in a few transplant centers [26, 28]. Warfarin seems ineffective due to its delayed onset of action, while graft thrombosis usually occurs more often three days after pancreas transplantation [22]. Warfarin could be used in patients with a known or suspected hypercoagulability state or to treat thrombosis events. Other than these conditions, the risk of bleeding probably outweighs any benefits [5, 15]. Using different tools as predictors for anti-coagulation, individualization of antithrombotic therapy after pancreas transplantation has been studied in different articles. A recent retrospective study by Gopal and associates suggested using a thromboelastogram (TEG) to guide anti-coagulation after SPK transplantation. That study compared the incidence of partial pancreas thrombosis, graft loss due to thrombosis, and bleeding complications of TEG versus conventional coagulation tests (CCT) directed anti-coagulation in 68 SPK transplant recipients. The thromboprophylaxis protocol consisted of an initial 100 IU/hr of heparin infusion titrated up to a maximum of 500 IU/hr guided by TEG results or clinical and laboratory parameters in the CCT group. This regimen is followed by 2500 or 5000 IU heparin subcutaneously, twice daily

during hospitalization, and LMWH once daily at discharge until six weeks post-transplantation. After that, aspirin 75 mg daily was continued indefinitely. Ten percent of grafts (7 pancreases and 4 kidneys) were lost due to thrombosis in the CCT group, while no graft loss was due to thrombosis in the TEG group (P= 0.06). The rate of partial thrombosis in the pancreas graft vasculature was 41.18% in the TEG group and 25.50% in the CCT group (P= 0.23). The incidence of anti-coagulation-related bleeding was 17.65% and 45.10% in the TEG and CCT groups, respectively (P= 0.05) [18]. Using the TEG guide in Vaidya *et al.* the study showed that 34% of the patients undergoing pancreas transplantation require therapeutic anti-coagulation to prevent graft thrombosis [25]. Additionally, Burke *et al.* performed intra-operative TEG to evaluate the patient's coagulation status and individualize IV heparin bolus from 0 to 5000 U prior to clamping off. In their experience, only one pancreas graft was lost due to thrombosis (1%) in the first week following transplantation [7].

DISCUSSION

Pancreas graft thrombosis, especially early after transplantation surgery, remains a challenging problem. Due to the lack of randomized controlled trials, insufficient evidence exists to ensure the best pharmacologic regimen for thrombosis prevention in pancreas transplant recipients. According to the available retrospective observational studies, low-dose aspirin in 75 to 325 mg daily is a common part of thromboprophylaxis regimens in most transplant centers. Although limited data supports more effective antiplatelet action of the upper limit of this aspirin dosing range, there are concerns regarding bleeding risk with doses in the upper mid-range of low doses of aspirin. Safety data derived from studies on cardiovascular prophylaxis indication comparing major bleeding risk with a lower- and upper-mid range of low doses of aspirin is reassuring. However, randomized controlled trials in pancreas transplant patients are needed to find the best dose of aspirin, balancing efficacy and safety for thromboprophylaxis in this population. Continuing aspirin administration after hospital discharge is common among pancreas transplant teams, varying from three months to life-long.

Regarding the role of anticoagulant drugs in preventing pancreas allograft thrombosis, although there are some doubts, it seems that intraoperative heparin administration decreases the risk of pancreas allograft thrombosis without an increase in the bleeding risk. Postoperative IV or SC heparin administration is essential to current thromboprophylaxis regimens after pancreas transplant surgery while the patient is homeostatically stable. According to the available retrospective data, adding prophylactic doses of heparin appears to be more effective than low-dose aspirin alone without an increase in the risk of hemorrhage, especially if PTT remains below 50-60 seconds. In pancreas transplantation, sometimes LMWH has been substituted for heparin. LMWH has been effective for thromboprophylaxis, but dose adjustment of LMWH according to renal function, especially early after SPK transplantation, is challenging. Some transplant centers continue the injectable anticoagulant for several weeks after patients' discharge. The need for this prophylaxis and stratifying patients to continue thromboprophylaxis with heparin and/or aspirin at home require more studies.

Warfarin is a less frequently used anticoagulant for graft thrombosis after pancreas transplantation, and it should be reserved for patients with a known or suspected hypercoagulability state or the treatment of thrombosis events. There is no data on the use of direct oral anticoagulant agents to prevent thrombosis after pancreas transplantation.

In conclusion, low-dose aspirin in the range of 75 to 325 mg daily is a standard part of thromboprophylaxis regimens in most pancreas transplant centers. In addition, intraoperative heparin administration seems to decrease the risk of pancreas allograft thrombosis without an increase in the bleeding risk. Postoperative IV or SC heparin administration is essential

to current thromboprophylaxis regimens after pancreas transplant surgery while the patient is homeostatically stable. LMWH has been effective for thromboprophylaxis, but dose adjustment of LMWH according to renal function, especially early after SPK transplantation, is challenging. Warfarin is a less frequently used anticoagulant for graft thrombosis after pancreas transplantation, and it should be reserved for patients with a known or suspected hypercoagulability state or the treatment of thrombosis events. There is no data on direct oral anticoagulant drugs for thromboprophylaxis among pancreas transplant recipients.

