Preoperative Oral Carbohydrate Load Versus Placebo in Major Elective Abdominal Surgery (PROCY)

A Randomized, Placebo-controlled, Multicenter, Phase III Trial

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Objective: To explore whether preoperative oral carbohydrate (CHO) loading could achieve a reduction in the occurrence of postoperative infections.

Background: Hyperglycemia may increase the risk of infection. Preoperative CHO loading can achieve postoperative glycemic control.

Methods: This was a randomized, controlled, multicenter, open-label trial. Nondiabetic adult patients who were candidates for elective major abdominal operation were randomized (1:1) to a CHO (preoperative oral intake of 800 mL of water containing 100 g of CHO) or placebo group (intake of 800 mL of water). The blood glucose level was measured every 4 hours for 4 days. Insulin was administered when the blood glucose level was >180 mg/dL. The primary endpoint was the occurrence of postoperative infection. The secondary endpoint was the number of patients needing insulin.

Results: From January 2011 through December 2015, 880 patients were randomly allocated to the CHO (n = 438) or placebo (n = 442) group. From each group, 331 patients were available for the analysis. Postoperative infection occurred in 16.3% (54/331) of CHO group patients and 16.0% (53/331) of placebo group patients (relative risk 1.019, 95% confidence interval 0.720–1.442, $P = 1.00$). Insulin was needed in 8 (2.4%) CHO group patients and 53 (16.0%) placebo group patients (relative risk 0.15, 95% confidence interval 0.07–0.31, $P < 0.001$).

Conclusions: Oral preoperative CHO load is effective for avoiding a blood glucose level >180 mg/dL, but without affecting the risk of postoperative infectious complication.

Keywords: hyperglycemia, infections, outcome, randomized trial, surgery

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Stress hyperglycemia in surgical patients is a well-known phenomenon; however, its consequences have been poorly investigated in patients who are not critically ill.[1] In elective surgical patients, preoperative starvation is one of the predisposing factors for hyperglycemia,[2,3] sustained by increases in glycogenolysis, gluconeogenesis, insulin resistance, and blunt insulin sensitivity.[3,4]

A large body of literature supports a relationship between the degree of postoperative hyperglycemia and an increased risk of the occurrence of surgery-related infections.[5] Considering these results, blood glucose levels should be strictly monitored to promptly treat hyperglycemia. Yet, in clinical practice, this is not followed for all patients unless they are under intensive care, high dose of intravenous glucose, or diabetic. Therefore, the real incidence of postoperative hyperglycemia and its potentially harmful consequences may be largely underestimated in nondiabetic or low-risk patients.[6,7]

Normal postoperative blood glucose levels may be achieved with several strategies. Continuous insulin infusion is commonly used in critically ill patients because of its protective effect on outcome.[8,9] However, there is a concern that intensive glucose control with insulin without rigorous monitoring may result in hypoglycemia with subsequent severe complications.[9]

In patients who are candidates for elective surgery, a safe and effective method to control postoperative hyperglycemia is administration of oral preoperative carbohydrate (CHO)-rich fluids,[10,11] but strong evidence on clinically relevant outcome measures, such as a reduction in the incidence of postoperative infection, are lacking.[12]

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Authors' contributions: L.G.—study supervisor, trial management, literature search, study design, data interpretation, and writing; R.B.—study supervisor, study design, data interpretation, and writing; M.S.—trial management, literature search, data analysis, data interpretation, and writing; D.M.—patient recruitment, study design, data interpretation, and writing; A.V.—patient recruitment, study design, data interpretation, and writing; R.C.—literature search, data collection, data interpretation, and writing; J.V.—literature search, patient recruitment, literature search, and data interpretation; A.S.—patient recruitment, data collection, and data interpretation; G.D.M.—patient recruitment, data collection, and data interpretation; M.A.—patient recruitment, data collection, and data interpretation; F.A.—study design, patient recruitment, data collection, and data interpretation; M.G.V.—study design, statistical analysis, data interpretation, and writing; D.P.B.—study design, trial management, statistical analysis, figure drawing, data interpretation, and writing. All the authors read and approved the final version of the manuscript and the authorship list.

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The present trial was designed to explore whether preoperative oral CHO loading could achieve a reduction in the occurrence of postoperative infection when compared with the occurrence of postoperative infection with placebo in patients undergoing elective major abdominal surgery.

METHODS

Study Design and Participants

This preoperative oral CHO load versus placebo in major elective abdominal surgery (PROCY) trial was designed as a randomized, controlled, multicenter, open-label, parallel, phase 3 trial. The study was performed at 5 Italian university tertiary hospitals. Subjects eligible for participation were adult (age $\geq$18) patients who were candidates for elective major abdominal operation (duration $\geq$2 hours) for surgical diseases of the gastrointestinal tract and urinary tract, and for gynecological diseases. The exclusion criteria were as follows: fasting glucose level $>$125 mg/dL, type 1 and 2 diabetes, gastro-esophageal reflux disease, hiatal hernia, pancreatic disease, American Society of Anesthesiologists (ASA) physical status classification $>$3, preoperative weight loss $>$10% of the usual body weight in the previous 6 months, ongoing corticosteroid therapy, and any previous infection in the past 3 months.

