Original Article

A randomized controlled trial of preoperative carbohydrate drinks on postoperative walking capacity in elective colorectal surgery

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Background and Objectives: Routine overnight fasting may increase the risk of postoperative complications and delay postoperative recovery. Oral carbohydrate drinks have been shown to reduce glucose utilization and postoperative negative nitrogen balance while preserving muscle mass and strength. This randomized controlled trial aimed to examine whether preoperative oral carbohydrate drinks can enhance postoperative physical recovery in patients undergoing major colorectal surgery. **Methods and Study Design:** Seventy patients were randomly assigned to receive either a 12.5% oral carbohydrate drink or pure water. Patients in both groups received 800-mL of one of the drinks on the evening before surgery, and another 400-mL drink on the morning of the operative day. The primary outcomes were the distances covered in 2-minute-walk tests at 24, 48 and 72-hours and 6-minute walk tests at 7-10 days postoperatively. The secondary outcomes were the postoperative serum insulin and glucose concentrations, nitrogen balance, duration of hospital stay, and the patient satisfaction scores. **Results:** There were no significant differences in the characteristics of the two patients-groups. The postoperative 2-minute and 6-minute walk test distances, serum insulin and glucose concentrations of both groups were not statistically different. Patients receiving carbohydrate drink had more positive nitrogen balance than the control group. The duration of hospital stay and patient satisfaction scores were similar for both-groups. **Conclusions:** There were no statistically significant differences in the postoperative walking capacities of patients receiving a carbohydrate drink or pure water; only the nitrogen balance on postoperative day 3 was higher for patients receiving the carbohydrate drink.

Key Words: oral carbohydrate drink, postoperative physical recovery, walking capacity, colorectal surgery, nitrogen balance

INTRODUCTION
Evidence to optimize preoperative management of surgical patients has been amassed in the past decade. It is well known that prolonged starvation leads to an increase in catabolic pathways that might increase the risk of postoperative complications.[1,2] In addition, overnight fasting has been shown to decrease protein synthesis and increase nitrogen excretion.[3] In response to surgical manipulation, complex cellular interactions produce cytokines, neurohumoral mediators and stress hormones, which alter many metabolic responses, induce catabolic processes, and affect wound healing. The characterizing features of the metabolic response to surgical stimuli are protein catabolism and postoperative insulin resistance. Hyperglycemia is commonly observed in postoperative insulin resistance, and it is associated with increased perioperative complications.[4-6] A new concept has been developed to minimize stress reactions by improving nutritional status before operation.[4,7]

The oral administration of a carbohydrate drink has been suggested as a means of reducing glucose utilization and metabolic disruption. A carbohydrate loading 2–3 hours before anesthesia reduces the prevalence of preoperative thirst, hunger, and anxiety.[8,9] Data from randomized controlled trials and a meta-analysis have indicated that carbohydrate treatment can accelerate recovery and reduce the length of hospital stays after major abdominal surgery.[10,11] The preoperative carbohydrate loading has been shown to reduce postoperative insulin re-

sistance by 50% in several placebo-controlled, randomized studies for various surgical procedures, including colorectal surgery, and to be an independent predictor of some important postoperative clinical outcomes, such as postoperative nausea and vomiting.[1,12,13] Moreover, a carbohydrate drink results in less postoperative loss of nitrogen and protein as well as better-maintenance of lean body mass and muscle strength.[14-19]

Postoperative walking performance has been used as one of the surrogate indicators of overall functional recovery.[20-28] The walking test is sensitive to change after surgery, can evaluate the capacity to maintain a moderate level of walking, and reflects the capacity to perform the activities of daily living.[22] The change in postoperative walking distance correlates well with changes in the levels of postoperative pain and physical function of the postoperative population.[20,29] While there have been reports on various clinical outcomes after preoperative oral carbohydrate loading, including the complication rate and length of hospital stay, the benefits of preoperative oral carbohydrate loading on postoperative functional recovery have not been published.

