

Prevention of Bleeding After Islet Transplantation: Lessons Learned from a Multivariate Analysis of 132 Cases at a Single Institution

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Islet transplantation is being offered increasingly for selected patients with unstable type 1 diabetes. Percutaneous transhepatic portal access avoids a need for surgery, but is associated with potential risk of bleeding. Between 1999 and 2005, we performed 132 percutaneous transhepatic islet transplants in 67 patients. We encountered bleeding in 18/132 cases (13.6%). In univariate analysis, the risk of bleeding in the absence of effective track ablation was associated with an increasing number of procedures (2nd and 3rd procedures with an odds ratio (OR) of 9.5 and 20.9, respectively), platelets count <150 000 (OR 4.4), elevated portal pressure (OR 1.1 per mm Hg rise), heparin dose ≥45 U/kg (OR 9.8) and pre-transplant aspirin (81 mg per day) (OR 2.6, $p = 0.05$). A multivariate analysis further confirmed the cumulative transplant procedure number ($p < 0.001$) and heparin dose ≥45 U/kg ($p = 0.02$) as independent risk factors for bleeding. Effective mechanical sealing of the intrahepatic portal catheter tract with thrombostatic coils and tissue fibrin glue completely prevented bleeding in all subsequent procedures ($n = 26$, $p = 0.02$). We conclude that bleeding after percutaneous islet implantation is an avoidable complication provided the intraparenchymal liver tract is sealed effectively.

Key words: Intraabdominal hemorrhage, intra-portal cell transplantation, Islet of Langerhans transplantation, portal vein thrombosis, postoperative complications, Transhepatic portal vein access

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Introduction

There has been an exponential increase in activity in clinical islet transplantation since the year 2000. Worldwide, almost 500 patients have undergone intraportal islet infusions in the past 5 years at 43 institutions (1). Insulin independence rates of 80% have been reported at 1 year, both in islet-alone and in simultaneous islet-kidney transplantation (2–7). At our own center, these rates have fallen to 50% at 3 years and 11% at 5 years, although 80% of grafts continue to function with C-peptide secretion and stable glycemic control over 5 years.

Islet transplantation can only be justified over whole pancreas transplantation provided the risk and side effects are substantially reduced for the less invasive procedure. Islet transplantation is offered as an alternative to insulin for highly selected patients with unstable forms of type 1 diabetes, to improve glycemic control and maybe to prevent secondary complications (8–10). The safety of the islet implant procedure is therefore of paramount importance.

Although some islet centers have elected to use an open surgical approach to avoid procedure-related bleeding (11), most centers have adopted the percutaneous transhepatic route for islet implantation to avoid a need for surgery (12,13). Life-threatening acute bleeds have been reported in islet recipients following the percutaneous approach (14–16) and this serious complication is potentially avoidable by obliteration of the intrahepatic portal catheter track.

We herein provide a detailed analysis of risk factors associated with acute bleeding following islet implantation and discuss alternative management that has proven to be effective to avoid this complication.

Patients and Methods

Between March 1999 and April 2005, a total of 147 islet-alone transplants were performed in 74 subjects with unstable type 1 diabetes at the

