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The benefits of a low dose complex carbohydrate/citrulline electrolyte solution for preoperative carbohydrate loading: Focus on glycemic variability

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ABSTRACT

Background: Perioperative insulin resistance is associated with significant hyperglycemia-related morbidity in patients undergoing major surgery. We sought to assess the effect of preoperative loading with a low-dose maltodextrin/citrulline solution compared to a commercially available sports drink on glycemic levels in an established colorectal enhanced recovery program.
Methods: Retrospective analysis was undertaken of elective non-diabetic colectomies and enterectomies from January 2016–March 2017. Cohorts included simple (SIM) and complex carbohydrate (COM) groups. Statistical analysis was performed with linear and logarithmic regression.
Results: 83 patients were included (42 SIM, 41 COM). SIM group was older (61.7 vs 52.7 $p = 0.012$) Glycemic variability was less in the COM group (7.6% vs 21.4% $P = 0.034$). The frequency of hyperglycemia, postoperative complications, and length of stay trended higher in the SIM group.
Conclusions: This retrospective analysis identifies significant improvement in the perioperative glycemic variability with preoperative low dose complex carbohydrate loading compared to simple carbohydrate loading in colorectal surgery patients.

1. Introduction/background

In recent years, the classic dictum of "nil per os" status prior to major gastrointestinal surgery has been challenged. Despite current American Society of Anesthesiology guideline permitting intake of solids 6 h and clear liquids 2 h before surgery, the practice of preoperative oral intake has lagged behind.[1] The catabolic state that occurs as a result of fasting and physiologic insult of surgery results in a surge of catecholamines and inflammatory cytokines.[2–5] Enhanced circulation of inflammatory mediators results in insulin resistance, increasing the risk of perioperative hyperglycemia.[2,3] Up to 40% of patients undergoing major abdominal operations experience perioperative hyperglycemia (≥140 mg/dL). Perioperative hyperglycemia has been implicated in an increased risk of perioperative complications including surgical site infection, reoperation, and mortality.[6,7]

Enhanced recovery programs (ERP) in colorectal surgery have the aim of minimizing the stress response of surgery and its associated catabolic state.[2,8–10] Interventions such as minimally invasive surgery, bowel preparation with oral antibiotics, opiate sparing analgesia, early mobility, and early postoperative dietary advancement have significantly improved outcomes.[4,6,8] As their complexity increases, it has become difficult to identify the relative impact of individual components within an ERP and which components offer the greatest value. In review of colorectal surgery ERPs, the greatest potential benefit with respect to surgical site infection appears to be related to four specific process measures: bowel prep with oral antibiotics, laparoscopy, mitigation of early hyperglycemic episodes, and appropriate use of prophylactic

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intravenous antibiotics.

Of the aforementioned process measures, the most ambiguous measure is the potential benefit of "appropriate" carbohydrate loading. The original work by Lundqvist focused on restoration of insulin sensitivity using 3 individual doses of a preoperative maltodextrin carbohydrate drink with an appropriate volume and osmolarity to assure prompt gastric emptying. This work and additional supporting evidence confirmed the improvement in insulin sensitivity and safety when administered up to two hours prior to surgery.[2,3,5] Interestingly, until the recently published PROCY Study no prior work assessed the impact of this strategy, nor other forms of carbohydrate, on the incidence of hyperglycemia.[11] As a result, there has been no standardization of preoperative carbohydrate loading in established ERPs. In particular, no data exists supporting the substitution of maltodextrin based drinks with simple sugar containing drinks (glucose, sucrose, and fructose).

To date, no study has evaluated the isolated impact of transitioning an ERP from the administration of a simple carbohydrate drink to a low dose complex carbohydrate solution on perioperative hyperglycemia in colorectal surgery. The purpose of this study was to compare the effect of preoperative low dose maltodextrin/citrulline based electrolyte solution versus a commercially available sports drink on perioperative glycemic levels in non-diabetic patients in an established colorectal ERP.

2. Methods

As a quality improvement project, this work was deemed exempt as per OHRP guidelines. A retrospective chart review was performed including all non-diabetic, elective, non-urgent segmental colectomy, enterectomy and proctectomy from January 2016–March 2017 in a pre-established ERP.