After the patients were screened according to the inclusion and exclusion criteria, the selected patients or their legal representatives were asked to provide written informed consent. The patients were then enrolled in the study and were randomly allocated into 2 arms [CHO-rich oral treatment (treatment arm) and water (placebo arm)]. We recorded all reasons for exclusion after screening.

The study was approved by the Ethics Committee of San Gerardo Hospital, Monza, Italy, on June 18, 2010 (reference number 378), as this was the coordinating centre. Patient recruitment was started on January 15, 2011. The study was also approved by the Ethics Committees of the other participating hospitals between October 2010 and April 2011.

The trial was registered at ClinicalTrials.gov (ID: NCT01167387).

This PROCY trial was designed, managed, coordinated, and analyzed by the School on Medicine and Surgery of the Milano-Bicocca University at the Department of Surgery of San Gerardo Hospital, Monza, Italy. The coordinating center was responsible for treatment allocation, central monitoring, and statistical analysis, and it received support from the Centre of Biostatistics for Clinical Epidemiology of Milano-Bicocca University.

Interventions

The study intervention was oral intake of 800 mL of a water solution containing 12.6 g of CHO (glucose, 0.2 g; fructose, 1.3 g; maltose, 0.7 g; maltodextrin, 10.0 g) per 100 mL [240 mosml/L; 500 kcal/L (215 kJ)] (PeriOp, Nutricia, Milan, Italy). Patients in the treatment arm were instructed to start the consumption of this solution from 8 PM on the evening before the operation and stop consumption 2 hours before the planned time of operation (scheduled in advance). During this timeframe, the patients were not allowed to drink any other solution or fluid.

Patients in the placebo arm were instructed to drink plain water (vehicle used in the treatment arm) with the same timing and volume as those in the treatment arm.

After induction of anesthesia and placement of an oro-tracheal tube, and before any manipulation of the abdomen, a naso-gastric tube was insert and the residual gastric volume was measured with a graduate syringe.

The capillary blood glucose level was measured at the following time-points: at hospital admission (after 6 hours of fasting), at arrival in the operating theatre, 1 hour after abdominal incision, at the end of the operation, and every day after surgery at 6 and 12 AM, and at 6 and 12 PM for 4 consecutive days. To ensure consistency, all measurements were performed with the same instrument in all centers (Accu-Chek Inform II; Roche Diagnostic SpA, Monza, Italy). The instrument was calibrated with plasma glucose standards obtained from a centralized laboratory.

Insulin was a mandatory therapy when the blood glucose level was $\geq$180 mg/dL, because such a level was considered as hazardous if not treated.

All patients were covered with a heated blanket during the surgical procedure and received warmed (38°C) intravenous fluid infusion. Core body temperature was monitored with a bladder catheter or an esophageal probe, and hypothermia was defined as a body temperature of $<$35.5°C for more than 30 minutes. No corticosteroid administration was allowed during the operation.

Artificial nutrition (enteral and parenteral) was not allowed unless patients could not resume oral intake within 7 days after the operation or patients experienced complications causing catabolism according to published guidelines.[13]

Antibiotic prescription, in cases of proven or suspected infection in the postoperative period, was left to the choice of the attending surgeon.

Data were collected on paper case report forms and were then transferred to an electronic database with double entry to ensure consistency of records. In case of missing or implausible data, queries were mailed to the participating centers to obtain integrations or corrections. Data collectors were blinded to treatment allocation.

Randomization and Masking

Patients were randomly allocated to a CHO group (CHO-rich oral treatment) or a placebo group (water) at 8 PM on the evening before the operation. We enrolled participants by using a web-based system, and randomization was performed by using a computer-generated permuted-block sequence. A specific code was generated for each centre to achieve equivalent groups. The allocation ratio was 1:1, and the block size was 4. Surgeons, anesthetists, and outcome assessors were blinded to the treatment allocation. Masking was possible because group allocation was performed by a research nurse from the surgical ward, and the attending surgeon and anesthetist welcomed the patients at the operating theatre the next morning without knowledge of the type of liquid taken. The outcome study-independent assessors were also masked because they evaluated patients postoperatively on a daily base during hospital stay and during outpatient visits without knowledge of the type of liquid taken.

Outcomes

The primary endpoint of the trial was the occurrence of at least 1 of the following postoperative infections: superficial or deep wound infection, organ/space infection, urinary tract infection, pneumonia, sepsis, and septic shock. The determination of the primary endpoint was based on a priori definition of postoperative infectious complications (Supplementary Table 1, http://links.lww.com/SLA/B247). All participating centers approved the definition before starting the trial enrolment. The outcome assessors were trained by the study coordinator to achieve concordance with respect to definitions. Each participating center had 2 independent outcome assessors. In case of discordance on the assignment of the primary endpoint, a third expert intervened to resolve the dispute and determine whether the patient met the definition of the primary endpoint.

If any of the above complications occurred along with a proven anastomotic dehiscence, the infection was not considered in the primary outcome rate. The rational for excluding those patients

was that the development of an infectious complication after a leakage could be judged as secondary to a technical failure and not to the potential harmful effect of hyperglycemia. The definition of anastomotic leakage is reported in Supplementary Table 1 (http://links.lww.com/SLA/B247).

