# Preoperative carbohydrate loading in diabetic patients undergoing gastrointestinal surgery: A pilot randomized trial

**Xue Li**
Peking University First Hospital https://orcid.org/0000-0003-3437-0870
**Lin Liu**
Peking University First Hospital
**Xin-Quan Liang**
Peking University First Hospital
**Yu-Ting Li**
Peking University First Hospital
**Dong-Xin Wang** ( wangdongxin@hotmail.com )
Peking University First Hospital https://orcid.org/0000-0002-3205-1836

**Research**

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# Abstract

Background

Preoperative carbohydrate loading is used to improve patients' comfort and recovery, but evidence remains limited in diabetic patients. We tested the feasibility of a preoperative carbohydrate drink with supplemental insulin in diabetic patients for gastrointestinal surgery.

Methods

Adult patients with type 2 diabetes mellitus who were scheduled for major gastrointestinal surgery were randomized to carbohydrate group (carbohydrate drink with supplement insulin selectively) or control group (clinical routine management). The primary outcome was the time to first flatus after surgery. Among secondary outcomes, subjective feelings of thirsty, hunger and fatigue were assessed with the Visual Analogue Scale (scores range from 0 to 100, where 0 indicate no discomfort and 100 the most severe discomfort) before and after surgery.

Results

A total of 63 patients were randomized. Time to first flatus did not differ between groups (median [95% CI], 40 hours [30, 50] in control group vs. 43 hours [37, 48] in carbohydrate group, hazard ratio [95% CI], 1.24 [0.74, 2.07], P = 0.411). Both pre- and postoperative subjective feelings of discomfort were all significantly lower in carbohydrate group than in control group (median difference from − 50 to 0; all $P < 0.05$). Patients with carbohydrate drink developed less intraoperative hypotension (40.6% [13/30] vs. 16.1% [5/31], P = 0.031) and postoperative nausea and vomiting within 24 hours (31.3% [10/32] vs. 9.7% [3/31], P = 0.034).

Conclusion

In diabetic patients undergoing gastrointestinal surgery, preoperative carbohydrate loading with supplemental insulin selectively did not affect gastrointestinal recovery; but it improved perioperative comfort, and reduced intraoperative hypotension and postoperative nausea and vomiting.

Trial Registration

ClinicalTrial.gov, NCT03204344; Registered July 2, 2017, https://clinicaltrials.gov/ct2/show/NCT03204344.


# Background

Previous studies proved benefits of preoperative carbohydrate loading, which not only improved perioperative well-being but also decreased insulin resistance after elective surgery (Bilku, et al., 2014; Awad, et al., 2013). Some studies also reported that preoperative oral carbohydrate promoted the recovery

of gastrointestinal function (ÖZdemİR, et al., 2011; An, et al., 2008) and shortened the length of hospital stay without increasing the risk of aspiration (Gianotti, et al., 2018; Smith, et al., 2014). Several guidelines recommend that carbohydrate drinks should be allowed in patients without diabetes undergoing elective surgery until 2 hours before initiating anesthesia (Gustafsson, et al., 2018; Feldheiser, et al., 2016). Currently, available evidences regarding the risks and benefits of preoperative carbohydrate loading mainly come from patients without diabetes. Data on diabetic patients are limited and there are no related recommendations until now.

In a preliminary study of patients with well-controlled type 2 diabetes, Gustafsson et al. (Gustafsson, et al., 2008) found there was no delayed gastric emptying after oral intake of carbohydrate drink, and they suggested it could be administered until 3 hours before anesthesia. Other studies also showed that preoperative carbohydrate loading was safe in type 2 diabetic patients; however, it did not affect postoperative insulin resistance or help to preserve lean body mass after surgery (Azagury, et al., 2015; Breuer, et al., 2006). To be noted, additional insulin was not provided after oral carbohydrate intake in the above studies; and hyperglycemia after surgery might be associated with worse outcomes, such as delayed intestinal recovery, more complications, and longer hospital stay (Hu, et al., 2016; Kiran, et al., 2013; Kwon, et al., 2013).

This pilot trial was designed to test the feasibility of preoperative carbohydrate drink with supplemental insulin in type 2 diabetic patients undergoing gastrointestinal surgery. We hypothesized it would facilitate the return of gastrointestinal function, and thus promote recovery after surgery without increasing hyperglycemia.

## Methods

# Study design

This pilot, observer-blinded, randomized trial was approved by the Biomedical Research Ethics Committee of Peking University First Hospital (2017 − 1362) and registered with clinicaltrials.gov (NCT03204344) on July 2, 2017. Written informed consent was obtained from each patient before enrollment.

# Participants

The inclusion criteria were: (1) age of 18 years and beyond; (2) diagnosed as type 2 diabetes with fasting blood glucose < 10 mmol/L before surgery; (3) scheduled to undergo elective gastrointestinal surgery with anticipated duration ≥ 2 hours. Patients who met any of the following criteria were excluded: (1) comorbid with diaphragmatic hernia or gastric esophageal reflux, or with pregnancy; (2) previous history of total or partial gastrectomy; (3) preoperative pyloric or intestinal obstruction; or (4) preoperative New York Heart Association class IV, renal failure, severe hepatic disease, or American Society of Anesthesiologists class IV or higher.

# Randomization and intervention

Random numbers were generated using the SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA) in a 1:1 ratio with a block size of 4. Randomization was stratified according to the approach of surgery, i.e., laparotomy or laparoscopic surgery. The randomization results were sealed in sequentially numbered envelops until shortly before the enrollment. On the afternoon of the day before surgery, an investigator (XL) opened the envelop and managed the intervention according to the allocation.

