Curr Diab Rep (2016) 16: 32
DOI 10.1007/s11892-016-0722-x

Perioperative Glycemic Control During Colorectal Surgery

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Published online: 29 February 2016

Abstract Hyperglycemia occurs frequently among patients undergoing colorectal surgery and is associated with increased risk of poor clinical outcomes, especially related to surgical site infections. Treating hyperglycemia has become a target of many enhanced recovery after surgery programs developed for colorectal procedures. There are several unique considerations for patients undergoing colorectal surgery including bowel preparations and alterations in oral intake. Focused protocols for those with diabetes and those at risk of hyperglycemia are needed in order to address the specific needs of those undergoing colorectal procedures.

Keywords Hyperglycemia · Perioperative · Colorectal surgery · Surgical site infections

Introduction

More than 600,000 colorectal surgeries are performed annually in the USA [1]. Compared to other surgical types, the rates of surgical site infection (SSI) for colorectal surgery are consistently higher, with reported rates ranging from 5 to 30 % [2]. Across the country, SSIs are the second leading healthcare-acquired infection—a close second to hospital-acquired pneumonia [3]. SSIs are associated with increased costs, increased length of stay, increased mortality, and decreased quality of life [2]. Both diabetes and perioperative hyperglycemia are well-known risk factors for SSI. Thus, efforts to decrease the risk of SSI for colorectal surgery often focus on improving perioperative glycemic control.

This article is part of the Topical Collection on *Hospital Management of Diabetes*

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Incidence of Hyperglycemia in Colorectal Surgery

Perioperative hyperglycemia is common, occurring in 30 to 40 % of all surgical patients [4, 5•, 6]. Evidence shows that as many as two thirds of patients with diabetes develop perioperative hyperglycemia [5•, 6]. Reported rates of perioperative hyperglycemia among patients without diabetes are highly variable, ranging from as low as 13 % to as high as 67 % [5•, 6, 7]. The definition of hyperglycemia, however, varies considerably in these studies in terms of the glucose level considered too high, and equally importantly studies vary in the timing, method, and frequency of blood glucose testing, which may contribute to the observed variation in hyperglycemia rates.

Among a cohort of over 5000 patients specifically undergoing colorectal procedures, observed rates of postoperative hyperglycemia mirrored the larger population studies. Glucose levels exceeded 180 mg/dL in 68 % patients of with diabetes and 14 % of patients without diabetes [8]. Thus, 43 % of patients exhibiting perioperative hyperglycemia did not have a known diagnosis of diabetes (Fig. 1).

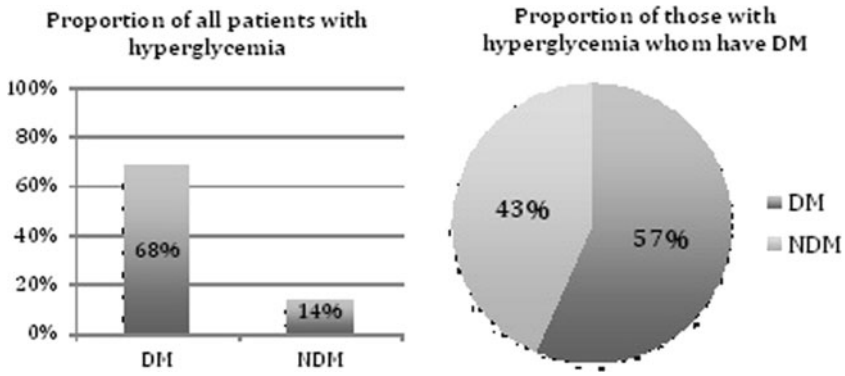

Fig. 1 Colorectal surgery patients with postoperative glucose level ≥180 mg/dL. *DM* patients with diabetes, *NDM* patients without diabetes. (Adapted from [8])

Impact of Hyperglycemia in Colorectal Surgery

Perioperative hyperglycemia is consistently associated with increased rates of complications [4, 5•, 6, 9–20]. These include increased rates of infection, need for reoperation, prolonged length of stay, and increased mortality. Of these complications, among colorectal surgery patients, significant focus has been on infection given the higher prevalence relative to other procedures. Among patients undergoing colorectal surgery, having a postoperative glucose greater than 140 mg/dL was associated with three times greater rate of surgical site infection compared to those with postoperative glucoses less than 140 mg/dL [9]. Simply having diabetes is associated with increased risk for SSI in colorectal surgery, even after adjusting for potential confounding variables [21]. Additionally, among patients with diabetes, postoperative hyperglycemia with 48-h average mean glucose over 200 mg/dL were found to have 3.6-fold the risk of surgical site infection compared to those with mean glucose under 200 mg/dL in a multivariate analysis [14].