This prospective, randomized controlled study was designed to investigate whether preoperative oral carbohydrate loading improved postoperative walking performance – one of the indicators of overall functional recovery, and measured with 2-minute and 6-minute walk tests in patients undergoing colorectal surgery.[20,29-33] The secondary outcomes were changing plasma insulin and glucose concentrations from preoperative baselines; perioperative morbidity, measured by postoperative complications; the duration of hospital stay; and the patients' satisfaction levels while staying at the hospital.

METHODS
Patient selection
After Siriraj Institutional Review Board approval (SI 407/2013) was obtained and ClinicalTrial.gov registration (NCT01844375) was finalized, recruitment commenced of patients aged 18–85 years undergoing elective major colorectal surgery at Siriraj Hospital between February 2014 and September 2016. Exclusion criteria were operations starting later than 12.00; anorectal surgery; clinical bowel obstruction; diabetes mellitus; any endocrine disorder or metabolic abnormality; an impaired renal function (glomerular filtration rate <60 mL/min/1.73 m^2); a body mass index >30 kg/m^2; an inability to communicate; and severe physical disability (inability to walk without moving aids). A written informed consent was obtained from each subject.

Randomization and study design
Upon the patients' hospital admission, a stratified randomization was performed regarding the surgical sites (colon or rectum) and surgical techniques (laparotomy or laparoscopy). The patients were randomly allocated to receive carbohydrate drinks or water in the ratio of 1:1, using a computer-generated randomization schedule. The allocation sequence was concealed in sequentially numbered, opaque, and sealed envelopes.

The control group was given pure water, while the carbohydrate group (CHO group) was given a carbohydrate drink (12.5 g of carbohydrate per 100 mL, 80% polysaccharides (maltrodextrin), 20% monosaccharide (glucose), 50 kcal/100 mL, 280 mOsmol/l, pH 7; minerals per 100 mL, sodium 50 mmol, potassium 122 mmol, chloride 13.3 mmol, calcium 6 mmol, phosphorus 1 mmol, magnesium 1 mmol), prepared by the hospital's pharmacy. All patients were given 800 mL of the assigned drink the night before surgery (between 19:00 and 24:00), and another 400 mL on the morning of the operation. The last drink was no later than 3 hours before the scheduled anesthesia induction. The patients' last meal was no later than 24:00 on the day before the operation.

Anesthesia and analgesia
Before induction of anesthesia, a mid-thoracic epidural catheter was inserted as routine in patients undergoing laparotomy surgery. Local anesthetics were injected in the epidural space to produce a bilateral segmental sensory block to ice and pinprick between the T6 and T12 dermatomes. The neural blockade was maintained during surgery through an additional infusion of bupivacaine. Epidural analgesia was omitted in patients undergoing laparoscopy. General anesthesia was done with balanced anesthesia techniques, active warming and zero balanced fluid.

As for the postoperative analgesia, all patients received oral acetaminophen and COX-2 inhibitors around the clock, unless contraindicated, for the first few days after the operation. Patients with a thoracic epidural catheter received 1-2 mg of morphine loading epidurally, and then a continuous epidural analgesia with bupivacaine (0.0625%) and morphine (20 mcg/dL), commencing in the Post-Anesthesia Care Unit; the infusion rate was individually adjusted by the Acute Pain Service (APS) within the range to achieve maximal analgesia without symptoms of paresis of the lower extremities. The postoperative analgesia was assessed daily by the APS and ward nurses as part of routine care. The epidural solution was continued for 48 hours in the surgical ward.

Surgical techniques
Preoperative mechanical bowel preparations were utilized in cases of left-sided colon cancer or rectal cancer. Intravenous prophylactic antibiotics were administered to every patient. All operations were performed by only two, well-experienced surgeons. The choice of incision and operation depended on the tumors' locations and the surgeons' discretion. Intra-abdominal drains, nasogastric tubes, and diverting stomas were not routinely used. Standard postoperative care was provided to every patient.

Patients were allowed to have fluid intake ad lib after the operation, and the ingestion of solid food resumed once their gastrointestinal function had recovered. Patients were discharged when they had adequate pain control, a good appetite, satisfactory mobility, and no fever.