The occurrence of postoperative infection was assessed every day during hospitalization and for 30 days after the operation. Postdischarge patient surveillance and follow-up involved weekly outpatient visits. Telephone interviews were allowed for monitoring the health status of patients; however, in case of warning signs or symptoms of infection, patients were asked to refer to the hospital where the operation was performed for further clinical evaluation.

Secondary outcome measures were the number of patients with at least 1 postoperative measurement of blood glucose >110 and <140 mg/dL, or at least 1 postoperative measurement of blood glucose >140 and <180 mg/dL; number of patients needing intraoperative or postoperative insulin treatment; rate and duration of empiric antibiotic therapy after surgery; rate, severity, and duration of all postoperative complications; rate of reoperation; rate and duration of intensive care treatment; and length of postoperative stay. The severity of complications was scored according to the Dindo-Clavien classification system.[14]Adverse treatment events were a gastric residual volume >100 mL (also the absolute gastric residual volume after induction of anesthesia); the occurrence of lung aspiration episodes (proven by bronchoscopy); and the occurrence of nausea, vomiting, diarrhea, and abdominal distension during preoperative oral fluid intake. A gastric residual volume >100 mL was considered a risk factor for aspiration during induction of anesthesia.

Statistical Analysis

A sample size of 440 patients per group was planned when the trial was originally designed. This sample size was calculated to provide an 80% power with a type I error rate fixed at 5% (2-tailed) to detect superiority in the reduction of the rate of postoperative infection. Based on a preliminary 1-year survey for the same type of surgery among the participating centers, we expected a rate of infection of 18% in the placebo group and a relative rate reduction of at least 40% in the CHO group, allowing for a dropout of about 15%.

For the binary endpoints, the relative risks (RRs) and corresponding 95% confidence intervals (CIs) were estimated on comparing the CHO and placebo groups. For the primary endpoint, the risk difference (RD) was estimated. Similarly, for the numerical endpoints, differences in the location parameters (ie, median pair-wise differences) between the 2 groups and the corresponding 95% CIs were estimated.[15] Fisher test and the Mann–Whitney test were used to evaluate univariate associations. The incidence of infection over time in the 2 groups was described according to the Kaplan–Meier estimator. Comparisons of the blood glucose levels before, during, and after the operation between the 2 groups were performed using the Mann–Whitney test with Holm adjustment for multiple comparisons and with box-plots for a graphical summary.

A multivariate logistic regression model was created to identify factors associated with the primary endpoint and to evaluate the effect of treatment after adjusting for possible residual confounding. Using logistic regression, the superiority of CHO over placebo with regard to the reduction in the infection rate was investigated within prespecified subgroups to account for possible effect modification. The prespecified risk factors for this analysis were blood glucose at admission (110–125 mg/dL), body mass index (BMI) (>30 kg/m^2), sex (male), age (>65 years), reduced dose of CHO-rich fluids (<800 mL), number of preoperative diseases (>2), target organ for operation, laparoscopy, diagnosis of cancer, ASA score of 3, level of contamination during surgery, blood loss (≥500 mL), and duration of surgery (≥3 hours).

To evaluate the possible superiority of CHO over placebo with regard to the prevention of postoperative episodes of a high blood glucose level (>180 mg/dL), the number needed to treat (NNT) was computed.

Analyses were based on the modified intention-to-treat analysis principle to represent clinical practice.

A P value <0.05 was considered to indicate statistical significance.

All analyses were performed using R software version 3.2.2 (http://cran.r-project.org).

RESULTS

The diagram of the trial is presented in Fig. 1. From January 2011 through December 2015, 2842 patients were screened for eligibility, and after applying the exclusion criteria, 880 patients were randomly allocated to the study groups (438 were allocated to the CHO group and 442 were allocated to the placebo group). Eleven patients in the CHO group and 13 in the placebo group did not receive the assigned treatment. For 91 patients in the CHO group and 94 in the placebo group, the study was prematurely terminated mainly because the operation lasted for less than 2 hours (30 in the CHO group and 33 in the placebo group) or anastomotic leakage occurred (42 in the CHO group and 46 in the placebo group).

The number of patients available for the modified intention-to-treat analysis was 331 in the CHO group and 331 in the placebo group. Follow-up was completed in all patients.

The baseline characteristics and risk factors for infection were well-balanced between the 2 groups (Table 1). The rate of complete adherence to the treatment protocol was 92.4% (306/331) in the CHO group and 94.9% (314/331) in the placebo group. In the CHO group, 24 (7.3%) patients consumed a beverage volume <800 mL and 1 (0.3%) patient had missing data, and in the placebo group, 17 (5.1%) patients consumed a beverage volume <800 mL (RR 1.41, 95% CI 0.77–2.58, $P = 0.26$).

Table 2 presents the rates of adverse events in the 2 arms. Side effects were absent in 92.1% (305/331) of the patients from the CHO group and in 97.0% (321/331) of the patients from the placebo group (RR 0.95, 95% CI 0.92–0.99, $P = 0.009$). In particular, nausea was reported in 17 (5.1%) patients from the CHO group and in 5 (1.5%) patients from the placebo group. The gastric residual volume and the proportion of patients with residual volume >100 mL were higher in the CHO group than in the placebo group. No aspiration episodes were observed in both groups.