Glycemic Control in Enhanced Recovery Programs

The concept of enhanced surgical recovery was first advanced among colorectal surgeries in the early 2000s, out of which was formed the enhanced recovery after surgery (ERAS) program. ERAS promotes implementing a bundle of care interventions targeted at improving time to recovery following surgery. Recognizing the association of hyperglycemia with poor outcomes, many ERAS programs include glycemic control interventions. A recent meta-analysis demonstrated a risk reduction in SSI from 15 to 7 % when implementing bundled care programs [22]. Of the 13 studies included in this analysis, eight included an intervention targeting glycemic control.

Special Considerations

There are specific considerations in preparation for colorectal surgery that have significant potential to affect glycemic control and thus influence outcomes. First, there is a unique need for bowel preparation, altering oral intake for days prior to the procedure. Second, there have been advances in colorectal surgery around perioperative oral intake, including preoperative carbohydrate loading and perioperative immunonutrition supplementation.

Glycemic Control and Bowel Preparation

Historically, bowel preparation has been a mainstay of risk reduction for colorectal surgery, with the goal of reducing bacterial load and thus decreasing risk for infection. While more recent evidence has challenged the necessity of bowel preparation, it remains a common preoperative preparatory step in many institutions [23]. Modified oral mechanical bowel preparations have been incorporated into some ERAS programs [22]. Oral mechanical bowel preparation includes ingestion of an oral preparation designed to clear the intestine of fecal material. Patients taking this preparation are often also instructed to ingest only clear liquids during preparation. This combination of electrolyte ingestion and altered oral intake will significantly alter glycemic homeostasis.

Nonetheless, there is limited data on achieving glycemic control in patients undergoing bowel preparation for procedures and surgeries. Routinely, patients with diabetes are instructed to ask primary care providers how to adjust medications while remaining on clear liquids and undergoing bowel preparation. There have been a few small evaluations of bowel preparation for colonoscopy that could help inform glycemic control issues during bowel preparation for colorectal surgeries. While some studies have evaluated tolerance to and adequacy of certain bowel preparations among patients with diabetes, to our knowledge, none have evaluated the impact of the preparation on glycemic control itself [24, 25].

To our knowledge, the first detailed report of glycemic control in the setting of bowel preparation is a recent abstract regarding standardization of diabetes medication management prior to colonoscopy. In this study, patients attended a group education class (Prep Clinic), during which an endoscopy nurse reviewed indications for colonoscopy, procedural risks and benefits, and

instructions on bowel cleansing preparation. In addition, instructions were developed for endoscopy nurses to educate patients with diabetes during the Prep Clinic. These instructions included checking blood sugars three times on the day before the procedure, avoiding clear liquids containing sugar, and written instructions regarding dosing of basal and meal-time insulin, Humulin 70/30, metformin, and sulfonylurea medications. Specifically, patients taking basal insulin were instructed to reduce the dose by 2/3 on the day prior to procedure and to stop taking any meal-time insulin the day before and on the day of colonoscopy. Patients taking metformin were instructed to continue taking that medication on the day prior to and the day of colonoscopy. Patients taking sulfonylurea medications were instructed to stop these medications the day prior to and the day of the procedure. Patients on Humulin 70/30 were instructed to take one-half dose on the day prior to procedure. From December 2014 through May 2015, the investigators evaluated capillary blood glucose values in all patients with diabetes upon arrival on the day of their colonoscopy. Among patients with diabetes who required outpatient oral and insulin or insulin therapy, the blood sugar was significantly lower for patients who attended the Prep Clinic compared to the patients who did not attend Prep clinic (141 vs. 174 mg/dL, $p = 0.03$). As patient participation in Prep Clinic was mostly correlated to the referring clinic rather than to any patient factor, the investigators concluded that standardization of outpatient medication recommendations prior to colonoscopy may improve peri-procedural glycemic control in patients with diabetes mellitus requiring oral and insulin and insulin therapy. (E Rosenblatt, A Korson, T Dejneka, B Griffin, L Kenny, D Corl, EK Broussard, 2015, Impact of standardized management of diabetes medications prior to colonoscopy, American College of Gastroenterology, accepted abstract)