Patients randomly assigned to the control group were managed according to routine practice, i.e., they were fasted from solid foods from 22:00 p.m. the night before surgery, but clear water was allowed until 06:00 a.m. on the surgery day. For patients whose surgery was scheduled after 12:00 a.m., 5% glucose (500–1000 ml) through intravenous infusion was prescribed with a glucose-to-insulin ratio of 4–6 to 1 and adjusted according to blood glucose level. Electrolytes were added when considered necessary.

Patients randomly assigned to carbohydrate group were provided with a carbohydrate-rich drink (Outfast [355 ml/bottle, 14.2% carbohydrate, osmotic pressure 280–300 mmol/L, pH 3.8–4.3, and contains maltodextrin, fructose, glucose, arginine, taurine, vitamin B, and electrolyte], Yichang Human-well Pharmaceutical Co., Ltd., China). They were instructed to ingest the carbohydrate drink at 22:00 p.m. the night before surgery, at 06:00 a.m. the morning of surgery. No other clear fluid was allowed. Insulin aspart was injected subcutaneously selectively 10 minutes before giving carbohydrate drink. The volume of carbohydrate drink and the dose of insulin were prescribed by an endocrinologist according to the situation of individual patients (Appendix 1).

# Anesthesia and perioperative management

No anesthetic premedication was administered. General anesthesia was performed in all patients with routine monitoring. Regional anesthesia including epidural or trunk block could be combined with general anesthesia at the discretion of anesthesiologists. Patient-controlled analgesic pump with unified drugs was provided after surgery.

Preoperative mechanical bowel preparation, nasogastric tube insertion and surgical approaches were decided by surgeons according to patients' condition. Parenteral nutrition was prescribed for all patients from the first postoperative day. The time to start water drinking and liquid diet were decided by surgeons. Patients were discharged to home when they met the following criteria: (1) do not require intravenous nutrition; (2) tolerate pain with/without oral analgesics; (3) able to ambulate without assistance; and (4) no severe complications requiring therapy (Fujikuni, et al., 2016; Surgery and Anesthesiology, 2018).

# Data collection and outcome assessment

Baseline data including demographics, comorbidities, laboratory test results and other necessary information were collected. The Charlson comorbidity index was also calculated (Quan, et al., 2011). Intraoperative data about details of anesthesia and surgery were documented.

Subjective well-being feelings including the severities of thirsty, hungry, and fatigue were assessed by investigators who didn't know the allocation (XQL and YTL) using the Visual Analogue Scale (VAS, scores

range from 0 to 100, where 0 indicate no discomfort and 100 the most severe discomfort) at 30 minutes before anesthesia induction and 4–6 hours after the surgery. Patients were followed up daily (09:00 a.m.) by XQL and YTL during the first 5 postoperative days and weekly until hospital discharge. On postoperative day 30, patients were followed-up by telephone interview. Postoperative complications (including re-hospitalization) were defined as newly occurred medical conditions that required therapeutic intervention (class 2 or higher in Clavien-Dindo classification) (Katayama, et al., 2016).

The primary outcome was the time to first flatus. Secondary outcomes included subjective well-being feelings before and after surgery, time to recovery (first ambulation, drink, defecation, and liquid diet, as well as walking distance) after surgery, blood glucose level, occurrence of postoperative complications within 30 days, length of stay in hospital after surgery, and all-cause 30-day mortality. As a post-hoc analysis, we also compared maximal blood glucose fluctuation between groups.

The capillary blood glucose level was measured with a glucometer (Omnitest plus, B.Braun Melsungen AG, Germany) at the following time-points: hospital admission (fasting blood-glucose); 00:00 a.m. (T1, 2 hours after drinking carbohydrate for those in the carbohydrate group) and 06:00 a.m. (T2) on the day of surgery; after anesthesia introduction (T3), the end of surgery (T4), and 21:00 p.m. (T5) on the day of surgery; 06:00 a.m. (T6), 13:00 p.m. (T7), and 21:00 p.m. (T8) on the first postoperative day. From the second postoperative day, blood glucose monitoring was decided by surgeons.

Adverse events were monitored from 22:00 p.m. (i.e., the beginning of carbohydrate drink in the carbohydrate group) until 24:00 p.m. on the first postoperative day. Hypoglycemia was defined as blood glucose < 3.9 mmol/L, with or without symptom. Hyperglycemia was defined as blood glucose > 13.3 mmol/L (Fayfman, et al., 2019; Pasquel, et al., 2017). Aspiration was defined as gastric content appeared in the mouth and entered the trachea or lungs. Hypotension was defined as systolic blood pressure < 90 mmHg or a decrease of > 30% from baseline (average value in the ward). Occurrence of postoperative nausea and vomiting (PONV) within the first 24 postoperative hours was noted. All adverse events were managed according to routine practice.

# Statistical analysis

# Sample size estimation

Based on a preliminary survey in our patients, time to first flatus after gastrointestinal surgery in patients without preoperative carbohydrate loading was 40 ±12.5 hours. We assumed that preoperative carbohydrate loading could decrease the time interval by 9.6 hours (Smith, et al., 2014). With the significance level set at 0.05 and power at 80%, the sample size required to detect differences was 56 patients (28 in each group). Taking into account a drop-out rate of approximately 10%, we planned to enroll 62 patients. Sample size calculation was performed with the PASS 15.0 software (Stata Corp. LP, College Station, TX).

# Outcome analyses

The balance of baseline data between the two groups was assessed with the absolute standardized differences, which were calculated as the absolute difference in means, medians, or proportions divided by the pooled standard deviation (Austin, 2009). Baseline variables with an absolute standardized difference ≥ 0.493 (i.e., $1.96\times\sqrt{(n1+n2)/(n1\times n2)}$) were considered imbalanced and would be adjusted for in all analyses when considered necessary.

