The American Journal of Surgery xxx (2017) 1–7

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

The impact of allogenic blood transfusion on the outcomes of total pancreatectomy with islet autotransplantation

Gumpei Yoshimatsu [a, 1], Rauf Shahbazov [b, 1], Giovanna Saracino [c], Michael C. Lawrence [a], Peter T. Kim [c], Nicholas Onaca [c], Ernest E. Beecherl [c], Bashoo Naziruddin [c, *], Marlon F. Levy [d]

[a] Islet Cell Laboratory, Baylor Research Institute, 3310 Live Oak Street, Dallas, TX 75204, USA
[b] Department of Surgery, University of Virginia, 1215 Lee Street, Charlottesville, VA 22909, USA
[c] Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, 3410 Worth Street, Suite 950, Dallas, TX 75246, USA
[d] Transplant Division, Department of Surgery, Virginia Commonwealth University Medical Center, 1200 East Marshall Street, Richmond, VA 23298, USA

ARTICLE INFO

Article history:
Received 13 January 2017
Received in revised form
10 March 2017
Accepted 12 March 2017

Keywords:
Total pancreatectomy with islet autotransplantation
Allogenic blood transfusion
Cytokines
Transfusion-related immunomodulation

ABSTRACT

Background: Allogenic blood transfusion (ABT) may be needed for severe bleeding during total pancreatectomy with autotransplantation (TPIAT), but may induce inflammation. This study investigated the impact of ABT.
Methods: With a population of 83 patients who underwent TPIAT from 2006 to 2014, this study compared cytokine levels, patient characteristics, islet characteristics, metabolic outcomes, insulin requirements, and hemoglobin A1c for those who received a blood transfusion (BT) versus no blood transfusion (NBT).
Results: Initially, proinflammatory cytokines were moderately higher in the BT group than the NBT group. Despite longer procedures and more severe bleeding, the BT group had similar values to the NBT group for insulin requirements, serum C-peptide, hemoglobin A1c, and insulin independence rate. The probability of insulin independence was slightly higher in patients receiving $\geq$3 units of blood.
Conclusion: ABT induced elevation of proinflammatory cytokines during the perioperative period in TPIAT, but these changes did not significantly change posttransplant islet function.
Summary for table of contents: When cytokine levels and transplant outcomes from patients receiving blood transfusions were compared with those receiving no blood transfusions during total pancreatectomy with autotransplantation, results showed that the group with blood transfusions had elevation of proinflammatory cytokines during the perioperative period. However, these moderate changes did not significantly change posttransplant islet function, and a higher volume of blood transfusion may improve posttransplant insulin independence.

1. Introduction

Chronic pancreatitis (CP) is characterized by a persistent destruction of the pancreatic parenchyma replaced by fibrosis due to continuous or recurrent inflammation. When CP patients suffer from debilitating pain, medical treatments for pain control based on the analgesic ladder are required, and other options such as nerve blockage, endoscopic intervention, or surgical procedures are sought.[1–3] Surgical treatments are typically performed for patients facing intractable pain despite the use of less-invasive treatments.[4] Although, total pancreatectomy results in removing the root cause of pancreatic pain, the endocrine function of the pancreas is lost in the process, leading to surgically induced type 3c diabetes. Autologous islet transplantation can preserve the islet function of patients who undergo total pancreatectomy. Over the past decades, total pancreatectomy with islet autotransplantation (TPIAT) has

* Corresponding author. Islet Cell Laboratory, Baylor Simmons Transplant Institute, 3410 Worth Street, Suite 950, Dallas, TX 75246, USA.
E-mail addresses: Gumpei.Yoshimatsu@BSWHealth.org (G. Yoshimatsu), rs2vj@virginia.edu (R. Shahbazov), Giovanna.Saracino@BSWHealth.org (G. Saracino), Michael.Lawrence@BSWHealth.org (M.C. Lawrence), Peter.Kim@BSWHealth.org (P.T. Kim), Nicholas.Onaca@BSWHealth.org (N. Onaca), Ernest.Beecherl@BSWHealth.org (E.E. Beecherl), Bashoo.Naziruddin@BSWHealth.org (B. Naziruddin), marlon.levy@vcuhealth.org (M.F. Levy).
[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.amjsurg.2017.03.007
0002-9610/

been increasingly performed, with reports of more effective pain control and prevention of brittle diabetes mellitus.[5,6] However, the severe inflammation of the pancreas makes the surgical procedure difficult. When bleeding is increased during surgical procedures such as periportal vein dissection, allogenic blood transfusion (ABT) is required to maintain the patient's condition.

ABT has been linked to inflammation and effects on the immune system, but the mechanism for these effects has not been clarified. The down-regulation of immune response due to ABT was reported as transfusion-related immunomodulation (TRIM). Clinical evidence for TRIM was first reported by Opelz in 1973, where recipients of renal transplants with ABT had improved renal allograft survival.[7] Moreover, the recurrence rate of oncological diseases was reported to increase due to TRIM.[8,9] On the other hand, ABT leads to inflammation. Soluble factors released during ABT may be pyrogenic, including cytokines released during storage, particularly at room temperature.[10,11] In fact, it was reported that interleukin (IL)-6 and IL-8 were elevated in patients after blood transfusions.[12] It is also known that ABT can cause transfusion-related acute lung injury (TRALI), which is explained by passively transferred donor human leukocyte antigen antibodies or biologically active substances such as lysophosphatidylcholine in the blood transfusion packs.[13–15] In our series, leukoreduced red blood cell concentrates were used to avoid the contamination of immune cells and cytokines.