Outcome measures and data collection
The perioperative data were collected daily. The data comprised the demographic characteristics; diagnoses; duration of anesthesia and surgery; conversions to different operating techniques; quality of pain relief; incidence of intraoperative and postoperative complications; length

of the postoperative hospital stays; patient satisfaction; and readmission rate during the 30 days postoperation. The APS and the ward nurses followed the clinical pathway as part of routine care. All data and postoperative outcomes were collected by research assistants who were blinded to group assignment.

Primary outcomes

The primary outcomes were the distances covered in 2-minute and 6-minute walk tests (2MWT and 6MWT). Both were measured before surgery to establish a baseline; the 2MWT was subsequently measured 24, 48 and 72 hours postoperation, while the 6MWT was measured when the patients returned for follow-up 7–10 days after the operation. Patients were asked to walk back and forth at the fastest speed possible along a 30 meters (m) stretch of hallway for 2 or 6 minutes. Walking distances were recorded in meters. If a patient was unwilling or unable to walk, the reason was noted. Calculations of the average walking distances were based on data for patients who were willing or able to walk only.

In keeping with the safety precautions recommended by the American Thoracic Society (ATS), the evaluator had a certification in basic life support and walked behind each patient.[34] Patients could rest, if necessary, and use their regular walking aids; any intravenous lines, tubes, or infusion pumps were attached to a pole and pushed by the patient. The contraindications for the tests were those specified by the ATS.[34] A test was also stopped if a patient reported chest pain, intolerable shortness of breath, or leg cramps, or exhibited staggering, diaphoresis, or a pale/ashen appearance.[34]

Secondary outcomes

Serum insulin and glucose concentrations were measured preoperatively and at 24 hours after the operation. The blood samples for insulin were centrifuged (Cobas 8000 Modular Analyzer Series; Modular Pre-analytics Evo, Roche) at 3000 rpm for 5 min at 22.5°C, and the insulin concentration was measured by a two-site immunoassay using electrochemiluminescence immunoassay (ECLIA; Cobas 8000 modular analyzer series: e 602 module, Roche). The blood samples for glucose were immediately centrifuged (Kokusan H-28F, Euroscan) at 3500 rpm for 10 min at 25°C, and the glucose concentration was measured using an enzymatic (Hexokinase) method (Cobas Integra 800 Analyzer; C 702 Module, Roche).

24-hour urine urea nitrogen was measured on the first-three postoperative days. The urine samples were centrifuged (Cobas 8000 Modular Analyzer Series; Modular Pre-analytics Evo, Roche) at 3000 rpm for 5 min at 22.5°C, and measured using a urease/glutamate dehydrogenase coupled enzymatic technique (Cobas 8000 Modular Analyzer Series: C 702 Module, Roche). The nitrogen balance was calculated by measuring urinary urea nitrogen and dietary nitrogen intake during the same 24-hour period. The nitrogen intake was estimated for each patient following a doctor's diet order and types of food formulas in hospital, and then dividing the daily protein intake by 6.25. The urine urea nitrogen was added by 4 to account for non-urinary losses of nitrogen.

The duration of the hospital stays were measured in days, from the day of surgery to the day of discharge. Patient satisfaction during the hospital stay was assessed upon discharge using a VRS from 0 to 100 (0 = least satisfied; 100 = most satisfied). The incidence of medical and surgical complications and the readmission rates in the 30 days after the operation were recorded.

Sample size calculation and statistical analyses

The calculation of the sample size was based on two previous studies, which showed a change of 20 m in the 6MWT is considered to be clinically meaningful, and a difference of approximately 10 m in the 2MWT has been shown to discriminate between people with New York Heart Association Functional Classification Classes I and II, and people with Classes III and IV.[31,35-37] The calculation was done to detect a 10-m difference with a standard deviation of 13-m in the 2MWT and provide a type I error of 0.05 and a power of 80%, using nQuery Advisor version 7.0 (Statistical Solutions, Cork, Ireland).[15,35] The calculated sample size per group was 29 patients; this figure was then increased to 35 patients per group to allow for a 20% dropout rate.