Normally distributed continuous variables were compared with two-tailed Student's t-test; non-normally distributed continuous variables and ordinal data were analyzed with Mann-Whitney U test. Categorical variables were compared with Chi-square analysis, continuity correction chi-square analysis or Fisher's exact test. Time-to-event data were analyzed using the Kaplan-Meier survival analysis, with the difference between groups tested by the log-rank test. Repeated measured variables (blood glucose and walking distance) were compared with generalized estimating equation method. Missing data were not replaced. Outcome analyses were performed in the intention-to-treat population. For the primary endpoint, a per-protocol analysis was also performed. A two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed on SPSS 25.0 software package (IBM SPSS, Chicago, IL).

# Results

From August 1, 2017 to May 7, 2018, 63 patients were enrolled and randomly assigned to either the carbohydrate group (n = 31) or the control group (n = 32). All enrolled patients received the allocated intervention, but three patients in carbohydrate group had protocol deviation as they took carbohydrate drink only once at 22:00 p.m. the night before surgery. No patients were lost to follow-up during hospitalization and at day 30 postoperative (Fig. 1).

Among baseline data, glycosylated hemoglobin, hemoglobin and Barthel index were higher in carbohydrate group than in control group; other variables were comparable between the two groups (Table 1). Intra- and postoperative management were comparable between the two groups (Tables 2).

Table 1
Baseline data

| | Control group (n = 32) | Carbohydrate group (n = 31) | ASD |
|---|---|---|---|
| Age, year | 68 (62, 73) | 62 (55, 66) | 0.390 |
| Body mass index, kg/m$^2$ | 25.2 ± 5.1 | 25.4 ± 2.7 | 0.045 |
| Male | 18 (56.2%) | 22 (71.0%) | 0.310 |
| Duration of diabetes mellitus, year | 8.0 (3.3, 12.3) | 7.0 (3.0, 10.0) | 0.215 |
| Antidiabetic therapy | | | 0.483 |
| Lifestyle modification only | 1(3.1%) | 3(9.7%) | |
| Monotherapy with OAD | 10 (31.3%) | 12 (38.7%) | |
| Insulin only | 11 (34.4%) | 5 (16.1%) | |
| Combined OADs w or w/o insulin | 10 (31.3%) | 11 (35.5%) | |
| Other comorbidities | | | |
| Stroke | 3 (9.4%) | 2 (6.5%) | 0.108 |
| Coronary artery disease | 7 (21.9%) | 3 (9.7%) | 0.339 |
| Hyperlipidemia | 19 (59.4%) | 13 (41.9%) | 0.354 |
| Hypertension | 19 (59.4%) | 14 (45.2%) | 0.287 |
| Asthma and/or COPD | 3 (9.4%) | 4 (12.9%) | 0.112 |
| Abnormal hepatic function [a] | 1 (3.1%) | 1 (3.2%) | 0.006 |
| Chronic kidney disease [b] | 2 (6.2%) | 1 (3.2%) | 0.143 |
| History of intestinal surgery | 2 (6.2%) | 0 (0.0%) | 0.365 |

Data are median (interquartile range), mean ± SD, or number (%). Numbers in square brackets indicate patients with missing data.

ASD, absolute standardized difference (an ASD of ≥ 0.493 is considered imbalanced between the two groups); OAD, oral antidiabetic drug; w or w/o, with or without; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association.

[a] Serum aspartate aminotransferase and/or alanine aminotransferase level higher than upper normal limit.

[b] According to the KDIGO (Kidney Disease Improving Global Outcomes) criteria.

scores indicating better daily life activity.

| | Control group (n = 32) | Carbohydrate group (n = 31) | ASD |
|---|---|---|---|
| Smoking within 1 month | 4 (12.5%) | 3 (9.7%) | 0.090 |
| Laboratory test results | | | |
| Glycosylated hemoglobin, % | 6.6 (5.9, 7.5) [1] | 7.3 (6.7, 7.7) [3] | **0.656** |
| Fasting blood-glucose, mmol/L | 7.5 (6.9, 10.4) | 8.1 (6.8, 10.4) | 0.245 |
| Albumin, g/dl | 43.0 (39.1, 45.1) | 42.0 (38.4, 45.6) | 0.222 |
| Creatinine, μmol/L | 76.8 (65.0, 91.0) | 74.8 (63.7, 88.3) | 0.201 |
| Hemoglobin, g/dl | 117.6 ± 30.0 | 133.1 ± 19.1 | **0.618** |
| ASA classification | | | 0.188 |
| II | 21 (65.6%) | 23(74.2%) | |
| III | 11 (34.4%) | 8 (25.8%) | |
| NYHA function class | | | 0.456 |
| I | 21 (65.6%) | 22 (71.0%) | |
| II | 8 (25.0%) | 9 (29.0%) | |
| III | 3 (9.4%) | 0 (0%) | |
| Charlson Comorbidity Index | 0 (0, 1) | 0 (0, 0) | 0.161 |
| Barthel index [c] | 100 (96, 100) | 100 (100, 100) | **0.663** |
| Preoperative preparation | | | |
| Mechanical bowel preparation | 29 (90.6%) | 30 (96.8%) | 0.255 |
| Nasogastric tube insertion | 22 (68.8%) | 27 (87.1%) | 0.454 |

Data are median (interquartile range), mean ± SD, or number (%). Numbers in square brackets indicate patients with missing data.

ASD, absolute standardized difference (an ASD of ≥ 0.493 is considered imbalanced between the two groups); OAD, oral antidiabetic drug; w or w/o, with or without; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association.