Cohorts were treated with an identical perioperative enhanced recovery program (ERP) differing only with respect to preoperative dosing with either a simple carbohydrate solution or a complex carbohydrate drink. All patients used a sports drink (64 oz) mixed with 238 g of polyethylene powder followed by 3 separate doses of 1 g neomycin/500 mg metronidazole for bowel preparation the day prior to surgery. The simple carbohydrate group (SIM) received a commercially available sports drink with osmolarity ranging from 210 to 650 milliosmolar, complex carbohydrates (range 0–3.6 mg/dl) and simple carbohydrates (range 14–63 mg/dl). Patients were allowed to drink this simple carbohydrate solution until hospital arrival the morning of surgery. The complex carbohydrate group (COM) received 3 separate 10 oz doses of the complex carbohydrate solution (maltodextrin 25 g; citrulline 3 g), taking 2 doses the evening prior and the final dose en route (completed by 2 h prior to surgery) to the hospital. These drinks were consumed within 5–10 min. The complex group was also allowed ad lib access to any non-carbohydrate containing beverages from completion of the bowel prep to the time of surgery.

Blood glucose was assessed preoperatively with either basic metabolic panel or finger stick rapid glucose test per nursing protocol and reassessed on each postoperative day, paying particular attention to postoperative days 1, 2, and 3. If more than one blood glucose level was obtained, as per hospital nursing protocol, the events were abstracted individually and averaged together over that 24 h period to establish a mean blood glucose level for that postoperative day.

Inclusion criteria consisted of all adult elective segmental colectomy and enterectomy patient's treated as part of an established ERP by a colorectal surgeon practicing at two community-based teaching hospitals during the study period from January 1, 2016 to March 28, 2017. Patients were excluded if they were treated outside of the defined study timeline or did not participate in the ERP. Additional exclusion criteria consisted of preoperative documentation of type I or type II diabetes mellitus or preoperative laboratory studies including Hgb A1c > 6.5 or history of treatment with insulin or other diabetic medication.

A retrospective analysis of each cohort was undertaken. Demographics were obtained through review of electronic medical record (EMR) data. BMI was calculated using a standardized metric-based calculation for BMI (mass (kg))/(height (m))^2. Patient medications were reviewed from the preoperative nursing medical reconciliation to identify patients undergoing active treatment with systemic corticosteroids. The surgical procedure performed was abstracted from the surgeon's dictated operative report. Postoperative days were defined as each subsequent day of inpatient hospital stay after the index day of surgery. Whether the patient received the preoperative complex carbohydrate solution was determined based on timing of operative intervention within the ERP after October 1, 2016, at which time the drink was routinely administered as part of the established ERP. Tolerance of preoperative mechanical bowel preparation and carbohydrate loading was assessed by the attending surgeon and no documentation of intolerance was appreciated during retrospective analysis. Preoperative glycemic levels were obtained in the preoperative holding area with standardized finger-stick device or intravenous blood draw (Basic Metabolic Panel) per individual hospital protocol. Hyperglycemia was defined as blood glucose $\geq$140 mg/dL. Glycemic variability was defined by the number of episodes of hyperglycemia compared to the total number of hospital days per cohort. Postoperative complications were assessed and identified if they occurred within 30 days of surgery and categorized based on Clavien-Dindo classification system.

Statistical analysis was performed with linear regression for all quantitative variables (age, BMI, etc) and logarithmic regression for all nominal outcome variables (gender, # of hyperglycemic episodes, and glycemic variability). Logarithmic regression with clustering was required in order to avoid statistical confounding bias through correction of the non-independence of variables like gender and number of hyperglycemic episodes because three of the patients were re-operative cases which occurred in each of the cohorts. Chi squared analysis was then used to analyze complications within 30 days of operative intervention.

3. Results

A total of 101 patients were reviewed. Of these, 18 carried the preoperative diagnosis of diabetes mellitus or previous treatment with insulin or other diabetic medication and, as a result, they were excluded from further analysis. The remaining 83 patients met inclusion criteria; 41 in the simple carbohydrate solution (SIM) cohort and 42 in the complex carbohydrate solution (COM) cohort. Patients ranged from 21 to 88 years of age. Gender distribution, mean weight, mean height, BMI, and perioperative corticosteroid use were not significantly different between the cohorts (See Table 1). Preoperative diagnoses varied and distribution within these diagnoses were not significantly different. Treatment provided included laparoscopic colectomy or enterectomy, open colectomy or enterectomy, abdominal perineal resection, laparoscopic proctectomy with/without J-pouch reconstruction, ileostomy takedown, colostomy takedown, and laparoscopic colostomy formation (See Table 1).