Categorical variables were presented as number and percentage, and analyzed by the Chi-square test or Fisher's exact test. Continuous variables were presented either as a mean and standard deviation (SD) or as a median and an interquartile range (IQR) if the data were not normally distributed. Comparisons between the groups were made using the Student's t-test or the Mann–Whitney U test, as appropriate. All statistical tests were two-tailed, and p values of less than 0.05 were considered as statistically significant. The statistical analyses were performed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL).

RESULTS

A total of 171 patients were assessed for eligibility, 70 of whom were enrolled for randomization; 68 were finally analyzed. A CONSORT flow diagram is at Figure 1. The demographic data of the patients from both groups is at Table 1; there were no statistically significant differences between the two groups.

The preoperative baseline 2MWT- and 6MWT-distances for the two study groups were comparable (p=0.792 and p=0.695; Table 2). A number of patients declined to perform the 2MWT. On postoperative day 1, 12 (35%) patients from the CHO group and 14 (41%) from the control group did not walk for multiple reasons: postoperative pain (18), dizziness (4), uncomfortable to walk (2), abdominal discomfort (1), and postoperative nausea (1), with no significant difference between the two groups. On postoperative day 2, 5 patients (15%) in each group did not participate, while on postoperative day 3, only 4 patients opted out.

After surgery, the median distances for the 2MWT on postoperative day 1 for both groups were approximately a half of the preoperative baseline figures. For each group, the median 2MWT distances increased slightly on postoperative day 2 and day 3, respectively. However, there were no statistically significant differences in the 2MWT distances of both groups on postoperative days 1, 2 or 3 (Table 2).
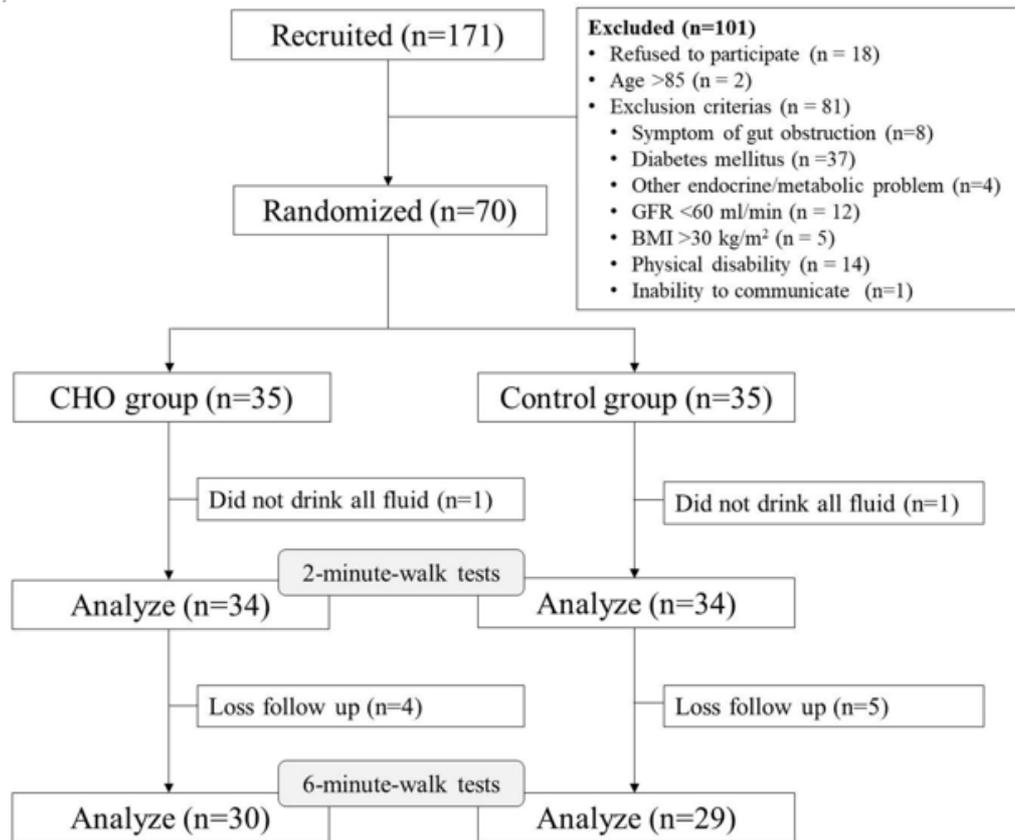
Figure 1. *CONSORT* flow diagram of study protocol.