[a] Serum aspartate aminotransferase and/or alanine aminotransferase level higher than upper normal limit.

[b] According to the KDIGO (Kidney Disease Improving Global Outcomes) criteria.

[c] Score ranges from 0 to 100, with higher scores indicating better daily life activity.

Table 2
Intra-and postoperative data

| | Control group (n = 32) | Carbohydrate group (n = 31) | P value |
|---|---|---|---|
| Type of anesthesia | | | 0.649 |
| General | 11 (34.4%) | 9 (29.0%) | |
| Combined regional-general [b] | 21 (65.6%) | 22 (71.0%) | |
| Intraoperative medication | | | |
| Sufentanil, μg | 67.0 (28.1, 94.5) | 45.0 (35.0, 64.0) | 0.120 |
| Use of NSAIDs [c] | 21 (65.6%) | 23 (74.2%) | 0.459 |
| Intraoperative fluid balance | 2060 ± 835 | 1941 ± 678 | 0.536 |
| Fluid infused, ml | 2648 ± 810 | 2610 ± 697 | 0.842 |
| Estimated blood loss, ml | 50 (50, 188) | 50 (50, 100) | 0.511 |
| Urine output, ml | 380 (250, 675) | 500 (350, 800) | 0.113 |
| Allogeneic blood transfusion | 2 (6.2%) | 0 (0.0%) | 0.492 |
| Duration of anesthesia, min | 286 ± 77 | 313 ± 70 | 0.149 |
| Type of surgery | | | 0.447 |
| Gastric | 6 (18.8%) | 4 (12.9%) | |
| Colorectal-without colostomy | 14 (43.8%) | 17 (54.8%) | |
| Colorectal-with colostomy | 7 (21.9%) | 3 (9.7%) | |
| Combined [a] | 5 (15.6%) | 7 (22.6%) | |
| Approach of surgery | | | 0.414 |

Data are mean ± SD, number (%) or median (interquartile range). Numbers in square brackets indicate patients with missing data.

NSAIDs, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia.

[a] Includes combined gastric and intestinal surgery, intestinal surgery combined with cholecystectomy/adnexectomy/appendectomy/partial hepatectomy, or reconstruction of bladder with ileum.

[b] Regional anesthesia includes epidural anesthesia or rectus sheath/transversus abdominis plane block.

[c].

| | Control group (n = 32) | Carbohydrate group (n = 31) | P value |
|---|---|---|---|
| Laparoscopic surgery | 23 (71.9%) | 25 (80.6%) | |
| Open surgery | 9 (28.1%) | 6 (19.4%) | |
| Number of drainage tube | 1.0 (1.0, 2.0) [1] | 1.0 (1.0, 2.0) | 0.644 |
| Duration of surgery, min | 198 ± 70 | 221 ± 67 | 0.188 |
| Postoperative PCA | | | > 0.999 |
| Intravenous | 31 (96.9%) | 30 (96.8%) | |
| Epidural | 1 (3.1%) | 1 (3.2%) | |
| Postoperative NSAIDs [c] | 20 (62.5%) | 19 (61.3%) | 0.921 |
| Postoperative fluid balance, ml | | | |
| Day 1 | 979 (80, 1825) | 668 (270, 1238) | 0.413 |
| Day 2 | 1113 (265, 1610) [1] | 850 (500, 1586) | 0.678 |
| Day 3 | 1034 (514, 1697) [3] | 977 (230, 1616) [1] | 0.722 |
| Day 4 | 1100 (320, 1475) [7] | 897 (161, 1643) [3] | 0.803 |
| Day 5 | 993 (888, 1461) [14] | 897 (549, 1556) [11] | 0.633 |

Data are mean ± SD, number (%) or median (interquartile range). Numbers in square brackets indicate patients with missing data.

NSAIDs, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia.

[a] Includes combined gastric and intestinal surgery, intestinal surgery combined with cholecystectomy/adnexectomy/appendectomy/partial hepatectomy, or reconstruction of bladder with ileum.

[b] Regional anesthesia includes epidural anesthesia or rectus sheath/transversus abdominis plane block.

[c] Includes flurbiprofen axetil and parecoxib.

# Effectiveness analysis

The time to first flatus did not differ significantly between groups (median 40 hours [95% CI 30–50] in control group vs. 43 hours [37–48] in carbohydrate group; hazard ratio [HR] 1.24, 95% CI 0.74–2.07, P = 0.411). After adjustment for imbalanced baseline variables in a Cox proportional hazard regression model, there was no significant difference in time to first flatus between the two groups (adjusted HR



ocol analysis also showed similar result (Table 3).

Table 3
Outcomes in all patients

| | Control group (n = 32) | Carbohydrate group (n = 31) | Estimated effects (95% CI) [a] | P value |
|---|---|---|---|---|
| **Primary endpoint** | | | | |
| Time to first flatus, hour | 40 (30, 50) | 43 (37, 48) | HR = 1.24 (0.74, 2.07) | 0.411 |
| Time to first flatus, hour (PP analysis) | 40 (30, 50) | 43 (35, 50) | HR = 1.19 (0.70, 2.00) | 0.522 |
| **Secondary endpoints** | | | | |
| Preoperative subject feeling, score [b] | | | | |
| Thirsty | 60 (20, 78) | 10 (0, 30) | Median D=-33 (-50, -15) | **< 0.001** |
| Hungry | 30 (10, 60) | 0 (0, 20) | Median D=-25 (-40, -10) | **< 0.001** |
| Fatigue | 20 (0, 58) | 0 (0, 10) | Median D=-5 (-30, 0) | **0.004** |
| Postoperative subject feeling, score [b] | | | | |
| Thirsty | 80 (60, 100) [1] | 30 (10, 50) | Median D=-50 (-60, -30) | **< 0.001** |
| Hungry | 30 (0, 60) [1] | 0 (0, 20) | Median D=-20 (-40, 0) | **0.003** |
| Fatigue | 20 (0, 60) [1] | 0 (0, 20) | Median D = 0 (-20, 0) | **0.020** |
| Time to recovery after surgery, hour | | | | |
| First ambulation | 38 (28, 48) | 26 (20, 32) | HR = 1.60 (0.97, 2.65) | 0.068 |
| First ambulation without help | 61 (44, 77) | 41 (29, 53) | HR = 1.17 (0.70, 1.94) | 0.547 |
| First drink | 83 (72, 93) | 92 (82, 101) | HR = 0.97 (0.58, 1.60) | 0.893 |
| First defecation | 93 (54, 132) | 92 (65, 118) | HR = 0.95 (0.58, 1.57) | 0.852 |