Carbohydrate Loading

Recent advances in perioperative care for colorectal surgery have identified prolonged fasting periods as potentially detrimental in recovery. As a result, some new guidelines, including the ERAS program, are recommending carbohydrate loading 4–6 h prior to surgery. Prolonged pre-operative fasting can cause insulin resistance and hyperglycemia. The mechanism is thought to be related to progressively reduced insulin signaling in combination with increased counter-regulatory hormone signaling from glucagon, cortisol, and norepinephrine, all of which favor increased glycogenolysis and gluconeogenesis. These hormones also cause increased lipolysis of triglycerides in white adipose tissue which results in increased free fatty acid levels and releases the glycerol backbone of triglycerides. Free glycerol delivery to the liver causes increased hepatic gluconeogenesis, while fatty acids are either broken down to form ketones or resynthesized into triglycerides in hepatocytes depending on energy requirements. Peripherally increased FFA signaling and uptake can result in insulin resistance in skeletal muscle—which causes decreased glucose uptake, saving glucose for glucose-dependent tissues and switching muscle to the use of FFA and ketones. These findings have been documented in numerous studies including studies focused on ERAS. Preventing pre-operative insulin resistance due to fasting is frequently stated is one of the goals of the ERAS initiative and one of the motivations to feed patients 4 h prior to surgery and multiple studies have shown that pre-operative carbohydrate loading reduces insulin resistance relative to control patient who have been fasting [26]. However, this mechanism—and the ability of ERAS to prevent insulin resistance—has been evaluated principally in individuals who are lean and insulin sensitive at baseline. Importantly, the mechanism whereby carbohydrate feeding reduces insulin resistance may not be valid in patients who are obese and insulin resistant at baseline. In patients with hepatic steatosis and insulin resistance, short- to intermediate-term fasting may improve blood glucose values and may cause a decrease in insulin resistance—the exact opposite of what occurs in lean individuals. Data on this issue related to pre-operative glycemic control and the ERAS program is sparse. Most ERAS studies have entirely excluded patients with diabetes mellitus or excluded them from the pre-operative feeding part of the program or administered a very low carbohydrate drink [27, 28]. One study did evaluate administration of the ERAS supplement to patients with diabetes mellitus [29]. They found no evidence of decreased gastric emptying of the liquid and insignificant differences in plasma glucose levels 3 h after ingesting the liquid supplement. However, glucose values at 1 h peaked at 240 mg/dL with a significantly increased glucose area-under-curve relative to non-diabetic subjects. Important to interpreting the data from this study, it was performed in only 25 subjects with type 2 diabetes with a mean HgbA1c of 6.2 %—suggesting strongly that the findings might not readily be extrapolated to the average population of patients with type 2 diabetes with much higher HgbA1c levels.

This raises the concern that pre-operative feeding in patients with diabetes mellitus will cause (rather than prevent) significant hyperglycemia which may cause negative physiological changes on immune/inflammatory function, fluid and electrolyte balance and coagulation all of which can negatively impact post-surgical outcomes. Pre-operative hyperglycemia will also necessitate more intensive medical management intra- and post-operatively which may be associated with increased cost and rare, but significant, negative outcomes including hypoglycemia.

Glycemic Control and Preoperative Immunonutrition Supplementation

There has been increasing focus on perioperative immunonutrition supplementation among patients undergoing

gastrointestinal and colorectal surgeries. Immunonutrition supplements include L-arginine, fatty acids, and nucleotides that are considered important elements within the effective formulas. These elements are thought to strengthen the immune system in preparation for major surgery. Randomized controlled studies have demonstrated significant reductions in perioperative complications for patients receiving immunonutrition [30]. In a recent meta-analysis, immunonutrition compared to no nutrition or standard nutrition was associated with a 33 % decrease in complications and nearly a 50 % decrease in infectious complications [30]. The authors caution that these findings need to be taken in light of some studies demonstrating adverse effects of arginine and fatty acids in critical care populations. Moreover, data regarding the effect of these supplements on perioperative glycemic control has not been examined. Theoretically, some patients even without known diabetes will become hyperglycemic while taking such supplements, though the impact is likely to be much less significant than carbohydrate supplementation prior to surgery. It is our recommendation that standard glucose screening and monitoring be implemented if these supplements are to be incorporated in perioperative colorectal care.

Perioperative Glycemic Management

No specific guidelines for glycemic management exist for patients having colorectal surgery. However, given the greater risk for infections with this type of surgery, careful attention to improved glycemic control is warranted. General recommendations are outlined here and in Table 1. For patients on oral hypoglycemic agents, these should be discontinued and insulin started on admission. For patients on insulin at baseline, several considerations are required.

