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Clinical Science

Effects of preoperative long-term glycemic control on operative outcomes following pancreaticoduodenectomy

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Abstract

BACKGROUND: Diabetes mellitus is postulated to be both a risk factor and manifestation of pancreatic adenocarcinoma. This study evaluated the effects of preoperative glycemic control as determined by hemoglobin A1c (HbA1c) on outcomes following pancreaticoduodenectomy (PD).

METHODS: A prospective cohort study whereby HbA1c was assessed preoperatively in 243 patients undergoing PD was performed. The primary outcome measure was operative morbidity. Secondary outcomes included individual adverse events, time to dietary resumption, and length of stay.

RESULTS: Preoperative HbA1c ranged from 4.0% to 13.5%. Overall morbidity and incidence of specific adverse events were similar regardless of preoperative HbA1c. No correlation between HbA1c and length of stay, dietary resumption, or readmission was observed. Pancreatic fistula formation had a decreased incidence in patients with elevated versus normal HbA1c (2.2% vs 9.6%, $P = .083$).

CONCLUSIONS: PD can be safely performed in patients with HbA1c levels suggestive of poor long-term preoperative glycemic control. Medical efforts to optimize HbA1c should not delay resection.

Diabetes mellitus (DM) has a prevalence in excess of 8.3% in the general US adult population and is an independent risk factor for complications after surgery, including increased morbidity, longer lengths of stay, and elevated mortality.[1–3] Similarly, perioperative and intraoperative hyperglycemia, with or without a clinical diagnosis of DM, has also been correlated with poor outcomes following a myriad of surgical procedures, including cardiac, vascular, orthopedic, and general surgical operations.[4–8] These include increased rates of infectious, cardiac, and renal complications, and are typically attributed to the known deficits in immune function, stress hormone metabolism, and vascular homeostasis that occur with derangements in glycemic control and insulin secretion.[1]

A well-known correlation exists between DM and pancreatic ductal adenocarcinoma (PDAC), with prevalence of DM or impaired glucose tolerance reaching up to 60% in patients with PDAC.[9,10] The relationship between DM and PDAC, and whether there are causal implications in either direction, is still being explored; however, a clear temporal correlation exists as patients with newly diagnosed DM (<4 years) have a 50% higher risk of harboring PDAC.[11] Despite this, the impact of DM or perioperative hyperglycemia on surgical outcomes following major pancreatic resection, such as pancreaticoduodenectomy (PD), remains controversial. Only a small number of studies have been performed addressing the topic and conflicting results

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have been reported, as some authors have found no increase in morbidity in DM patients following PD,[12,13] while others describe a correlation between increased morbidity and postoperative hyperglycemia.[14] This is especially notable considering that several known sequelae of aberrant glycemic control, such as gastroparesis and impaired wound healing, would seem to directly impact common PD-specific causes of morbidity like delayed gastric emptying (DGE) and postoperative pancreatic fistula (POPF) formation, respectively. However, even in studies examining these specific adverse events following PD, different groups have come to opposite conclusions regarding the role of DM as a risk factor for DGE[15,16] or POPF formation.[12,17] Accordingly, the importance of glycemic control in the perioperative setting remains unclear in patients in whom PD is planned.

Measurement of glycosylated hemoglobin, or hemoglobin A1c (HbA1c), has been conclusively shown to correlate reliably with serum glucose concentration and is the most common method of assessing long-term glycemic control.[18] Since the standardization of the HbA1c assay across most laboratories,[19] measurement of HbA1c has been shown to be a valuable adjunct to DM management, where serial evaluation improves outcomes in DM patients.[20] Furthermore, HbA1c is effective as a screening tool for de novo diagnosis of DM,[21] with a cutoff HbA1c greater than or equal to 6.5% (48 mmol/mol) considered diagnostic of DM by the American Diabetes Association and World Health Organization.[22] Given the efficacy of HbA1c measurement in evaluating glycemic control and screening for DM, and the known deleterious effect of DM and perioperative hyperglycemia on certain operative outcomes, several studies have examined the impact of HbA1c level and surgical morbidity/mortality. Elevated preoperative HbA1c was found to have a negative effect on both specific outcomes and general postoperative morbidity in a variety of surgical disciplines[23–27]; however, other authors have found no correlation between HbA1c and outcomes.[28,29] The effects of HbA1c level on patient outcomes following pancreatic resection have not yet been rigorously investigated.

Operative mortality has greatly improved in PD over the past several decades, especially in high-volume centers[30]; however, morbidity remains stubbornly frequent, with major complications occurring in up to 30% of cases.[31,32] Accordingly, strategies to minimize risk of operative complications following PD are currently an area of particular interest to pancreatic surgeons. Given the hypothetical impact many known sequelae of hyperglycemia may have on patients undergoing pancreatic resections and the conflicting reports currently addressing this topic, further investigation seems merited. HbA1c is already widely utilized to evaluate glycemic control in recognized diabetics. Additionally, HbA1c appears to be an ideal metric to gauge the impact of hyperglycemia on patients undergoing PD as emphasis of HbA1c on long-term glycemic control could mitigate the uncertain impact of new onset or undiagnosed DM on outcome data. As such, this prospective study was designed with the primary aim of evaluating whether preoperative serum HbA1c concentration among patients undergoing PD was correlated with either general postoperative morbidity or specific PD-related complications of interest. Any associations revealed would then be further assessed in detail. Furthermore, a secondary aim was to assess whether increased preoperative HbA1c was indicative of postoperative hyperglycemia and increased insulin requirements to achieve glycemic goals.

Patients and Methods

Patient selection

A prospectively constructed database of 243 consecutive patients who underwent PD at Yale–New Haven Hospital from September 2006 to December 2012 by a single surgeon (R.R.S.) was analyzed for study purposes. Patients were included for study regardless of indication for PD. Exclusion criteria included patients with prior pancreatic resection, without preoperative HbA1c measurement, or with less than 3 properly recorded postoperative serum glucose measurements. Among patients meeting inclusion criteria, data on preoperative past medical history, American Society of Anesthesiologist score, and body mass index were obtained.

Defining diabetes mellitus and assessment of glycemic control

Presence of absence of DM for study purposes was based on the diagnosis of DM by each participant's primary medical practitioner before preoperative surgical evaluation. While nearly all patients with DM were receiving pharmacologic therapy for glycemic control, those with a clinical DM diagnosis who were diet controlled were still considered to have DM. HbA1c was determined during preoperative surgical workup; however, patients without a clinical DM diagnosis found to have HbA1c greater than or equal to 6.5 were not assigned a de novo diagnosis of DM for study purposes and counted as non-DM patients. All HbA1c assays were performed in the clinical laboratory at Yale–New Haven Hospital within 2 weeks before surgery. Postoperatively, all patients were initially placed on an intermittent sliding scale regimen of regular insulin according to institutionally defined goals for glycemic control. Capillary glucose monitoring was instituted at 6-hour intervals for sliding scale dosing if required. In patients with 2 consecutive capillary glucose measurements greater than 180 mg/dL, an insulin infusion was instituted; such patients had their capillary glucose monitored at 1-hour intervals for infusion dosing adjustment according to an institutional protocol. All serum capillary glucose measurements and need for initiation of an insulin infusion initiation were recorded for 48 hours postoperatively. To