In TPIAT, the ABT-induced inflammation may negatively impact the islet graft, whileTRIM may improve the endocrine outcome of the transplantation (Fig. 1). One of the major hurdles for the engraftment of islets after intraportal infusion is the occurrence of an instant blood-mediated inflammatory reaction (IBMIR).[16,17] We recently demonstrated IBMIR-mediated autologous islet loss under in vitro and in vivo conditions.[16,17] The aim of this study was to determine the impact of ABT on the inflammation and the endocrine outcome of TPIAT.

2. Materials and methods

2.1. Patient selection

A query of the patient database of the Baylor Simmons Transplant Institute identified 83 patients undergoing TPIAT from October 2006 to January 2014. These CP patients were evaluated by a multidisciplinary team that included a gastroenterologist, endocrinologist, and transplant surgeon. The diagnosis of CP was based on the patient's history, laboratory results, endoscopic imaging, radiological imaging, and pathologic diagnosis. The indications of TPIAT were intractable pain despite previous medical and surgical interventions. This study was approved by the Baylor University Medical Center Institutional Review Board (ID: 008-311).

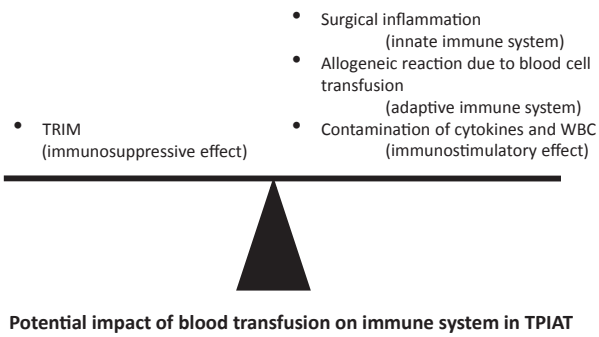

Fig. 1. *Potential impact of allogeneic blood transfusion on the immune system in the context of total pancreatectomy with autotransplantation (TPIAT).* TRIM indicates transfusion-related immunomodulation; WBC, white blood cells.

2.2. Operative procedure, procurement, isolation, and islet infusion

Total pancreatectomy was performed with splenectomy and duodenectomy. The blood supply from the gastroduodenal and splenic artery into the pancreas was sustained as long as possible to protect islets from ischemia. Viable islets were isolated as previously described.[16] Briefly, the excised pancreas was trimmed to remove excess fat, the duodenum, and the spleen. A cannula was inserted into the main pancreatic duct, and the pancreas was placed in a container filled with cold storage preservation solution. Islets were then isolated using a modified Ricordi method in a good manufacturing practice facility. Collagenase enzyme in combination with either neutral protease or thermolysin was perfused into the main pancreatic duct, and the pancreas was digested. If the digested pancreatic tissue volume was in excess, islets were purified from the acinar cells using a continuous gradient of iodixanol-based solution with a COBE2991 processor. Following assessment of quality, isolated islets were infused into the portal vein via the superior mesenteric vein while the patient was under general anesthesia.

2.3. Postoperative care and assessment of clinical outcome

All patients were monitored in the intensive care unit after surgery with strict blood glucose control. The patients were then transitioned to a basal bolus insulin regimen starting on postoperative day 3. All patients were discharged with an individual insulin regimen.

Adverse events were recorded retrospectively and graded using the Common Terminology Criteria for Adverse Events (https://ctep.cancer.gov; ver4.0). Portal vein flows were monitored by Doppler echogram before and after surgery, with a lack of detection of portal vein flow indicating portal vein thrombosis. Narcotic requirements were reported as morphine-equivalent quantity per day. The average daily insulin requirement, along with hemoglobin A1c and C-peptide levels, was measured before surgery, on hospital discharge, and at each subsequent postoperative patient encounter. Postoperative C-peptide levels were measured after fasting at 3 months, 6 months, and 1 year. Patients with detectable C-peptide values (>0.3 ng/mL) were considered to be C-peptide positive.

2.4. Cytokine measurement

Serum samples were obtained at admission and at 1 h, 3 h, 6 h, 24 h, 3 days, 5 days, and 7 days after islet infusion.[16] Serum samples were stored at −80 °C until assayed. The serum levels of IL-6, IL-8, IL-10, interferon gamma-induced protein 10 (IP-10; also known as C-X-C motif chemokine ligand 10, or CXCL10), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor alpha (TNFα) were measured with a Luminex®200 system (Millipore, Billerica, MA, USA) using xMAP technology (Luminex, Austin, TX, USA). The bead assay was performed according to the manufacturer's instructions with sample duplications.

2.5. Statistical analysis

The Wilcoxon two-sample test was used to compare continuous variables (expressed as medians with interquartile ranges [IQR]), and the two-sided Fisher's exact test was used to compare categorical variables (expressed as counts with percentages). A *P* value of ≤0.05 was considered statistically significant. Each clinical outcome measured over time was analyzed using linear mixed

Please cite this article in press as: Yoshimatsu G, et al., The impact of allogenic blood transfusion on the outcomes of total pancreatectomy with islet autotransplantation, The American Journal of Surgery (2017), http://dx.doi.org/10.1016/j.amjsurg.2017.03.007