| | Control group (n = 32) | Carbohydrate group (n = 31) | Estimated effects (95% CI) [a] | P value |
|---|---|---|---|---|
| First liquid diet | 115 (106, 124) | 136 (118,153) | HR = 0.79 (0.48, 1.30) | 0.350 |
| Length of hospital stay after surgery, day | 8.0 (6.9, 9.1) | 10.0 (8.7, 11.3) | HR = 0.80 (0.49, 1.33) | 0.391 |
| Postoperative complications within 30 days | 7 (21.9%) | 7 (22.6%) | OR = 1.04 (0.32, 3.42) | 0.946 |
| All-cause 30-day mortality | 1 (3.1%) | 0 (0.0%) | — | > 0.999 |
| **Exploratory analysis** | | | | |
| Maximal blood-glucose fluctuation, mmol/L[c] | 6.9 ± 2.8 | 7.1 ± 3.1 | Mean D = 0.2 (-1.3, 1.7) | 0.791 |
| Data are median (95% CI), median (interquartile range), mean ± SD, or number (%). Numbers in square brackets indicate patients with missing data. | | | | |
| HR, hazard ratio; D, difference; OR, odds ratio. | | | | |
| [a] Calculated as carbohydrate group *vs.* or minus control group. | | | | |
| [b] Assessed with visual analogue scale; scale ranges from 0 to 100 where 0 = no uncomfortable feeling and 100 = the most severe uncomfortable feeling. One patient in control group did not provide subject feeling in 4–6 hours after surgery because of mechanical ventilation with moderate sedation. | | | | |
| [c] Calculated as maximal minus minimal blood glucose concentration from the night before surgery to the night of the first day after surgery. | | | | |

Preoperative subjective feeling scores of thirsty (median difference − 33 [95% CI -50 to -15], P < 0.001), hunger (-25 [-40 to -10], P < 0.001), and fatigue (-5 [-30 to 0], P = 0.004), as well as postoperative subjective feeling scores of thirsty (-50 [-60 to -30], P < 0.001), hunger (-20 [-40 to 0], P = 0.003), and fatigue (0 [-20 to 0], P = 0.020) were all significantly lower in carbohydrate group than in control group. Blood-glucose level from the night before surgery to the night of the first day after surgery was higher in carbohydrate group than in control group (P = 0.012, Fig. 2). Other secondary outcomes including time to recovery (first ambulation, drink, defecation, and liquid diet), walking distance, length of hospital stay after surgery, complications within 30 days and all-cause 30-day mortality did not differ between groups. Maximal blood glucose fluctuation was also similar between groups (Table 3; Figs. 3; Appendix 2).

# Safety analysis

Intraoperative hypotension (40.6% in control group vs. 16.1% in carbohydrate group, P = 0.031) and PONV within 24 hours (31.3% in control group vs. 9.7% in carbohydrate group, P = 0.034) were significantly less

in carbohydrate group. The percentage of hypoglycemia and hyperglycemia were similar between groups. No patient developed aspiration during induction (Tables 4).

Table 4
Safety outcome

| | Control group (n = 32) | Carbohydrate group (n = 31) | P value |
|---|---|---|---|
| Hypoglycemia [a] | 1 (3.1%) | 1 (3.2%) | > 0.999 |
| Hyperglycemia [b] | 16 (50.0%) | 15 (48.4%) | 0.898 |
| Aspiration during induction [c] | 0 (0.0%) | 0 (0.0%) | — |
| Hypotension during surgery [d] | 13 (40.6%) | 5 (16.1%) | **0.031** |
| PONV within 24 hours | 10 (31.3%) | 3 (9.7%) | **0.034** |
| Nausea | 10 (31.3%) | 3 (9.7%) | **0.034** |
| Vomiting | 4 (12.5%) | 1 (3.2%) | 0.371 |
| Data are number (%). | | | |
| PONV, postoperative nausea and vomiting. | | | |
| [a] Defined as blood glucose < 3.9 mmol/L, with or without symptom from the night before surgery to the night of the first postoperative day. | | | |
| [b] Defined as blood glucose > 13.3 mmol/L from the night before surgery to the night of the first postoperative day. | | | |
| [c] Defined as gastric content appeared in the mouth and entered the trachea or lungs. | | | |
| [d] Defined as systolic blood pressure < 90 mmHg or a decrease of more than 30% from baseline (average value in the ward). | | | |

# Discussion

Our results showed that, for patients with type 2 diabetes undergoing elective gastrointestinal surgery, preoperative carbohydrate loading with supplemental insulin selectively did not promote the recovery of gastrointestinal function; however, it improved patients' comfort and decreased intraoperative hypotension and PONV.