Table 1: Demographics and findings

	Bleed (N = 18)	No bleed (N = 114)	Overall (N = 132)
Patient characteristics			
Female (procedures)	13 (17.3%)	62 (82.7%)	75
Female (patients)	12 (30.8%)	27 (69.2%)	39
Male (procedures)	5 (8.8%)	52 (91.2%)	57
Male (patients)	5 (17.9%)	23 (82.1%)	28
Age yrs	42.9 ± 10.4	43.4 ± 9.8	43.3 ± 9.9
Duration of diabetes yrs	23.5 ± 8.5	29.0 ± 11.2	27.6 ± 11.1
Number of transplant			
1st	2 (3.0%)	65 (97.0%)	67
2nd	12 (22.2%)	39 (77.8%)	54
3rd	4 (36.4%)	7 (63.6%)	11
Pre-procedure factors			
ASA pre procedure	8 (22.9%)	27 (77.1%)	35
No ASA	10 (10.3%)	87 (89.7%)	97
Intra-procedure factors			
Peak portal pressure (mmHg)	17.1 ± 5.0	14.5 ± 5.5	14.9 ± 5.4
Islet mass (IE/kg)	5,732 ± 1,190	5,761 ± 1,649	5,757 ± 1,590
Packed cell volume (mL)	5.0 ± 1.9	4.2 ± 1.7	4.3 ± 1.7
Number of procedures performed by radiologist	8.4 ± 5.7	9.6 ± 7.0	9.4 ± 6.8
Catheter size: 4 French	15 (13.3%)	98 (86.7%)	113
Catheter size: 5–7 French	3 (15.8%)	16 (84.2%)	19
Hematology & anticoagulation			
Platelets <150 000/mm ³	7 (31.8%)	15 (68.2%)	22
Platelets ≥ 150 000/mm ³	11 (10.0%)	99 (90.0%)	110
INR pretransplant	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
PTT pretransplant	113.5 ± 13.3	130.6 ± 16.1	128.3 ± 16.8
Hb drop: pre–post (%)	27.9 ± 9.7	7.8 ± 5.9	10.6 ± 9.5
Heparin dose U/infusion	3300 ± 1422	2536 ± 1378	2641 ± 1404
Heparin <25 U/kg	1 (4.8%)	20 (95.2%)	21
Heparin ≥25; <45 U/kg	7 (8.8%)	73 (91.2%)	80
Heparin ≥45 U/kg	10 (32.3%)	21 (67.3%)	31
Post-procedure findings			
Portal vein thrombosis	2	3	5

University of Alberta. We excluded 6 procedures performed surgically and 9 procedures in 4 patients enrolled in the Immune Tolerance Network trial. Therefore, a total of 132 procedures carried out in 67 patients have been analyzed herein. Ethical approval was obtained from the Human Research Ethics Board of the University of Alberta and all patients gave written consent to participate.

Demographic and clinical information are documented in Table 1. The selection criteria for islet-alone transplantation included severe hypoglycemic unawareness or uncontrolled glycemic lability despite compliance with optimal insulin delivery and monitoring regimens (2).

Percutaneous access to the portal vein was carried out in the interventional radiology suite using ultrasonic and/or fluoroscopic guidance, as described previously (12,13,17). Briefly, portal vein access was gained using a 22 gauge Chiba needle and exchanged over a 0.018 inch guidewire for a 4 Fr catheter (stiffened micropuncture introducer set, Cook Inc., Bloomington, IN) (12). Portal venous pressure was measured before, at intervals throughout and after completion of the islet infusion. The mean islet packed tissue volume was 4.3 ± 1.7 mL. The mean implanted islet mass per transplant was 391 564 ± 117 403 IE, or 5757 ± 1590 IE/kg (recipient body weight). The mean recipient weight was 68.5 ± 10.7 kg (range 47–92 kg). Heparin was added to the islet suspension just prior to infusion at 35 U/kg; the dose was increased to 70 U/kg if the packed tissue volume exceeded 5 mL. Low

molecular weight heparin (enoxaparin sodium 30 mg s.c. twice daily for 7 days) and acetylsalicylic acid (ASA, 81 mg p.o. per day for 14 days) was initiated on the first post-transplant day, provided there was no evidence of bleeding.

The techniques used to seal the catheter tract have evolved over time and are summarized in Table 2 (12). A Doppler ultrasound is obtained prior to discharge, both to confirm patency of the portal vein and its intrahepatic tributaries and to look for free fluid. Most patients are discharged on the day following islet infusion (median hospital stay 2.0 days, range 1–17).

All procedures were carried out under corticosteroid-free, sirolimus-based immunosuppression. A total of 94 procedures were performed under daclizumab/sirolimus/low-dose tacrolimus (Edmonton Protocol), 19 were given the Edmonton Protocol plus infliximab (10 mg/kg i.v. prior to islet infusion), 15 were carried out following T-cell depletion with combined infliximab plus alemtuzumab (20 mg i.v. per day × 2) with sirolimus/low-dose tacrolimus maintenance and four transplants were completed after thymoglobulin induction and sirolimus/mycophenolate mofetil maintenance therapy.

