Effect of preoperative carbohydrate intake on inflammatory factors and clinical outcomes in elderly patients undergoing radical prostatectomy: a single-center, double-blind randomized controlled trial

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Research article

Keywords: carbohydrate, radical prostatectomy, inflammatory factors

DOI: https://doi.org/10.21203/rs.3.rs-26717/v2

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Abstract

BACKGROUND: To investigate the advantages of Carbohydrate (CHO) in inflammatory markers, comfort and clinical outcomes in elderly patients undergoing open radical prostatectomy.

METHODS: Patients of ≥65 years old with radical prostatectomy who underwent open radical prostatectomy were randomized to the CHO group, water group, and fasted group. Patients in the CHO group and water group received oral CHO, 800 ml of placebo water before surgery, and oral CHO and placebo water 400 ml 2 to 3 hours before surgery; the fasted group did not drink any liquid. The main outcomes are inflammatory markers. The secondary outcomes are cellular immunity, comfort, the index of grip strength of body mass and clinical outcomes.

RESULTS: A total of 90 patients were included in current study (i.e., CHO group, n=28; water group, n=30; fasted group, n=32). The three groups matched well in age, body mass index, the grade of (American Society of Anesthesiologists) ASA, operation time, blood loss, and fluid volume. CHO reduces IL-6 of Day1 and Day7 (P = 0.009, 0.005, respectively), IL-8 (P=0.005) of Day1, Day1, Day 3, and Day 7 TNF (P = 0.001, 0.006, 0.003 respectively) compared with the fasted group ; placebo water reduced Day 1 and Day 7 TNF (P = 0.005, 0.038, respectively), Day 1 of IL-8 (P = 0.045). CHO reduced Day3 of TNF (P=0.026) compared to placebo water. In the CHO group and the water group, the morning thirst scores (0.68, 1.26, respectively) and starvation (0.24, 0.47, respectively) were decreased. The first time to leave bed in the fasted group (39.21 (15-93) h) was much later than in the CHO group (28.57 (10-100) h) and the water group (28.71 (12-70) h).

Conclusion: Compared with routine water ban, preoperative CHO and placebo water can reduce the levels of IL-6, IL-8 and TNF in elderly patients undergoing radical prostatectomy, which can improve the patient's preoperative comfort and shorten the patient's first time to leave bed. Compared with placebo water, CHO has no significant advantage in improving inflammatory markers and clinical outcomes.

Background:

Patients who undergo radical prostatectomy are generally old with more comorbidities. Surgical trauma generally cause a longer recovery times therefore a need for accelerated rehabilitation is required. . With the popularity of enhanced recovery after surgery(ERAS) [1-2], preoperative oral carbohydrate (Carbohydrate, CHO) has become a common clinical practice [3-4]. Drinking CHO before operation can reduce insulin resistance, reduce protein loss, and significantly reduce hunger and anxiety of patients before operation without affecting gastric emptying. CHO can make the intestinal function recover early and shorten the hospitalization time [6]. At present, the most common studies are the effects of CHO on insulin resistance and comfort, and the effects of minimally invasive surgery [9] and unconventional fasting [10] on postoperative immune function. There are few studies on the improvement of postoperative immune function by CHO.
Major open abdominal or pelvic surgery has a higher incidence of postoperative adverse events, like cardiopulmonary insufficiency, pain, thromboembolic complications and infection. The main reason is the stress response caused by surgical trauma, followed by a relatively high-level demand of patient's immunity and energy reserve. The relatively high-level demand for patient's organ function is thought to be mediated by endocrine and metabolic changes caused by trauma.

The levels of cytokines C-reactive protein and cytokines are closely related to the immune reaction, the inflammatory response and the extent of the inflamed tissue. The level of IL-6 is related to the incidence of postoperative complications, and it is one of the predictors of the incidence of adverse events after surgical intervention.