Return of gastrointestinal function is crucial for postoperative recovery after gastrointestinal surgery (Hedrick, et al., 2018). Time to first flatus/defecation are widely used variables indicating the return of

. In the present study, the median time to first flatus and

defecation were 40 and 93 hours in control group, which were consist with previous results (Dulskas, 2015; Liang, et al., 2011). It was reported that preoperative carbohydrate loading improved the recovery of gastrointestinal function in various surgeries (ÖZdemİR, et al., 2011; An, et al., 2008; Noblett, et al., 2006). However, up to now, sample sizes of available studies were small and conclusions couldn't be drawn regarding gastrointestinal function. For the first time, we investigated the effect of preoperative carbohydrate loading on gastrointestinal function in diabetic patients but did not find any difference between the two groups.

As for secondary outcomes, we found that preoperative carbohydrate loading significantly reduced patients' discomfort and the occurrence of PONV, which improved patients' well-beings during the perioperative period. Our results were consistent with previous studies (Cakar, et al., 2017; Kaska, et al., 2010). In the present study, another interesting finding was that preoperative carbohydrate loading facilitated intraoperative volume and hemodynamic maintenance, evidenced by less intraoperative hypotension. We also found time to first ambulation tended to be earlier in patients with carbohydrate drinks. Other studies reported that preoperative carbohydrate loading was helpful in preserving muscle strength which might promote early ambulation after surgery (Liu, et al., 2018; Gava, et al., 2016; Lidder, et al., 2013).

We did not find any difference in the incidence of postoperative complications and length of stay in hospital after surgery, which were in line with results of recent meta-analyses (Smith, et al., 2014; Amer, et al., 2017). Two reasons might explain this. First, as an important predictor for length of hospital stay, time to return of gastrointestinal function did not differ between groups. Second, alleviating stress and promoting early recovery require multi-disciplinary and multi-module management interventions (Helander, et al., 2019), whereas preoperative carbohydrate loading is only a part of the Enhanced Recovery After Surgery (ERAS) bundles (Gustafsson, et al., 2019; Mortensen, et al., 2014). It is difficult to demonstrate the absolute benefit from a single intervention due to its limited value.

For many years, gastric emptying was thought to be decreased in diabetic patients and they were excluded from trials investigating preoperative carbohydrate loading for aspiration concerns. As a matter of fact, gastric emptying might be accelerated in diabetic patients (Gustafsson, et al., 2008; Mihai, et al., 2018). Studies reported that rapid gastric emptying occurred in those early type 2 diabetic patients (Schwartz, et al., 1996; Phillips, et al., 1992). Similar result was also found in patients with long diabetic course (Weytjens, et al., 1998). In accord with these, none of our patients in carbohydrate group developed aspiration. Another worry when administering carbohydrate loading in diabetic patients is hyperglycemia [9], which may worse perioperative outcomes (Kwon, et al., 2013). To avoid significant blood-glucose fluctuation, we designed a protocol of prescribing volume of carbohydrate drink and dose of insulin according to the individual situation of patients. Our results showed that, although carbohydrate drink increased blood-glucose level, the maximal blood-glucose fluctuation and the rate of hyperglycemia were similar between the two groups, indicating the feasibility of our carbohydrate loading regimen in diabetic patients.

Our study had several limitations. First, we did not measure the residual gastric volume before anesthesia induction, thus direct evidence of sufficient gastric emptying was lacking. Second, carbohydrate drink used in this trial has a high glycemic index. Intermittent blood-glucose monitoring might have missed some higher values. A continuous glucose monitoring device may be more helpful in the future. Thirdly, we did not detect insulin resistance on the first day after surgery.

# Conclusions

Preoperative carbohydrate drinks with supplemental insulin selectively was feasible in diabetic patients undergoing gastrointestinal surgery. Although it did not promote the recovery of gastrointestinal function, it improved patients' comfort and decreased intraoperative hypotension and PONV.

# Abbreviations

**ASA**
American Society of Anesthesiologists
**ERAS**
Enhanced Recovery After Surgery
**ITT**
Intention to treat
**NYHA**
New York Heart Association
**PONV**
Postoperative nausea and vomiting
**PP**
Per-protocol
**VAS**
Visual Analogue Scale

# Declarations

### Ethics approval and consent to participate

This study was approved by the Biomedical Research Ethics Committee of Peking University First Hospital [2017-1362].

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

None


### Funding

None


### Authors' contributions

XL, LL and D-XW contributed to the study concept and design. XL, X-QL and Y-TL contributed to acquisition of data. XL and D-XW analyzed and interpreted the data. XL and LL drafted the manuscript. D-XW critically revised the manuscript for intellectual content. All of the authors read and approved the final manuscript.