Significant bleeding was defined as: (a) A drop in hemoglobin of more than 20% compared with the initial pre-transplant value, combined with the presence of free intraperitoneal fluid on ultrasound evaluation; (b) Evidence of

Table 2: Association of risk of bleeding related to catheter size and sealing methods (%)

Catheter size	Gelfoam® plug	Gelfoam® plug/Coils	Laser	Tisseel® Coils	No sealant used	Total
4 Fr	10/57 (17.5%)	0/9	1/3	0/26 (0%)	3/18 (16.7%)	14/113 (12.4%)
5–7 Fr	4/17 (23.5%)	0/0	0/1	0/0 (0%)	0/1 (0%)	4/19 (21.1%)
Total	14/73 (19.2%)	0/9	1/4	0/26 (0%)	3/19 (15.8%)	18/132 (13.6%)

hemodynamic instability with tachycardia and/or hypotension in patients requiring blood transfusion and/or open surgical or laparoscopic intervention for control of hemorrhage or (c) Evidence of intrahepatic hematoma on imaging associated with a fall of hemoglobin of >20% compared to baseline. To further sub-categorize the impact of intraportal heparin, we grouped patients depending on the dose of heparin used, as (a) none or low-dose (<25 U/kg), (b) intermediate (25–44 U/kg) or high-dose (45–80 U/kg).

Statistical analysis

Fisher's exact test was used to define the significance associated with categorical variables. Odds ratios for factors predicting a hemorrhagic event were estimated using binary generalized estimating equations (GEE). The GEE technique, introduced by Liang and Zeger, provides a method of analyzing correlated data that otherwise could be modeled as a generalized linear model (18). In this case, observations were correlated because patients may have had more than one islet cell transplant and were at risk of bleeding following every procedure. $P \leq 0.05$ was regarded as statistically significant throughout. Statistical comparisons were carried out using SAS version 8.2 (SAS Institute Inc., Carry, NC).

Results

There were 39 (58.2%) women and 28 men who received 75 (56.8%) and 57 transplants, respectively (total procedures 132). Mean \pm SD age and duration of diabetes at the time of first transplant were 43.3 ± 9.9 and 27.6 ± 11.1 years, respectively. A total of 13 patients (19.4%) had undergone one percutaneous procedure, 43 (64.2%) had undergone two procedures and 11 (16.4%) had undergone three procedures.

Eighteen bleeding events (13.6% of all procedures) were experienced in 17 patients (25.4%). There was not difference in INR and PTT pretransplant in the bleed and non-bleeding groups. In univariate analyses, five factors were found to significantly increase the risk of bleeding ($p \leq 0.05$) after percutaneous access to the portal vein (Table 3). Increased portal pressure (peak) was associated with an increased risk with an odds ratio of 1.1 per mmHg (95% CI: 1.0–1.2, $p = 0.04$). The risk of bleeding increased with the number of procedures performed per patient; compared to the first transplant, the estimated odds of bleeding after the second and third transplant were 9.5 (95% CI: 2.3–38.7, $p = 0.001$) and 20.9 (95% CI: 3.4–127.2, $p = 0.001$), respectively. Low platelet count (defined as <150 000) prior to the procedure was also identified as a risk factor for a bleeding event (OR = 4.4; 95% CI: 1.6–12.1, $p = 0.005$). Compared to no heparin, there was not an increased risk of bleeding when a low dose regimen was applied, however there was an increased risk when a high heparin dose was given (OR 9.8; 95% CI: 1.3–74.6, $p = 0.03$). Patients who were on

Table 3: Univariate GEE models predicting the risk of bleed

	Overall (N = 132)	Odds ratio	95% confidence interval	p-value
Female	75	2.1	0.8–5.9	0.14
Age		1.0	0.7–1.3	0.87
Number of transplant				
1st	67	1.0		–
2nd	54	9.5	2.3–38.7	0.001
3rd	11	20.9	3.4–127.2	0.001
ASA (pre-procedure)	35	2.6	1.0–6.8	0.05
Platelets (<150 000/mm ³)	110	4.4	1.6–12.1	0.005
Heparin low dose <25U/kg	21	1.0		–
Intermediate	80	1.9	0.3–14.7	0.52
≥ 25 ; <45 U/kg				
High dose ≥ 45 U/kg	31	9.8	1.3–74.6	0.03
No track closure material	19	1.2	0.3–4.5	0.76
Edmonton protocol	94	0.4	0.2–1.2	0.10
immunosuppression				
Number of procedures by radiologist		1.0	0.9–1.0	0.46
Portal pressure (per mm Hg)		1.1	1.0–1.2	0.04
Islet mass (per 1000 IE/kg)		1.0	0.8–1.2	0.88
Packed cell volume		1.3	0.9–1.7	0.12

ASA prior to the transplant had an increased risk with an odds ratio of 2.6 (95% CI: 1.0–6.8, $p = 0.05$).