A quantitative illustration of blood glucose variations over time is presented in Fig. 2. The blood glucose levels were comparable between the groups at hospital admission and at arrival in the operative theatre. In the CHO group, the median glucose levels remained within the normal range at any time point assessed, whereas in the placebo group, hyperglycemia was constantly observed from the end of operation to the first 24 hours of the study. The medians and interquartile ranges (IQRs) of the glucose levels at each assessment in the 2 groups are shown in Supplementary Table 2 (http://links.lww.com/SLA/B247). The glucose levels from the first hour after surgery to postoperative day 3 at 6 PM were significantly higher in the placebo group than in the CHO group.

Composite postoperative infection (primary endpoint) occurred in 54 (16.3%) patients from the CHO group and in 53 (16.0%) patients from the placebo group (RR 1.019, 95% CI 0.720 to 1.442; relative difference 0.003, 95% CI −0.053 to 0.059, $P = 1.00$) (Table 3). The incidence curves of the primary endpoint in the 2 groups were superimposable [hazard ratio (HR) 1.01, 95% CI 0.69–1.47) (Supplementary Fig. 2, http://links.lww.com/SLA/B247).

No significant differences in the rates of individual primary endpoint components of postoperative infection were observed

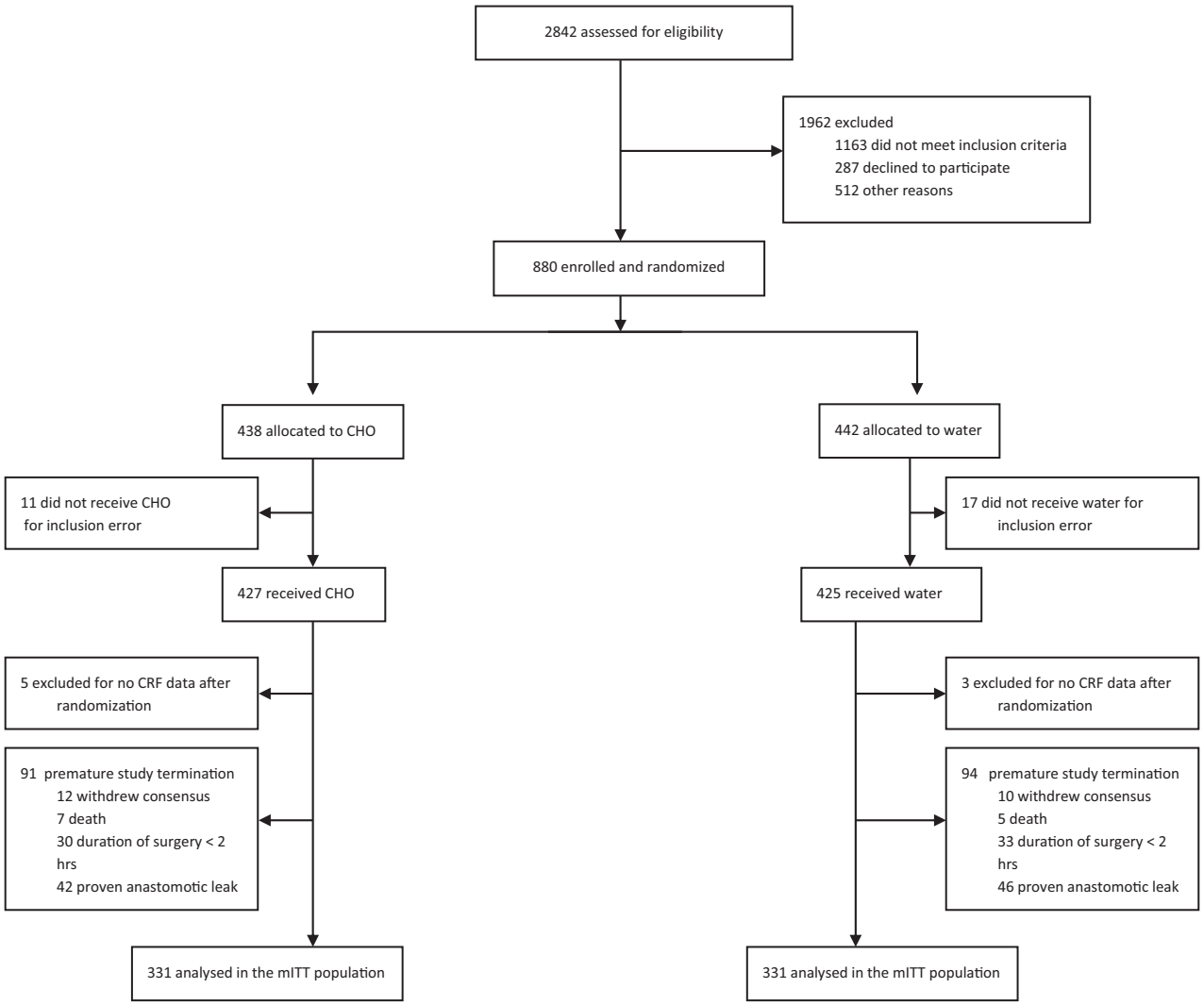

FIGURE 1. Trial profile. CRF, case report form; mITT, modified intention-to-treat.

between the groups (Supplementary Table 3, http://links.lww.com/SLA/B247).