Hospital protocoled assessment of blood glucose throughout hospital stay facilitated evaluation of both glycemic variability and the total number of episodes of hyperglycemia for each hospital day. The glycemic variability of the COM group was significantly lower compared to the SIM group (8% vs 21%; $p = 0.034$). The preoperative and daily trends (POD 1–3) were also lower for the

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Table 1
Demographics.

	SIM Group	COM Group	P-value
Number of Cases (n = 83)	41	42	
Gender			
Male	18 (44%)	17 (40.5%)	NS
Female	23 (56%)	25 (59.5%)	NS
Age (years)*	61.7 ± 17.0	52.7 ± 17.2	0.012
Height (cm)*	171.1 ± 11.1	171.7 ± 10.4	NS
Mean Weight (kg)*	84.1 ± 35.4	78.9 ± 21.1	NS
Mean BMI*	28.5 ± 10.6	26.7 ± 6.3	NS
Concurrent corticosteroid use (% Yes)	3 (7.3%)	3 (7.1%)	NS
Treatment provided			
Laparoscopic colectomy/enterectomy	23	22	NS
Open colectomy/enterectomy	9	5	NS
Abdominal perineal resection	1	0	NS
Laparoscopic Proctectomy	2	4	NS
Ileostomy takedown	3	9	NS
Colostomy takedown	2	0	NS
Laparoscopic colostomy	1	2	NS

* Mean value ± Standard Deviation, NS = Not Statistically Significant.

COM group, however the study was insufficiently powered to confirm statistical significance (See Table 2).

The length of stay (LOS) was calculated with mean length of stay in the SIM group of 3.86 days compared to 2.91 in the COM group. While median length of stay in the SIM group of 3 days (Range 1–21.3 days) compared to 2.9 days in the COM group (Range 0.4–10.8 days). Perioperative complications were assessed and categorized based on diagnosis using Clavien-Dindo classification system. A total of 13 (32%) of complications occurred in the SIM cohort compared to 7 (24%) in the COM group (p = NS). 3 Grade I complications (7.3%) were identified in the SIM group compared to 4 in the COM group (9.5%). 7 Grade II Complications (17.1%) occurred in the SIM group compared to 2 (4.8%) in the COM group while 3 Grade III complications occurred in the SIM group (7.3%) and only 1 in the COM group (2.4%). Neither group sustained Grade IV or V complications.

4. Discussion

Standardized assessment and testing of insulin resistance is well established in animal models. This has been expanded to bariatric surgery patients through assessment with HOMA-IR and further validated using the euglycemic-hyperglycemic clamp technique.[12–14] Although there is some debate regarding the precise physiology assessed by either of the techniques, they both define metabolic dysfunction related to insulin, and therefore risk of hyperglycemia. Previous research has confirmed the perioperative catabolic state and the impact on the metabolic homeostasis and subsequent insulin resistance.[5,15] Additional literature has substantiated the resulting physiologic insult of surgery and impacts on circulating catecoholamines, insulin resistance, and patient well-being.[3,5] Through retrospective meta-analysis Bilku et al. analyzed data from 1445 patients who underwent preoperative carbohydrate loading and documented improved outcomes including decreased insulin resistance, decreased gastric acidity, and improved patient perception of well-being. However, this meta-analysis was unable to assess the impact on hyperglycemia or surgical site infection.[3] The recently completed PROCY Study was the first attempt to assess the role of the commonly recommended strategy for carbohydrate loading (50 g doses) in non-diabetic patients. The incidence of hyperglycemia decreased from 57% to 24% and the need for perioperative dosing of insulin diminished, suggesting that complex carbohydrate improved insulin sensitivity compared to fasting (water only), albeit to a population rate below the threshold to impact SSI rates.[11]

The present study is the first data to demonstrate that administration of 3 separate lower doses of a maltodextrin (25 g)/citrulline (3 g) drink in the absence of any additional carbohydrates to significantly reduced the incidence of serious hyperglycemic events from 24% to 7% in a bowel resection population managed within an otherwise stable and well established institutional ERP. It should be noted that the SIM cohort in the present study aligns with all available data from previous studies which has demonstrated population incidence of hyperglycemia in the 20–30% range.[16] The trend in the data was for a reduced risk of hyperglycemia both preoperatively and at each time interval, suggesting that this approach improved insulin sensitivity at each time interval over 72 h consistent with the pivotal work of Lundqvist.[15] However, the strategy used in this trial (3 doses of 25 g) appears to offer superior reduction in hyperglycemia compared to the commonly recommended doses of 150 g. This study also assessed the concept of perioperative glycemic variability because the strategy of intermittently dosed carbohydrate loading is designed to improve insulin sensitivity, and therefore the hyperglycemic rate in a surgical population. However, it is important to understand that the risk of stress induced hyperglycemia approaches 50–60% for patients with extended NPO periods, but may decrease to 20–30% for patients using typical carbohydrate loading strategies.[11,12] The data in this study suggests that the use of the low dose maltodextrin/citrulline combination resulted in a 70% reduction in hyperglycemic events compared to the higher dose/non citrulline supplement used in PROCY.[11]