Preoperative Glycemic Management

In cases where patients must undergo bowel preparation in the 24 h prior to surgery, it is common to discontinue mealtime insulin and sulfonylureas for that day in addition to the morning of surgery and this option is reasonable for many patients with diabetes. However, in patients with clear beta cell dysfunction and an absolute meal-time insulin requirement this may cause significant hyperglycemia as clear liquid caloric options (juices, sports drinks) are high in simple carbohydrates. Therefore the medication regimen during bowel preparation needs to be individualized for some patients, including more frequent, lower dose rapid-acting analog insulin for some patients with diabetes. Patients taking metformin, should take their last dose the evening prior to the day of surgery, but can continue this during bowel preparation. Basal insulin should be reduced prior to bowel preparation and for the day of surgery. The specific reduction is highly patient dependent and can be customized given the right resources. In settings with fewer resources, taking only two thirds of the basal insulin is a reasonably safe recommendation, though for some patients this will lead to hyperglycemia. It is significantly less clear what to do for glycemic management with carbohydrate-loading drinks in patients with diabetes as this may cause post-prandial hyperglycemia that will not resolve prior to surgery. Most commonly, patient with diabetes are being excluded from pre-operative carbohydrate loading. If patients with diabetes are required to take a carbohydrate-

Table 1 Perioperative evaluation and management of hyperglycemia

	Evaluation	Glycemic goal	Management
Preoperative	•DM: record A1c for patients •NDM: consider checking FBG or A1c for those with DM risk factors	Insufficient evidence to determine need or level	•If time allows and glucose not well controlled, adjust home regimen
Day of bowel preparation (if indicated)	•DM: home monitoring of BG minimum of TID •NDM: no specific recommendations	Insufficient evidence to determine need or level	•Insulin: take 2/3rd usual basal dose; stop mealtime insulin •Metformin: continue •Sulfonylureas: stop
Day of surgery	•DM: check glucose level on presentation and every 30–60 min for procedures >1 h in length •NDM: check glucose on presentation at least among those with DM risk factors	100–180 mg/dL	•Insulin infusion preferred •Intravenous insulin if unable to do infusion •*Avoid* subcutaneous insulin
Postoperative	•DM: follow BG every 6 h or QAC and QHS once eating •NDM: at a minimum, all patients with elevated glucoses on the day of surgery should have glucoses monitored for 24–48 h postoperatively	100–180 mg/dL	•Insulin infusion or basal insulin alone for those not yet eating •Basal-bolus regimen once eating

DM patients with diabetes, *NDM* patients without diabetes, *BG* blood glucose, *QAC* prior to meals, *QHS* at bedtime

loading drink, it may be reasonable to administer low dose (2–4 units) rapid-acting analog insulin to prevent or blunt hyperglycemia, either at home or in the pre-admission area.

Insulin on the Day of Surgery

On the morning of surgery, glucose should be checked for all patients with diabetes or diabetes risk factors. Some institutions check glucose on all patients over the age of 40 regardless of diabetes history. In patients with diabetes or elevated glucose on the morning of surgery when surgery duration is greater than 1 h, glucoses should be checked periodically throughout the surgery at 30–60-min intervals depending on the trajectory of the glucose. Goal glucose should be 100–180 mg/dL. Insulin infusion is the treatment of choice for maintaining glucose control on the day of surgery as long as resources exist to support this level of care. In cases where infusions are not available, intravenous boluses of insulin are reasonable. Subcutaneous insulin administration in the operating room is less unreliable.

Postoperative Insulin Management

For patients on insulin infusion in the operating room, this should be continued postoperatively until the patient is ready to consume oral calories—at which point the regimen should be transitioned to subcutaneous insulin. For patients not on an insulin infusion, basal-bolus insulin should be ordered based either on the home insulin regimen or using weight-based calculations of a total daily dose (0.4–0. units/kg). The total daily dose should be split 50:50 into basal and mealtime insulin [31••]. There is evidence that basal plus correction without mealtime insulin is as good a strategy as basal-bolus. In this study, patients received a basal dose of 0.2 units/kg [32]. For patients who are not on an insulin infusion and not yet consuming calories orally, this basal only regimen is a reasonable place to start, but should be altered to include scheduled mealtime insulin when the patient begins eating meals.

Conclusions

Perioperative hyperglycemia is common and is associated with worsened outcomes for patients undergoing colorectal surgery. There are several specific considerations for colorectal surgery. Firstly, when implementing bowel preparation, standardization of diabetes medication management should be implemented, though specific protocols need to be developed and tested. Secondly, while insulin sensitivity is improved with preoperative oral carbohydrate ingestion for those with normal physiology, for those patients at risk of developing hyperglycemia, this increasingly common practice may worsen pre- and post-operative glycemic control. Thirdly, while initial reports of perioperative immunonutrition supplements suggested beneficial effects for all, data is lacking for those patients who are more likely to develop hyperglycemia. As enhanced recovery programs are increasingly an essential component of mainstreaming colorectal perioperative care, specific pathways will be needed for those with diabetes mellitus and those at risk for perioperative hyperglycemia.

Compliance with Ethical Standards

Conflict of Interest Rachel E. Thompson, Elizabeth K. Broussard, and David R. Flum declare that they have no conflict of interest. Brent E. Wisse is a consultant for Transformative Medicine.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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