Table 1. Patients' demographic characteristics, operations and surgical techniques

	CHO group (n=34)	Control group (n=34)	p value[†]
Age	62.9±10.2	62.7±9.7	0.942
Men	17 (50.0)	21 (61.8)	0.464
Body mass index (kg/m^2)	22.1±3.1	23.2±3.9	0.201
ASA ≥3	5 (14.7)	4 (11.8)	0.670
Diagnosis: Cancer	29 (85.3)	33 (97.1)	0.197
Operations			0.330
Colon surgery	18 (52.9)	13 (38.2)	
Rectal surgery	16 (47.1)	21 (61.8)	
Surgical techniques			0.270
Open surgery	21 (61.8)	17 (50.0)	
Minimally invasive surgery	13 (38.2)	17 (50.0)	

CHO: carbohydrate; ASA: American society of anesthesiologists physical status.

Data are presented as mean±SD for continuous variable or number (%) for categorical variable.

[†]p value based on analyses between two studied groups using Student's t-test for continuous variable; chi-square test or Fisher's exact test for categorical variable.

For the biochemical analyses, there were no significant differences in the changes to the postoperative blood sugar and insulin concentrations of both groups. However, patients from the CHO group tended to have nitrogen balance figures which were more positive than the figures of patients from the water group, especially on postoperative days 2 and 3 (p = 0.086 and 0.022, respectively; Table 3).

The medians duration of hospital stay were 5.5 days for the CHO group and 6 days for the control group (p=0.494). Moreover, the patients' postoperative satisfaction score was higher for the CHO group (90/100 vs 90/100), but there was no significant difference (p=0.794).

Six CHO-group patients and four control-group patients had postoperative complications. Two patients in each group had an infected surgical wound, but recovered with antibiotics and dressing. In addition, 2 CHO-group patients and 1 control-group patient had bowel ileus and needed conservative treatment, while 1 patient in each group had an anastomosis leakage requiring a reoperation.

DISCUSSION

This study demonstrated that preoperative carbohydrate drinks had no effect on supporting postoperative functional recovery, as evaluated by walking performance. The authors recruited only two, experienced surgeons for this study to minimize the impact of variations in surgical

Table 2. Baseline and postoperative 2- and 6-minute-walk-test distances

Meters	CHO group (n=34)	Control group (n=34)	p value†
Preoperative baseline			
2MWT	112 [90, 135]	109 [97, 127]	0.792
6MWT	327 [288, 406]	327 [282, 371]	0.695
Postoperative 2MWT			
Day 1	52.5 [35, 68] (n=22)	48.5 [38, 59] (n=20)	0.668
Day 2	75 [49.5, 98] (n=29)	58 [47, 66] (n=29)	0.155
Day 3	70 [48, 102] (n=30)	64 [55, 94] (n=33)	0.751
Postoperative 6MWT			
Day 7–10	325 [287, 377] (n=30)	333 [246, 373] (n=29)	0.505

CHO: carbohydrate; MWT: minute walk test.
Group data are presented as median [interquartile range].
†p value based on analyses between two studied groups using Mann–Whitney U Test.