**Methods:**

Patients who underwent open radical resection of prostate cancer in the Shanghai Tenth People's Hospital were selected for this study. The inclusion criteria were as follows: elective radical resection of prostate cancer, age range from 65 to 85 years old, body mass index (BMI): 17.0-32.0 kg/m², American Society of Anesthesiologists (ASA) grade: I~III, and normal heart, lung, liver, kidney, and blood coagulation function. Oral anticoagulants were stopped for 5-7 days before operation. The exclusion criteria were as follows: below 65 years of age, inability to drink transparent liquid or allergy, gastrointestinal emptying disorder or obstruction, diabetes, liver cirrhosis, severe cardiac and renal insufficiency, corticosteroids for more than 5 mg/ days and (ASA) IV and above of the American Association of Anesthesiologists. The trial was approved by the Ethics Committee of the Shanghai Tenth People's Hospital, and all patients signed a written informed consent form before randomization.

All patients were randomly divided into three groups: carbohydrate group (CHO), placebo group (Water group) and routine water abstinence group (Fasted group). The patients were randomly divided into three groups by the method of random number table and the method of random number remainder grouping. The specific operation method is as follows: according to the required sample size of 120 cases, 120 two-digit random number series are generated by the method of random number table. The order of the remainder obtained by dividing the two-digit random number series by 3 is the order in which the patients are randomly divided into three groups. Finally, the grouping scheme is written in a sealed envelope. The patients in the group were assigned to the grouping scheme marked in the sealed envelope in turn: carbohydrate group or placebo group or routine water abstinence group. Patients and researchers are unaware of the patient's fluid distribution. Fluid was given to patients by a person who knew the distribution of CHO and placebo water and was not involved in the study.

Patients who met the criteria were selected and randomly assigned to the CHO group (CHO) or water group (placebo) or routine water deprivation group (fasted group) according to the envelope clue. CHO (Su Qian, commonly known as maltodextrin fructose drink) and placebo products are produced by
Jiangsu Zhengda Fenghai Pharmaceutical Co., Ltd., and both products have the same outer packaging. After completing data entry and database locking, the company released the product code to the researchers. The study design is shown in Figure 1 and Flow chart is shown in Figure 2.

All three groups of patients were fasted with solid food for at least 6 hours before surgery. From 19:00 to 24:00 on the evening before the operation, patients in the CHO group were given 800 ml of a CHO drink (Su Qian contains 12.6% CHO, 50 kcal/100 ml, 290 mOsm/kg, pH 5.0, 200 ml per bottle). On the day of the operation, the patients in the CHO group consumed about 400 ml of Su Qian 2 to 3 h before the scheduled induction of anesthesia, with an interval of more than 20 minutes. Patients in the water group were given the same amount of seasoning water at the same time (sucralose 0 kcal/100 ml, citric acid 0 kcal/100 ml, 107 mOsm/kg, pH 5.0), which had the same taste and appearance as the CHO drink. In the routine fasted group, no uid was given before operation. To ensure the smooth implementation of the experiment, these patients were usually scheduled for the first operation on the surgery day. All operations were performed by the same group of experienced urological surgeon.

All patients received the same general anesthesia regimen, sufentanil 0.25 ~ 0.5 μg / kg, propofol 1.5~2mg/kg, cis atracurium benzenesulfonate 0.2mg/kg general anesthesia induction. After endotracheal intubation, sevoflurane inhalation maintained anesthesia to maintain the end-expiratory sevoflurane volume fraction at 0.9-1.2 minimum alveolar effective concentration, remifentanil 2-5 μg / kg/h for analgesia, and cis-atracurium besylate for 4-10 mg/h to maintain muscle relaxation. During the operation, fluid infusion was guided according to blood pressure, heart rate, bleeding and urine volume. Sodium lactate Ringer's solution was mainly used, hydroxyethyl starch was used as a supplement, crystal: glue = 3 / 1, and appropriate adjuvant vasoactive drugs.

After the operation, the patients were encouraged to sit by the bedside or get out of bed as soon as their health conditions permit. If there was no nausea and vomiting, the patients were asked to drink water and eat as soon as possible. Infection is defined as the presence of sepsis, which can be diagnosed as sepsis: body temperature > 38 °C or < 36 °C; heart rate > 90 beats / min; systolic blood pressure ≤ 100mmHg; respiratory rate > 22 beats / min or PaCO2 < 32 mmHg (< 4.3 kPa); white blood cell count > 12 × 109xL or < 4 × 109xL or immature cells > 10%); change of consciousness.