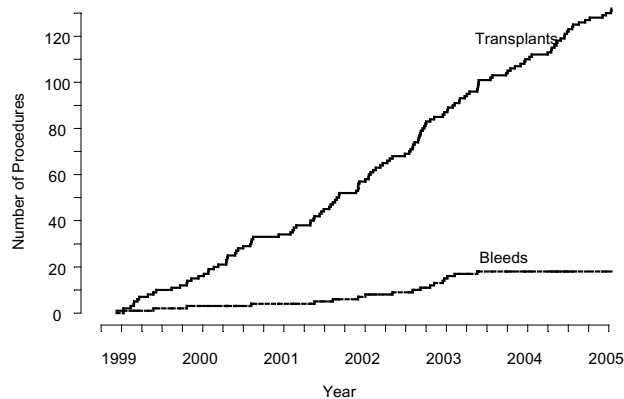
When these factors were entered into a multivariate model, the number of transplant procedures (second: OR 12.1, 95% CI: 2.9–50.4, $p < 0.001$; third: OR 52.3, 95% CI: 8.9–308.6, $p < 0.001$) and high dose heparin use (OR 23.9, 95% CI: 1.5–371.9, $p = 0.02$) were all recognized as independent risk factors for bleeding (Table 4).

Finally, due to statistical modeling constraints (0 events) it was not possible to fit a GEE model to estimate the effect of the Tisseel® and coils closure material compared with no closure technique. There were no bleeds in the most recent 26 consecutive cases where this combination was used, compared to 18 in 106 earlier cases (unadjusted Fisher's exact test $p = 0.02$) (Figure 1).

A total of 10 radiologists were initially involved with the islet program, performing between 1 and 27 procedures each (median 10, SD ± 8.3). Six of 18 bleeds occurred when the procedure was performed by inexperienced radiologists (≤ 5 islet procedures). A total of 40 of 114 non-bleed

Table 4: Multivariate GEE model

	Odds ratio	95% confidence interval	p-value
Number of transplant			
1st	1.0		–
2nd	12.1	2.9–50.4	<0.001
3rd	52.3	8.9–308.6	<0.001
Heparin			
Low <25 U/kg	1.0		–
Intermediate ≥25; <45 U/kg	2.8	0.2–36.0	0.42
High ≥ 45 U/kg	23.9	1.5–371.9	0.02

**Figure 1:** Cumulative risk of bleeding and number of transplant procedures per year.

procedures (35.1%) were done by inexperienced radiologists. The experience of the radiologist was not a risk factor for bleeding ($p = 0.89$).

Technical details of the procedure, amount of islets per kg infused or experience of the team expressed as year of the procedure were not identified as risk factors for bleeding. Patients who developed post-procedural bleeding did not experience detrimental outcomes in regard to islet function and rates of C-peptide secretion and insulin independence were not significantly different compared to those patients without bleeds. The beta score, an indicator for islet function, was 5.8 ± 1.1 for patients with bleeding after islet infusion vs 4.6 ± 1.9 for patients without bleeding (19).

We encountered five episodes of partial thrombosis of the portal vein for an overall rate of 3.8%. In these patients, the peak portal pressure was 21.8 ± 7.7 mmHg and the islet packed tissue volume was 6.3 ± 1.2 mL. In contrast, in patients with no thrombosis peak portal pressure was 14.6 ± 5.2 and the pack tissue volume consisted of 4.3 ± 1.7 mL.

Patients with evidence of bleeding were managed as follows: Nine received blood transfusions (mean 3.4 units; SD ± 1.74) and 2 of these had additional erythropoietin and

4 received iron therapy. Three patients underwent surgical exploration with laparotomy in one and laparoscopic treatment in 2 patients. In the surgical cases, bleeding was only identified from the dilated catheter tract, and not from any of the Chiba-needle puncture sites.

Discussion

If ongoing expansion of islet transplantation is to be justified, it is imperative that the procedure-related safety is optimized. While percutaneous access to the portal vein for islet transplantation is relatively safe, potentially life-threatening complications can occur and have indeed been reported (14–16).