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REFERENCES

1. Wallace DF, Bunnett J, Fryer E, *et al*. Early allograft pancreatectomy—Technical failure or acute pancreatic rejection? *Clin Transplant* 2019;**33**:e13702.
2. Hanlon M, Cooper M, Abrams P. Quality of life after pancreas transplantation: time to look again. *Curr Opin Organ Transplant* 2019;**24**:451-5.
3. Gruessner AC, Gruessner RW. Pancreas transplantation for patients with type 1 and type 2 diabetes mellitus in the United States: a registry report. *Gastroenterol Clin* 2018;**47**:417-41.
4. Farney AC, Rogers J, Stratta RJ. Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. *Curr Opin Organ Transplant* 2012;**17**:87-92.
5. Roberto FMJ, Paolo S, Alvaro P-S. Pancreas Transplantation. *Einstein* (Sao Paulo, Brazil) 2015;**13**:305-9.
6. Burke III GW, Ciancio G, Figueiro J, *et al*. Hypercoagulable state associated with kidney–pancreas transplantation. Thromboelastogram-directed anti-coagulation and implications for future therapy. *Clin Transplant* 2004;**18**:423-8.
7. Hakeem A, Chen J, Iype S, *et al*. Pancreatic allograft thrombosis: Suggestion for a CT grading system and management algorithm. *Am J Transplant* 2018;**18**:163-79.
8. Muthusamy AS, Giangrande PL, Friend PJ. Pancreas allograft thrombosis. *Transplantation* 2010;**90**:705-7.
9. Blundell J, Shahrestani S, Lendzion R, *et al*. Risk Factors for Early Pancreatic Allograft Thrombosis Following Simultaneous Pancreas-Kidney Transplantation: A Systematic Review. *Clin Appl Thromb Hemost* 2020;**26**:1076029620942589.
10. Humar A, Ramcharan T, Kandaswamy R, *et al*. Technical failures after pancreas transplants: why grafts fail and the risk factors—a multivariate analysis. *Transplantation* 2004;**78**:1188-92.
11. Schaser KD, Puhl G, Vollmar B, *et al*. In vivo imaging of human pancreatic microcirculation and pancreatic tissue injury in clinical pancreas transplantation. *Am J Transplant* 2005;**5**:341-50.
12. Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complicat* 2001;**15**:44-54.
13. Drachenberg CB, Papadimitriou JC, Farney A, *et al*. Pancreas transplantation: the histologic morphology of graft loss and clinical correlations. *Transplantation* 2001;**71**:1784-91.
14. Patel SR, Hakim N. Prevention and management of graft thrombosis in pancreatic transplant. *Exp Clin Transplant* 2012;**10**:282-9.
15. Aboalsamh G, Anderson P, Al-Abbassi A, *et al*. Heparin infusion in simultaneous pancreas and kidney transplantation reduces graft thrombosis and improves graft survival. *Clin Transplant* 2016;**30**:1002-9.
16. Arjona-Sánchez A, Rodríguez-Ortiz L, Sánchez-Hidalgo J, *et al*., editors. Intraoperative Heparinization During Simultaneous Pancreas-Kidney Transplantation: Is It Really Necessary? Transplant Proceeding 2018: Elsevier.
17. Gopal JP, Dor FJ, Crane JS, *et al*. Anticoagulation in simultaneous pancreas kidney transplantation-On what basis? *World J Transplant* 2020;**10**:206.
18. David A, Frampas E, Douane F, *et al*. Management of vascular and nonvascular complications following pancreas transplantation with interventional radiology. *Diagn Interv Imaging* 2020;**101**:629-38.
19. Schenker P, Vonend O, Ertas N, *et al*. Incidence of pancreas graft thrombosis using low-molecular-weight heparin. *Clin Transplant* 2009;**23**:407-14.
20. Scheffert JL, Taber DJ, Pilch NA, *et al*. Clinical outcomes associated with the early postoperative use of heparin in pancreas transplantation. *Transplantation* 2014;**97**:681-5.
21. Kopp WH, van Leeuwen CA, Lam HD, *et al*. Retrospective study on detection, treatment, and clinical outcome of graft thrombosis following pancreas transplantation. *Transpl Int* 2019;**32**:410-7.
22. Raveh Y, Ciancio G, Burke GW, *et al*. Susceptibility-directed anticoagulation after pancreas transplantation: A single-center retrospective study. *Clin Transplant* 2019;**33**:e13619.
23. Fertmann JM, Wimmer CD, Arbogast HP, *et al*. Single-shot antithrombin in human pancreas–kidney transplantation: reduction of reperfusion pancreatitis and prevention of graft thrombosis. *Transpl*

Int 2006;**19**:458-65.