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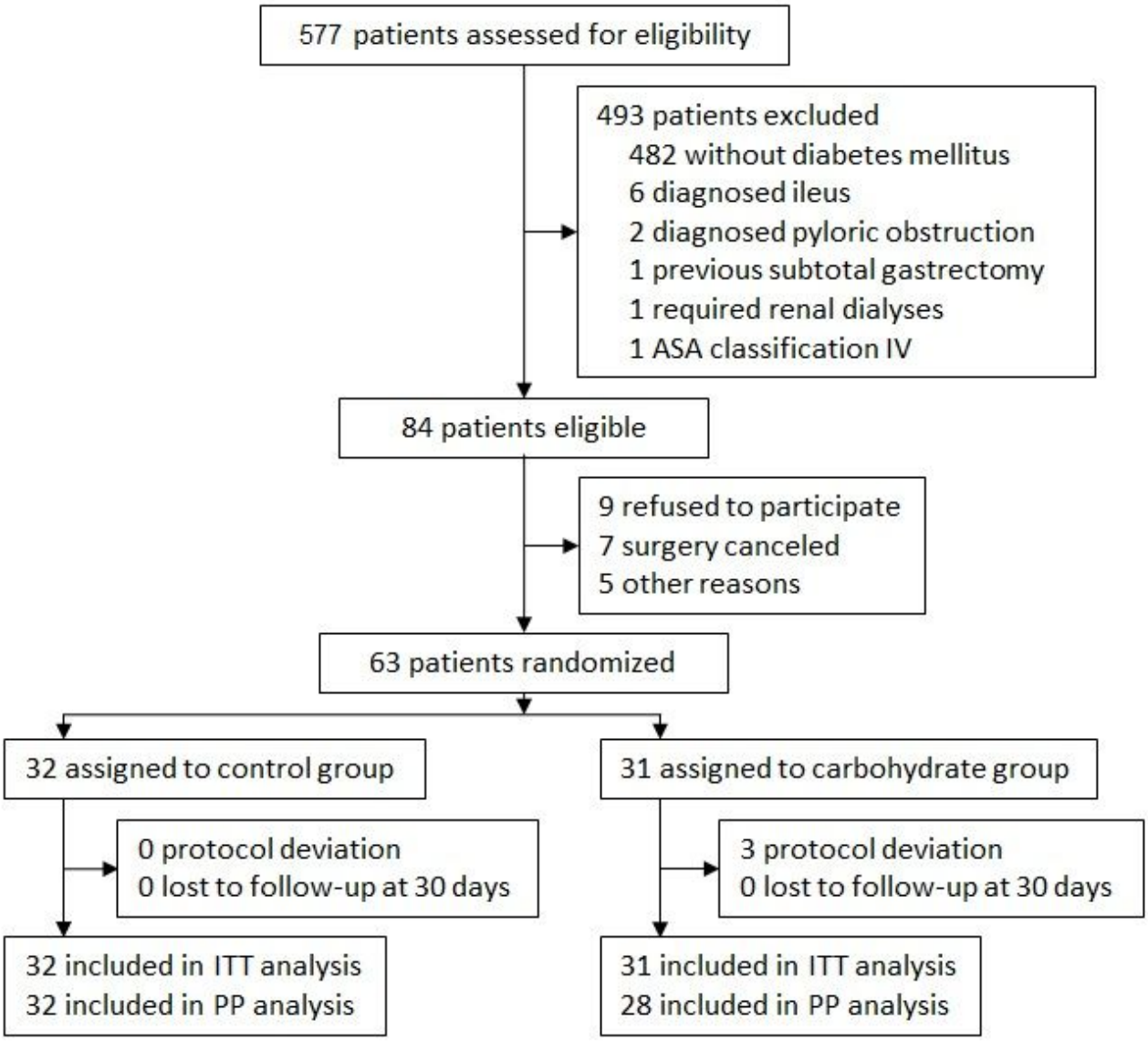
# Figures




## Figure 1

Trial diagram. ASA, American Society of Anesthesiologists; ITT, intention to treat; PP, per-protocol.