Intraperitoneal bleeding from the liver is a concerning complication in patients with longstanding type 1 diabetes because: (a) up to 43% of asymptomatic islet-alone recipients have significant coronary arterial stenosis (19) and could be at increased risk of myocardial ischemia, infarction or arrhythmia during hypovolemic shock and (b) autonomic neuropathy is often associated with impaired compensatory mechanisms during hypovolemia. These patients therefore may not manifest early clinical signs of impending shock, further delaying diagnosis and increasing risk. Indeed, one of our patients requiring immediate surgical intervention with laparoscopy demonstrated no tachycardia but had 1.5 L hemoperitoneum and a 46% drop in hemoglobin compared with baseline.

We herein report our experience with risk and avoidance of acute hemorrhagic complications following percutaneous islet transplantation in 132 procedures performed between 1999 and 2005. Over a 74 month period, we encountered 18 potentially life-threatening or serious bleeds, for an overall rate of 13.6% of all procedures. We encountered an unexpectedly high rate of procedural bleeds in the year 2003 (7 of 22 procedures, 31.8%) which prompted us to analyze our data and implement immediate further measures to avoid this complication. Over this time, we have modified our techniques in an attempt to lower the risk of bleeding. Univariate and multivariate analysis have been used to define clinical impact of the factors associated with risk of bleeding. In the univariate analysis (UVA), the number of transplant procedures per recipient, lower platelets counts, use of aspirin pre-transplant, high dose heparin and elevated portal pressure were all associated with increased risk. After multivariate analysis (MVA), only the number of transplant procedures and use of high dose of heparin were statistically significant. The cumulative number of islet transplant procedures was associated with an odds ratio of 9.5 UVA (12.1, MVA) increased risk for second transplants and 20.9 times UVA (52.3, MVA) risk for patients undergoing third islet infusions.

The relative risk of an acute bleed or portal vein thrombosis after repeated islet infusions must be carefully balanced by

the benefit sustained by further improvement in glycemic control. Avoidance of bleeding or portal thrombosis is critical to the safety of the islet transplant procedure, but measures used for prophylaxis against thrombosis may potentially exacerbate risk of bleeding. In our experience thus far, the risk of acute bleeding far exceeds the risk of partial portal thrombosis by a factor of almost 3.5:1. In contrast to complete thrombosis of the main portal vein (which we have not encountered to date), partial thrombosis of main or segmental branches likely does not carry risk of portal hypertension or death, provided anticoagulation is given to prevent propagation of thrombus.

While the MVA highlighted repeated islet infusions as a risk factor for bleeding, it should be noted that this occurred in a relatively small experience (4 of 11 third transplant procedures).

A high heparin dose (~70 U/kg) was identified as an independent risk factor for bleeding (MVA OR 23.5, $p = 0.02$). If the risk of bleeding can be completely prevented by effective plugging of the catheter tract, we would advocate an upper packed tissue volume of 7mL for purified islet infusions, together with 70 U/kg intraportal heparin. Indeed, the Minnesota center recently reported no episodes of bleeding after percutaneous intraportal access using up to 70 U/kg heparin combined with Gelfoam®-coil sandwich technique for complete sealing of the entire catheter tract in 15 patients (4,20).

Increased portal vein pressure was identified as a further potential risk factor for bleeding which may partly explain the increased risk of bleeding with cumulative procedures (21). Additionally, increased portal pressure is a recognized risk factor for partial portal vein thrombosis after islet infusion. The portal vein thrombosis occurred within 2 days after the transplantation on four occasions and 7 days after the procedure in one case. In three patients, the thrombosis recanalized completely with an anticoagulation treatment after 3–6 months, in one partial recanalization within 3 months and one case of left main portal branch thrombus failed to recanalize after 14 months of follow-up developing an atrophy of the left lateral segments. Our current recommendation is to administer therapeutic heparinization (70 U/kg intraportal) followed by a continuous heparin infusion of 300–500 U/hour in patients that exceed a peak portal pressure of 21 mmHg, provided the catheter tract has been sealed effectively with coils/Tisseel® or similar alternative technique that addresses the entire length of the intraparenchymal tract.

We have not shown an effect of platelet count as an independent risk factor for bleeding. In the setting of second and third transplant, the platelet count is often lower as a side effect of immunosuppression. However, none of our patients experienced a critically low platelet count (<100 000 per mm^3).