24. Vaidya A, Muthusamy A, Hadjianastassiou V, *et al*. Simultaneous pancreas–kidney transplantation: to anticoagulate or not? Is that a question? *Clin Transplant* 2007;**21**:554-7.
25. Kim YH, Park JB, Lee SS, *et al*. How to avoid graft thrombosis requiring graftectomy: immediate posttransplant CT angiography in pancreas transplantation. *Transplantation* 2012;**94**:925-30.
26. Walter M, Jazra M, Kykalos S, *et al*. 125 Cases of duodenoduodenostomy in pancreas transplantation: a single-centre experience of an alternative enteric drainage. *Transpl Int* 2014;**27**:805-15.
27. Han K, Ko HK, Tsauo J, *et al*. Endovascular management for the treatment of pancreas transplant venous thrombosis: a single-center experience. *J Vasc Interv Radiol* 2016;**27**:882-8.
28. Grabowska-Derlatka L, Grochowiecki T, Pacho R, *et al*., editors. Role of 16-Multidetector Computerized Tomography in Evaluation of Graft Failure Risk in Patients with Pancreatic Graft Thrombosis After Simultaneous Pancreas and Kidney Transplantation. Transplantation proceedings; 2014: Elsevier.
29. Innes A, Tingle S, Ibrahim I, *et al*., editors. Use of Dextran 40 After Pancreas Transplant May Reduce Early Inflammation and Significant Bleeding Compared to a Heparin-Based Protocol. Transplantation proceedings; 2021: Elsevier.
30. Ciancio G, Cespedes M, Olson L, *et al*. Partial venous thrombosis of the pancreatic allografts after simultaneous pancreas–kidney transplantation. *Clin Transplant* 2000;**14**:464-71.
31. Adrogué HE, Matas AJ, McGlennon R, *et al*. Do inherited hypercoagulable states play a role in thrombotic events affecting kidney/pancreas transplant recipients? *Clin Transplant* 2007;**21**:32-7.
32. Finger EB, Radosevich DM, Dunn TB, *et al*. A composite risk model for predicting technical failure in pancreas transplantation. *Am J Transplant* 2013;**13**:1840-9.
33. Kjøsen G, Rydenfelt K, Horneland R, *et al*. Early detection of complications in pancreas transplants by microdialysis catheters, an observational feasibility study. *PLOS one* 2021;**16**:e0247615.
34. Shahrestani S, Hitos K, Hort A, *et al*., editors. Successful Expectant Management of Nonocclusive Thrombosis in Simultaneous Pancreas-Kidney Transplantation. Transplantation Proceedings; 2021: Elsevier.
35. Montiel-Casado M, Fernández-Burgos I, Pérez-Daga J, *et al*., editors. Impact of blood amylase peak over vascular graft thrombosis in pancreas transplantation. Transplantation proceedings; 2012: Elsevier.
36. Robbins AJ, Skube ME, Bellin MD, *et al*. Portal vein thrombosis after total pancreatectomy and islet autotransplant: prophylaxis and graft impact. *Pancreas* 2019;**48**:1329-33.
37. Shaikh SA, Regal RE. Dosing of enoxaparin in renal impairment. *Pharm Ther* 2017;**42**:245.
38. Moiz A, Javed T, Bohorquez H, *et al*. Role of special coagulation studies for preoperative screening of thrombotic complications in simultaneous pancreas-kidney transplantation. *Ochsner J* 2015;**15**:272-6.
39. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;**119**:624-38.
40. Berger JS, Sallum RH, Katona B, *et al*. Is there an association between aspirin dosing and cardiac and bleeding events after treatment of acute coronary syndrome? A systematic review of the literature. *Am Heart J* 2012;**164**:153-62.e5.
41. Harbell J, Morgan T, Feldstein V, *et al*. Splenic vein thrombosis following pancreas transplantation: identification of factors that support conservative management. *Am J Transplant* 2017;**17**:2955-62.
42. Ramessur Chandran S, Kanellis J, Polkinghorne KR, *et al*. Early pancreas allograft thrombosis. *Clin Transplant* 2013;**27**:410-6.
43. Sudhindran S, Sunil S, Sinha S. Platelet counts are persistently increased following simultaneous pancreas and kidney transplantation. *Transplant Proc* 2006;**38**:1549-51.
44. Gilabert R, Fernandez-Cruz L, Real M, *et al*. Treatment and outcome of pancreatic venous graft thrombosis after kidney–pancreas transplantation. *Br J Surg* 2002;**89**:355-60.