The secondary endpoints are also summarized in Table 3. Preoperative CHO loading significantly reduced the rate of insulin administration. Insulin was administered to 8 (2.4%) patients in the CHO group and 53 (16.0%) patients in the placebo group for treating blood glucose levels >180 mg/dL (RR 0.15, 95% CI 0.07–0.31, $P < 0.001$). The NNT was 7, indicating that for every 7 participants treated with CHO, the need of insulin treatment is avoided for 1 additional patient when compared with not treating anyone. The frequency of empiric antibiotic prescription and the duration of treatment did not differ between the groups. We did not observe any significant differences in the rate of overall surgery-related complications, their severity, and their duration between the groups. Additionally, the proportions of patients requiring reoperation and intensive care treatment were comparable between the groups. The median length of postoperative hospitalization was 11.0 days in both groups (RR 0, $P = 0.44$).

Postoperative mortality occurred in 7 (2.1%) patients from the CHO group and 5 (1.5%) patients from the placebo group (RR 1.4, 95% CI 0.449–4.366, $P = 0.77$).

We performed a post-hoc subset analysis to identify potential interactions between the postoperative infection rate and prespecified risk factors. The occurrence of the primary composite outcome was similar in all subgroups (Fig. 3).

The results of the logistic regression analysis performed to evaluate the odd ratios of single risk factors showed that the laparoscopic approach and clean surgery were the only significant protective factors for the occurrence of infection (Supplementary Table 4, http://links.lww.com/SLA/B247).

DISCUSSION

The results of our trial support the null hypothesis as the occurrence of postoperative infection was similar between patients treated with CHO load and those who received placebo, although our data fully support, on a large-scale, the findings of previous studies

TABLE 1. Baseline Characteristics and Risk Factors

	CHO (n = 331)	Placebo (n = 331)	*P*
Age, yrs	68.0 [58.0; 75.5]	67.0 [57.0; 75.0]	0.233
Sex, male	189 (57.1)	179 (54.1)	0.481
Body mass index	25.5 [23.11; 27.47]	25.2 [23.12; 27.68]	0.561
Fasting blood glucose at admission, mg/dL	93.0 (86.0–100.0)	93.0 (85.0–102.0)	0.969
Pts with fasting impaired glucose tolerance (Blood sugar at admission >110 ≤125 mg/dL)	31 (9.4)	34 (10.3)	0.698
Hemoglobin, g/L	131.0 [117.0; 145.0]	129.0 [113.0; 146.0]	0.615
Albumin, g/L	38.4 [35.0; 41–0]	38.0 [34.8; 41.0]	0.513
Creatinine, mg/dL	0.90 [0.70; 1.00]	0.90 [0.70; 1.04]	0.852
C-reactive protein, mg/L	0.60 [0.20; 2.03]	0.60 [0.20; 1.32]	0.981
Adherence to treatment protocol			0.267
Total volume	306 (92.4)	314 (94.9)	
Other volume	24 (7.3)	17 (5.1)	
Missing	1 (0.3)	0	
Time between last intake and operation, min	265.0 [185.0; 425.0]	260.0 [185.0; 385.0]	0.747
Number of comorbidities			0.088
0	115 (34.7)	139 (42.0)	
1	111 (33.5)	91 (27.5)	
2	63 (19.0)	77 (23.3)	
>2	42 (12.7)	24 (7.3)	
Target organ for operation			0.832
Stomach	57 (17.2)	60 (18.2)	
Rectum	61 (18.4)	49 (14.8)	
Colon	114 (34.4)	118 (35.8)	
Liver	34 (10.3)	35 (10.6)	
Kidney	18 (5.4)	12 (3.6)	
Prostate	17 (5.1)	15 (4.5)	
Bladder	8 (2.4)	12 (3.6)	
Retroperitoneum	9 (2.7)	12 (3.6)	
Oesophagus	6 (1.8)	10 (3.0)	
Uterus/ovary	7 (2.1)	7 (2.1)	
Cancer	282 (85.2)	278 (84.0)	0.748
ASA physical status classification			0.745
1	25 (7.6)	24 (7.4)	
2	212 (64.2)	217 (67.0)	
3	93 (28.2)	83 (25.6)	
Type of surgery			0.296
Clean	118 (35.6)	116 (35.0)	
Clean-contaminated	197 (59.5)	191 (57.7)	
Contaminated	14 (4.2)	22 (6.6)	
Dirty	2 (0.6)	0	
Missing	0	2 (0.6)	
Epidural analgesia	110 (33.2)	111 (33.5)	0.934
Intraoperative hypothermia	7 (2.1)	12 (3.6)	0.255
Laparoscopic procedure	87 (26.3)	70 (21.1)	0.148
Blood loss, mL	200.0 [50.0; 300.0]	200.0 [100.0; 300.0]	0.156
Intraoperative blood transfusion	21 (6.3)	31 (9.4)	0.150
Number of blood units transfused	2.0 [2.0; 2.0]	2.0 [2.0; 3.0]	0.132
Duration of surgery, min	175.0 [140.0; 225.0]	170.0 [140.0; 210.0]	0.331

Data as numbers (%) or median [IQR]. To convert glucose to mmol/L, multiply values by 0.0555; to convert creatinine to mmol/L, multiply values by 88.4; to convert C-reactive protein to mmol/L, multiply values by 9.524.

that showed a significant effect of preoperative oral CHO in maintaining normoglycemia in surgical patients.[11,12,16-18]

The lack of a significant difference in the primary endpoint between the 2 groups is supported by the findings of the analyses of the secondary endpoints and the subgroup analyses. Relevant parameters of clinical outcome were similar between arms, implying that the clinical courses of the patients allocated to the 2 groups did not substantially differ. Similarly, the post-hoc analysis stratified according to different risk factors was not able to reveal the hypothesized protective effect of the administration of CHO with regard to the occurrence of infection in any of the prespecified subgroups.