Table 3. Biochemical analyses

	CHO group (n=34)	Control group (n=34)	p value†
Blood sugar concentration (mmol/L)			
Preoperative baseline	6.0 (4.9, 6.7)	5.1 (4.8, 5.6)	0.025
Postoperative 24 hours	7.4 (6.7, 8.2)	6.8 (5.9, 7.6)	0.032
Postoperative - Preoperative	1.4 (0.5, 2.6)	1.5 (0.9, 2.2)	0.893
Serum insulin concentration (μU/mL)			
Preoperative baseline	9.5 (5.8, 20.6)	7.6 (4.8, 19.4)	0.367
Postoperative 24 hours	12.9 (9.7, 27.1)	13.6 (5.6, 24)	0.397
Postoperative - Preoperative	3.2 (-7.1, 11.9)	3.8 (-3.5, 8.2)	0.825
Nitrogen balance (g/day)			
Postoperative day 1	-7.4 (-10.4, -4.8)	-9.9 (-12.3, -7.5)	0.114
Postoperative day 2	2.4 (-6.8, 4.9)	-3.8 (-9, 4.1)	0.086
Postoperative day 3	4.7 (2.9,6.3)	3.1 (-4.8, 5.3)	0.022

CHO: carbohydrate.
Group data are presented as median (interquartile range).
†p value based on analyses between two studied groups using Mann–Whitney U Test.

techniques. Nevertheless, there were many confounding factors influencing patients' walking performance. This was especially evident on postoperative day 1, when factors such as the following came into play: postoperative pain, abdominal discomfort, dizziness, nausea, discomfort from multiple line access, or simply bargaining because patients wanted to rest.

A study published in 2002 demonstrated the effects of preoperative oral carbohydrates and peptides on the postoperative strength of patients undergoing abdominal surgery; it employed a dynamometer to assess patients' hand grip and quadriceps muscle function 7 days, 1 month and 2 months postoperatively.[17] However, this study did not examine the effects of the preoperative carbohydrate drink on walking capacity during the first-three postoperative days. This may be because a change to only one factor influencing the strength of the quadriceps muscles is not enough to enable patients to walk better. Alternatively, patients may simply require a longer recovery period to build more quadriceps muscle strength in order to manage longer walking distances.

In this study during 24-hours postoperatively, less-changed blood sugar and insulin concentrations for the CHO group than the control group were presented; nevertheless, the actual changes in the blood sugar and insulin concentrations of the two groups were not statistically significant (p=0.893 and p=0.825; Table 3). This data is similar to the results about the insulin resistance of a study published in 2005, which showed no difference in

patients undergoing abdominal surgery who received a preoperative carbohydrate drink and those who were given placebo drinks.[16] A similar result was found in the 2005 study for the nitrogen balance in the first-three postoperative days: patients receiving the carbohydrate drinks tended to have a more-positive figure for the nitrogen balance than those patients receiving pure water. Although a 2007 study demonstrated the effects of the preoperative oral carbohydrate on insulin resistance, the present study did not examine this effect.[15] A larger sample size may be required to demonstrate an effect on insulin resistance.

The median duration of the hospital stay in this study was similar to the results of previous studies, which demonstrated that the ingestion of preoperative carbohydrate drinks did not decrease the duration.[16,38] Moreover, the patients' satisfaction levels in this study were quite high for both groups. This is also comparable to previous studies, which used a VAS score to assess patients' well-being, thirst, anxiety, and fatigue: no significant differences between the carbohydrate and water groups were evident.[16,38]

No obvious complications were associated with the preoperative carbohydrate drinks: the incidences of postoperative complications in the two groups were not significantly different, and no incidents of aspiration were reported. Therefore, this study clearly demonstrates that the ingestion of preoperative carbohydrate drinks does not increase postoperative morbidity and mortality, compared

with pure water. This confirms the study published in 2005 that showed that the preoperative imbibing of carbohydrate-containing fluids is safe; in that study, there were no instances of perioperative aspiration, and no significant differences in the incidence of postoperative complications in the carbohydrate and placebo groups.[16]

Conclusion

The ingestion of preoperative oral carbohydrate drinks is safe. There were no statistically significant differences in the clinical outcomes, the biochemical analyses or the recovery times of patients undergoing elective colorectal surgery who received the preoperative oral carbohydrate drink versus those given pure water. Further studies are required to evaluate the improvements in functional recovery over a longer postoperative period.

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