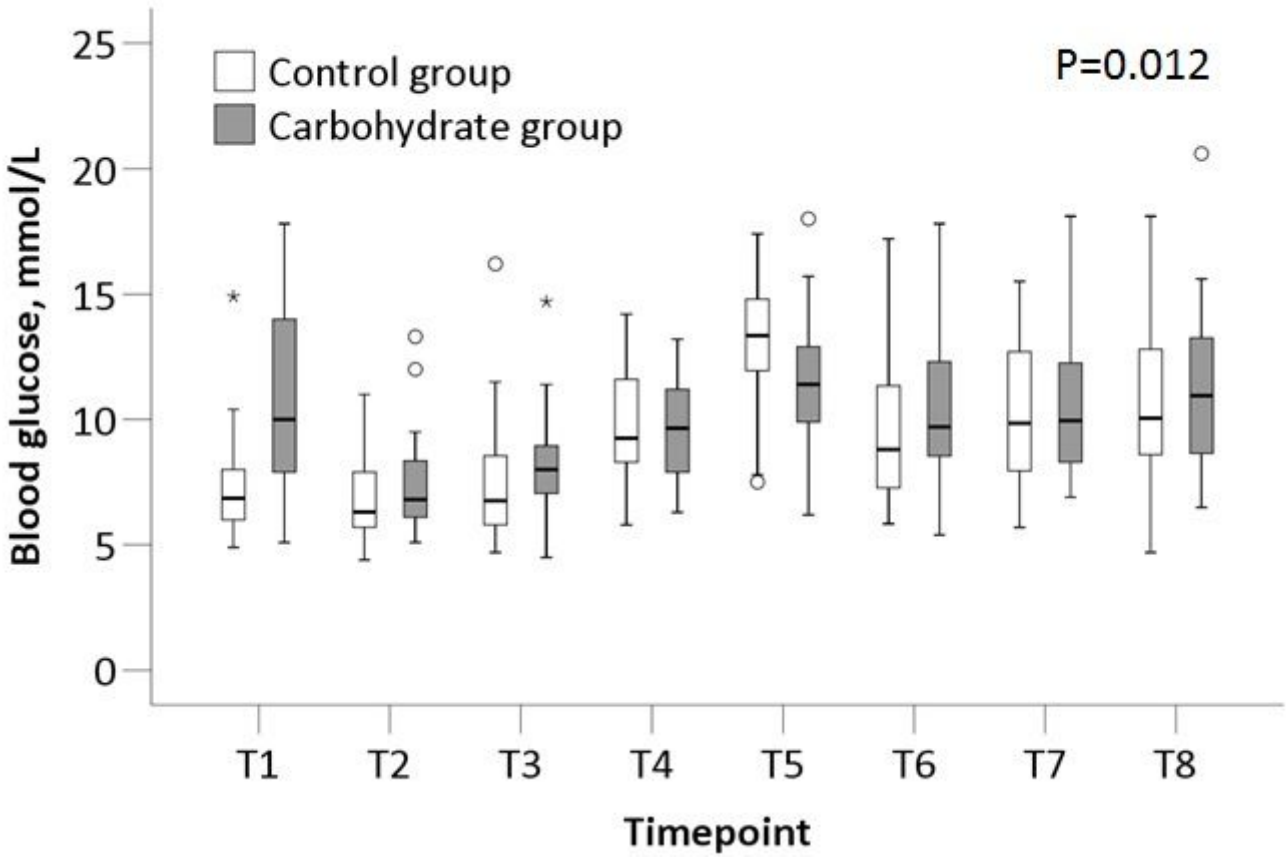



**Figure 2**

Blood-glucose level was higher in carbohydrate group than in control group. T1, at 00:00 a.m. on the day of surgery; T2, at 06:00 a.m. on the day of surgery; T3, immediately after anesthesia induction; T4, at the end of surgery; T5, at 21:00 p.m. on the day of surgery; T6, at 06:00 a.m. on the first day after surgery; T7, at 13:00 p.m. on the first day after surgery; T8, at 21:00 p.m. on the first day after surgery. The box and whiskers plots show medians, interquartile ranges and outer ranges, and individual points mean mild outliers (●, which are outside 1.5 times of interquartile range) and extreme outliers (*, which are outside 3 times of interquartile range).

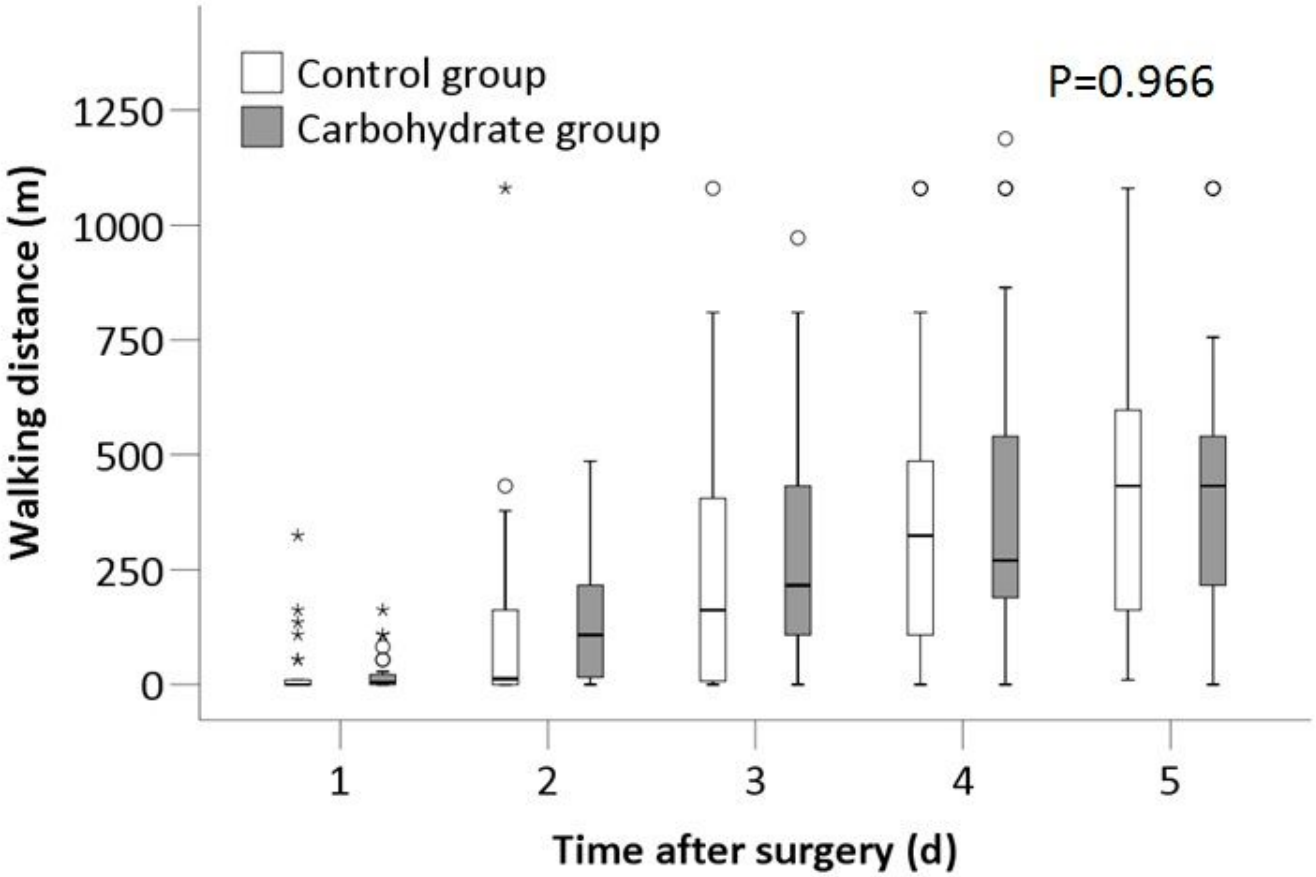



**Figure 3**

Walking distance during the first 5 days after surgery was similar between the two groups. The box and whiskers plots show medians, interquartile ranges and outer ranges, and individual points mean mild outliers (●, which are outside 1.5 times of interquartile range) and extreme outliers (*, which are outside 3 times of interquartile range).

## Supplementary Files

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