The administration of a preoperative oral CHO-rich drink has been shown to have several metabolic and functional advantages over the intake of water or starvation. The most clinically relevant benefit appears to be the ability to modulate postoperative alterations of glucose metabolic pathways by blunting insulin resistance mechanisms.[19] Avoiding high glucose levels may be of paramount importance because persistent hyperglycemia affects key immune defense mechanisms, predisposing the patient to develop infectious complications after the operation.[5,20]

Based on the abovementioned observations, our trial was designed with the hypothesis that by controlling hyperglycemia through the administration of a preoperative CHO load, we could observe a reduction in the incidence of infection.

In our treated patients, the median blood glucose levels remained within the normal range after the operation at all examined

TABLE 2. Adverse Events Reported*

	CHO (n = 331)	Placebo (n = 331)	Estimated Effect (95% CI)	P
None				
Diarrhoea	305 (92.1)	321 (97.0)	0.95 (0.92; 0.99)	
Abdominal distension	3 (0.9)	0 (0)	—	0.009
Nausea	5 (1.5)	2 (0.6)	2.5 (0.49; 12.79)	
Vomiting	17 (5.1)	5 (1.5)	3.4 (1.27; 9.11)	
	1 (0.3)	3 (0.9)	0.33 (0.03; 3.19)	
Gastric residual, mL				
Median [IQR]	0.00 [00.0; 10.00]	0.00 [0.00; 30.00]	0 (0; 0)	0.024
Mean (standard deviation)	28.93 (73.48)	23.89 (47.68)	5.03 (−4.49; 14.55)	
Gastric residual >100 mL	25 (7.6)	15 (4.5)	1.67 (0.90; 3.10)	0.141
Aspiration episodes	0	0	—	1.00

Data as numbers (%) unless otherwise specified. The estimated effect measure is relative risk for categorical variables, mean difference and median pair-wise difference for continuous variables. *P* value is according to Fisher test for categorical variables, Mann–Whitney test for continuous variables.

*For each patient, only the more relevant side effect was reported.

time-points, whereas in our control patients, the median levels were above the upper limit of normality from the end of surgery up to 24 hours after the operation. Additionally, the glucose levels were significantly higher in the control patients than in the treated patients over the first 3 days of the postoperative course. Yet, this derangement of glucose metabolism appears to be a self-limiting event, as the blood glucose levels tended to normalize within postoperative day 3 in the placebo group. This could possibly indicate the lack of a beneficial effect of CHO load. Another potential explanation is the magnitude and severity of hyperglycemia. In our study, episodes of hyperglycemia between 110 and 140 mg/dL, and up to 180 mg/dL were significantly less common in the treated patients than in the control patients; however, these differences did not affect the rate of infection, suggesting that these levels do not substantially increase the risk and may be considered within the limits of a physiological response to surgical stress. A previous retrospective study reported a linear correlation between poor postoperative glycemic control and the risk of occurrence of postoperative infection.[21] Our results are in contrast with those previous data showing that every 40 mg/dL increase beyond the upper limit in the postoperative glucose level led to a 30% increase in the risk.[21] The divergence in the findings might have resulted from differences in the population examined, but are mostly associated with the lack of causality of retrospective data regarding the association between postoperative hyperglycemia and the occurrence of infection.

Also, Kwon et al[22] reported that in patients with severe hyperglycemia (>180 mg/dL), the risk of developing an infectious complication doubled, but the risk was voided in patients adequately treated with insulin and thus achieving successful glucose control. Our results do not allow any speculation with regard to the real impact of severe hyperglycemia on the occurrence of infection because all patients with blood glucose >180 mg/dL received insulin treatment. This may also justify the similar rate of infectious complications observed in the 2 arms.

With the inadequacy of relying on secondary endpoints, we emphasize the significant difference between the treated and