The potential advantages of the supplement used in this study versus other options includes a lower dose of maltodextrin (25 g vs 50 g per dose), elimination of fructose which can induce gluconeogenesis in the liver, a balanced pH compared to highly acidic pH, balanced osmolarity with electrolytes, and 3 g of citrulline. The amount of maltodextrin administered with the recommended dosing strategy used in this study provided a lower rate of

Table 2
Outcomes.

	SIM	COM	P – value
Number of Hyperglycemic Episodes (Blood Glucose ≥ 140 mg/dL)			
Preoperative	7/41 (17%)	3/41 (7.3%)	NS
POD#1	10/41 (24%)	6/41 (14.6%)	NS
POD#2	5/27 (18%)	1/23 (4.3%)	NS
POD#3	2/18 (11%)	0/11 (0%)	NS
Percentage is derived through assessment of the incidence of hyperglycemia in comparison to the number of patients remaining hospitalized within the respective cohort on that particular day.			
Glycemic Variability (# hyperglycemic episodes/hospital day)	37/173 (21.4%)	10/132 (7.6%)	0.034
Length of Stay (median and range)	3 (1–21.3)	2.9 (0.4–10.8)	NS
Total Number of Complications within 30 days of admission	13 (31.7%)	10 (23.8%)	NS

NS = Not Statistically Significant.

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hyperglycemic events compared to other data sets.[16] This is an important concept because even modest hyperglycemia increases the risk of SSI and acute kidney injury in non-diabetic patients. The citrulline provided in this supplement offers two potential advantages: 1) support of systemic arginine levels; and 2) inhibition of hepatic gluconeogenesis. Citrulline has also demonstrated improved hepatic insulin sensitivity via the PI3K/Akt signaling pathway which is adjunctive to the insulin sensitivity driven via maltodextrin.[13,14,17]

Although the current study identifies potential advantages of complex carbohydrate loading prior to colorectal surgery there are several shortcomings. First, the retrospective nature of the study lends itself to selection bias, as seen with the age discrepancy between the two cohorts, in addition to limitation of available data and standardization that comes with more structured analysis. For example, blood glucose assessment was limited only to hospital protocol, nursing care sets and daily laboratory studies. As a result, there is no data regarding intraoperative blood glucose levels in this non-diabetic population as it is not hospital protocol to reassess blood glucose levels intraoperatively on non-diabetic patients with hyperglycemia <180 mg/dL. The retrospective nature of the study also limits data points regarding completion and tolerance of mechanical bowel preparation and tolerance of carbohydrate loading solution. The single-surgeon nature creates a confounding bias within the study that should be recognized. Furthermore, the sample size raises the concern of a Type 1 statistical error, however given the p value of 0.034 the analysis suggests that significance level was below 3.5% vs the more typically accepted 5% level (ie $p < 0.05$). Confirmation in a larger data set to further assess the impact on hyperglycemia, SSI or other complications is warranted.

5. Conclusion

This is the first study to assess the incremental benefits of switching preoperative carbohydrate loading from a simple sugar containing sports drink to a low dose complex carbohydrate/citrulline containing electrolyte solution within an established colorectal ERP. The study demonstrated a lower rate of hyperglycemic events in the complex carbohydrate loaded group compared to sports drink previously used and compared to the previously published data using the more commonly recommended maltodextrin doses. Further assessments of ERP benefits should be focused on identification of the impact of this treatment on perioperative outcomes, complications, and length of stay.

Conflict of interest disclosure

Dr. Kielhorn and Dr. Asgeirsson have no conflicts of interest to disclose. Dr. Senagore is the owner and founder of SOF Health that manufactures glycemic endothelial drink (G.E.D).

Summary

Retrospective analysis of perioperative glycemic levels in colectomy and enterectomy patients treated within an established enhanced recovery program. Comparison between preoperative simple and complex low-dose carbohydrate/citrulline loading with identification of significant improvement in perioperative hyperglycemic events and trend towards decreased incidence of length of stay and postoperative complications among the low-dose complex carbohydrate cohort.

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