Aspirin in the pretransplant setting was identified as a risk factor but was not confirmed in the MVA as independent. We believe that omission of aspirin while the patient is on the top of the transplant list may not be required when the catheter track is completely obliterated.

There was no procedure-related mortality, but three patients required operative intervention to control hemorrhage (laparoscopic drainage of hematoma and local cautery to the liver surface catheter puncture site in 2 cases, and segmental liver resection as reported previously in 1 case (2)).

It can be debated whether it is safe and appropriate to manage an acute hemorrhagic complication in an islet recipient by laparoscopic means rather than by open laparotomy. The former approach is generally contraindicated in hemodynamically unstable patients with blunt or penetrating trauma to the abdomen in the presence of hemoperitoneum. However, in the setting of percutaneous islet transplantation, where the site of injury is defined and typically localized to the right anterior aspect of the liver, we have found that rapid laparoscopic assessment, hemostatic cautery of the catheter puncture site and extensive peritoneal lavage can be carried out safely and effectively in our limited experience of two cases. Furthermore, use of a cell-saver can be helpful in avoiding need for transfusion of donated blood products.

The use of thrombostatic agents for sealing the intraparenchymal tract after cannulation of the hepatic portal vein is not a new concept. It was first described both in ablation of the portal access route in portal embolization of liver tumors and to seal the intraparenchymal tract during transjugular intrahepatic portal access (TIPS) in early trials of hepatocyte transplantation (22–24). The Miami group recently reported the effective use of D-STAT, a collagen-thrombin paste, in prevention of bleeding after percutaneous intraportal islet transplantation in five cases (25). No coils but Gelfoam® plugs were used to prevent central embolization and portal thrombosis was not encountered. Comparing our results with other centers (Table 5), we have a high incidence of bleeding events (13.6%) while others have between 0 and 6.5%.

The recent modification of complete sealing of the catheter tract with coils and Tisseel® in our case, with Gelfoam® and D-Stat (University of Miami) (25) or with complete packing of the catheter tract with a series of coils and Gelfoam® sandwich (University of Minnesota) (4,20) have all been shown to be effective in avoiding risk of procedural bleeding. Our current univariate and multivariate analyses define the risk of intraperitoneal bleeding when ineffective methods were used to partially plug the catheter tract (no track treatment as was our early practice at the inception of our program in 1999, Gelfoam® pledgets or use of a Nd:YAG laser).

Table 5: Comparison with other centers

Center	Ref	Year	Percutan. procedures	Bleed	Blood transfusion	Surgery or angiography	Hematoma	PV thrombosis
Geneva	(26)	1992–03	62	4 (6.5%)	4	3	3 (4.8%)	2 (3.2%)
Giessen	(17)	1994–98	44	0	0	0	1 (2.3%)	
Houston	(27)	2002–03	25	0	0	0	0	0
Miami	(25)		66	4 (6.1%)	2			
Milan	(28)	1989–02	58	2 (3.5%)	1			1 (1.7%)
Minnesota	(20)	2001–03	8	0	0	0	0	0
NIH	(15)	2000–01	10	1 (10%)	1			1 (10%)
Edmonton		1999–04	132	18 (13.6%)	9	3	2 (1.5%)	5 (3.8%)

Effective track management with mechanical sealing of the entire length of the intraparenchymal liver tract and surface using two coils and tissue fibrin glue completely prevented bleeding, and we have not encountered a single bleed in 26 consecutive procedures after implementation of this combined approach. We surmise that provided the catheter tract is completely sealed with the above or similar approaches that the risk of bleeding associated with more aggressive heparinization, use of aspirin or with repeated islet infusions may not be associated with increased risk of bleeding, but ongoing experience is needed to confirm this.

There are several limitations to the current analyses. First, this was a retrospective review of the data from a single islet transplantation program where modifications in catheter sealant techniques and anticoagulation approaches have evolved over time. A prospective assessment of risk factors for bleeding would be helpful. The analyses are limited by a low event rate which precluded appropriate statistical modeling in some cases. Finally, the majority of the models yielded odds ratios with very wide confidence intervals. All these factors lead to the suggestion that the results should be interpreted with caution.

In conclusion, we believe that acute bleeding is a potentially dangerous complication following percutaneous transhepatic islet infusion. Furthermore, we regard this as an entirely preventable complication, provided that effective methods are used to completely ablate the hepatic intraparenchymal portal access tract.

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