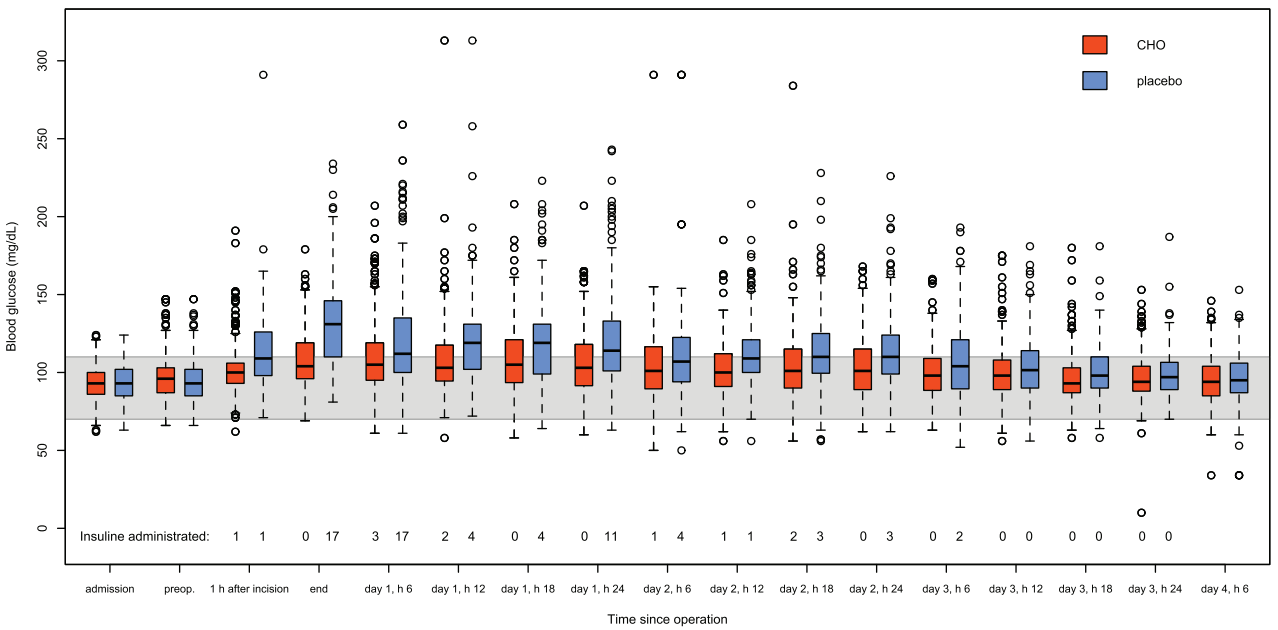

FIGURE 2. A quantitative illustration of blood glucose variations over time.

TABLE 3. Primary and Secondary Endpoints

	CHO (n = 331)	Placebo (n = 331)	RR (95% CI)	*P*
Primary				
Infections	54 (16.3)	53 (16.0)	1.02 (0.720; 1.442)	1.00
Secondary				
Patients receiving at least 1 dose of insulin after surgery	8 (2.4)	53 (16.0)	0.15 (0.07; 0.31)	<0.001
Patients with at least 1 postoperative measurement of blood glucose >110–mL/dL e <140	249 (75.2)	318 (96.1)	0.78 (0.73; 0.84)	<0.001
Patients with at least one postoperative measurement of blood glucose >140–mL/dL e <180	80 (24.2)	190 (57.4)	0.20 (0.34; 0.52)	<0.001
Antibiotic therapy	102 (30.8)	99 (29.9)	1.03 (0.82; 1.30)	0.87
Duration of antibiotic therapy, d	8.00 [6.00; 11.00]	7.00 [6.00; 11.75]	0 (−1; 1)	0.55
Total complications	93 (28.1)	94 (28.4)	0.99 (0.78; 1.26)	1.00
Severity of complications				0.67
I	43 (46.2)	34 (36.2)	1.28 (0.90; 1.81)	
II	21 (22.6)	27 (28.7)	0.79 (0.48; 1.29)	
IIIa	13 (14.0)	9 (9.6)	1.46 (0.66; 3.25)	
IIIb	7 (7.5)	12 (12.8)	0.59 (0.24; 1.43)	
IV	3 (3.2)	4 (4.3)	0.76 (0.17; 3.29)	
IVb	2 (2.2)	2 (2.1)	1.01 (0.15; 7.03)	
Missing	3 (3.2)	3 (3.2)	1.01 (0.21; 4.88)	
Duration of the complication, d	8.00 [3.00; 15.00]	7.00 [4.00; 11.75]	0 (−1; 3)	0.56
Reoperation	14 (4.2)	14 (4.2)	1.0 (0.48; 2.07)	1.00
Intensive care treatment	28 (8.5)	34 (10.3)	0.82 (0.51; 1.33)	0.43
Duration of intensive care, d	2.00 [1.00; 4.00]	2.00 [1.00; 3.00]	0 (0; 1)	0.45
Length of stay, d	11.00 [8.00; 15.75]	11.00 [8.00; 15.00]	0 (0; 1)	0.44

Data as numbers (%) or median [IQR]. The estimated effect measure is relative risk (RR) for categorical variables and median pair-wise difference for continuous variables. *P* value is according to Fisher test for categorical variables and Mann–Whitney test for continuous variables.

To convert glucose to mmol/L, multiply values by 0.0555.

control patients with regard to the need of insulin administration for severe hyperglycemia. As per the protocol, glucose levels were measured and strictly monitored, allowing appropriate evaluation of the occurrence of severe hyperglycemia. This approach is not part of the standard clinical practice, particularly in nondiabetic patients or patients who are not critically ill, and thus, the real incidence of postoperative hyperglycemia may be largely underestimated.[6,7]

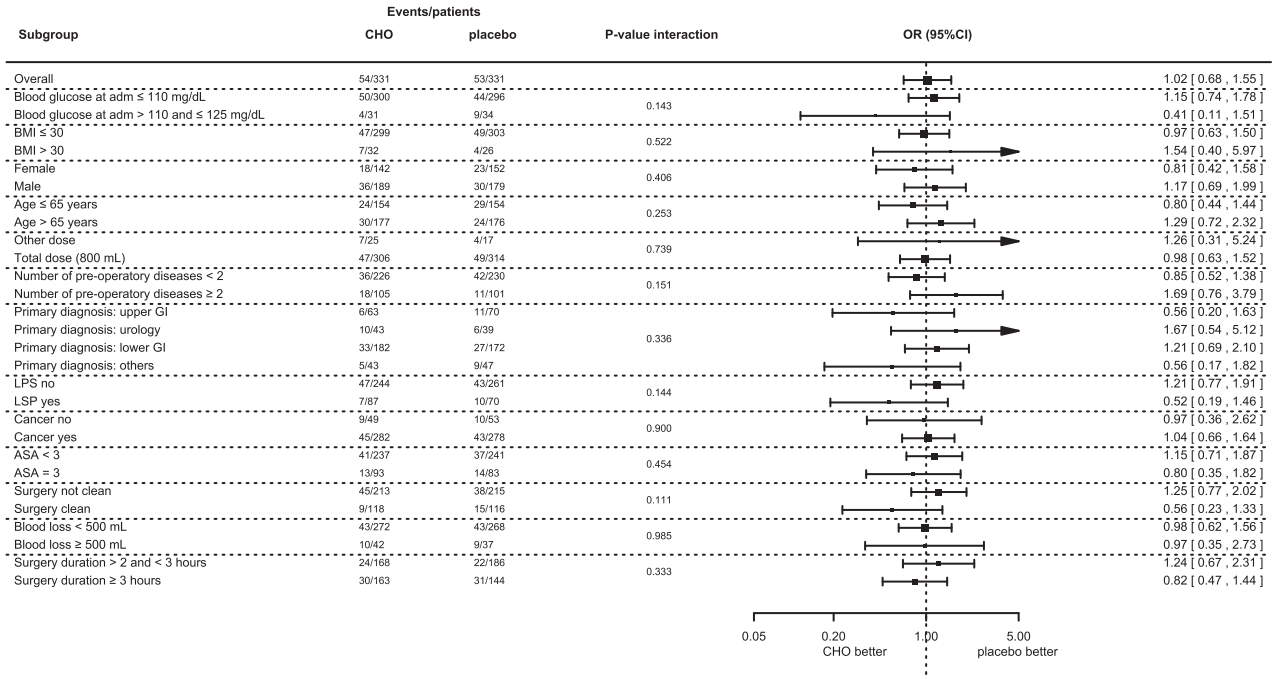

FIGURE 3. Subset analysis of infection in the modified intention-to-treat analysis. GI, gastrointestinal; LPS, laparoscopy.

The NNT analysis found that to avoid 1 episode of potentially harmful hyperglycemia, 7 patients had to be treated with preoperative oral CHO load. In this context, the routine use of preoperative CHO load in patients who are candidates for elective major abdominal operation may help avoid the requirement of protocols for rigid glucose control that can be time-consuming for nurses and uncomfortable for patients when capillary measurement is used.

The present trial validated the safety of CHO-rich oral drinks up to 2 hours before surgery, as previously suggested.[23] A gastric residual volume >100 mL was more common, and the mean volume of gastric content was greater in treated patients than in control patients. As no case of aspiration was observed, the clinical significance of these differences is limited.

The present trial has several limitations. First, we did not blind patients to the treatment because a placebo drink with the same texture and appearance as those of the treatment was not realizable without support from the manufacturer. We tried to limit the consequences of the lack of a double-blind design by masking surgeons, anesthesiologists, and outcome assessors. Second, the glucose level was measured using blood capillary samples. Although this blood glucose assessment is routinely used for in-patients and out-patients, its accuracy and reproducibility may not be comparable with those of a standard laboratory test. Nevertheless, this approach allowed instantaneous measurement and therapeutic intervention, as required by our protocol. Third, although our findings failed to demonstrate that it is possible to reduce the rate of infection by controlling postoperative hyperglycemia up to 180 mg/dL, the role of blood glucose levels >180 mg/dL could not be ruled out from the design of the trial. We believe that further randomized controlled trials will not be able to adequately address this issue because it would be unethical to not treat severe hyperglycemia, when detected.

The fourth potential constraint is about generalization of results. Roughly, 70% of the screened patients did not qualify for trial inclusion. It is reasonable to extrapolate that patients having an operation lasting less than 2 hours will behave similarly to the study population, but applying the findings to the excluded patients with a recent infection, diabetes or glucose intolerance, malnutrition, or candidate to pancreatic resection may be arguable. Lastly, the relatively low BMI of our patient population may not reflect the reality of other countries.

CONCLUSIONS

In conclusion, the PROCY trial is the first prospective randomized study with adequate power and an ad-hoc design to investigate the effect of perioperative blood glucose control through oral CHO loading and its influence on the occurrence of surgery-related infection. Our results confirm that this strategy is safe and effective for maintaining a euglycemic state, but without a significant adjustment of the risk of developing infectious complications. Routine administration of oral CHO-rich solution to nondiabetic patients who are candidates for major abdominal operation could be an alternative strategy to prevent serial and repeated blood glucose measurements performed to strictly monitor the kinetics of glucose metabolism and thus could reduce the risk of unidentified potentially dangerous hyperglycemia episodes in the vast majority of patients.

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