At approximately 7 AM before the operation, the venous blood of the patients was collected to the measure the levels of interleukin (IL), tumor necrosis factor (TNF), C-reactive protein (CRP), and cellular immunity. Venous blood samples were obtained repeatedly at the same time on days 1, 3, and 7 after the operation. In addition, the comfort and grip strength of the patients were measured at the same time before the operation and on days 1, 3, and 7 after the operation. Comfort was measured by a 100-mm visual analogue scale (VAS) [11] on the following parameters: anxiety, hunger, thirst, nausea, and fatigue. The grip strength was measured using a grip force device, and all measurements were performed using the same dominant hand. The first exhaust time, the independent standing time after surgery, the time to intake of water, and the time to intake of oral diet were recorded, and the results related to postoperative infection were assessed.
Outcome indicators:

1. Main outcome indicators: level of inflammatory markers (IL-1, IL-2, IL-6, IL-8, IL-10, TNF, and CRP).
2. Secondary outcomes: cellular immunity level (CD3, CD4, CD8, CD4/CD8, CD19, CD16/CD56), comfort (anxiety, hunger, thirst, nausea, fatigue), the index of grip strength of body mass (grip strength (kg)/body weight (kg) × 100%), clinical outcomes (first exhaust time, independent standing time after surgery, time to intake of water, time to intake of oral diet, and incidence of postoperative infection).

Statistical analysis: SPSS 19.0 statistical software was used for analysis. The measurement data of normal distribution were expressed as mean ± standard deviation ( ), and t-test was used to compare two independent samples. For the repeated measurement data, repeated measures analysis of variance was used to compare different time points in the group, and multivariate analysis of variance was used to compare the groups at the same time point. The measurement data of non-normal distribution were expressed as median, and the counting data were compared by the chi-square test. Multivariate logistic regression was performed using the pre- and intra-operative factors, including age, BMI, operation time, group, blood loss, fluid intake to determine the factors associated with elevated IL-6 level after operation. Differences with \( P \leq 0.05 \) were statistically significant.

Results:

It has been shown in Table 1 that three groups matched well in age, body mass index, preoperative blood glucose, ASA, operation time, bleeding volume and fluid replacement volume. The patient characteristics, operation time, and fluid replacement volume is shown in (Table 1). One patient in Placebo Group with intraoperative bleeding of 900ml was infused with 1U of red cell suspension.

It has been shown in Figure 3 and Table 2 that compared with conventional water deprivation, CHO decreased the IL-8 of Day1 and Day1, IL-6 of Day1 and TNF of Day 7; placebo decreased the TNF of Day1 of Day7 and IL-8 of Day1. Compared with the placebo group, CHO decreased the TNF of Day3. There was no statistical difference in IL1, IL2, IL10, CRP among the three groups. There was no statistical difference in the indexes of cellular immunity.

It has been shown in Table 3 that compared with the routine fasted group, the CHO and water groups showed a significant decrease in the thirst score (0.68 and 1.26, respectively, \( P \leq 0.001 \)) and hunger score (0.24 and 0.47, respectively, \( P<0.05 \)) in the morning of the operation day, but no difference was observed in the weight grip strength index among the groups.

It has been shown in Table 4 that the independent standing time after surgery of the routine fasted group was 39.21 h (15-93 h), which was much later than those of the other two groups (CHO, 28.57 (10-100) h; water group, 28.71 (12-70) h). There was no difference in the first exhaust time, the time to intake of
water, and the time to intake of oral diet among the three groups. Moreover, no significant difference in postoperative infection incidence was noted among the three groups within 7 days after the operation.

Furthermore, in order to determine whether group was an independent variable among various pre- and intra-operative factors for post-operative inflammatory reaction, taking elevated IL-6 level 7 days post operation as representative, we performed multivariate analysis. The results showed that older age, higher BMI, longer operation time and group were all independent factors associated with higher IL-6 level (all \( p < 0.05 \)). (Table 5)

**Discussion:**

The indexes of clinical evaluation of immune function are inflammatory markers (IL such as IL-2, IL-6, IL-8, and IL-10; TNF; and CRP) and cellular immunity (T cells, T helper cells, NK cells, and human leukocyte antigen DR (HLA-DR)). Usually, the decrease in inflammatory markers and the increase in the level of cellular immunity indicate a better immune function of the individual [13-14]. To reduce the incidence of postoperative complications, some studies have suggested that accelerating rehabilitation surgery, especially minimally invasive surgery [15], and unconventional fasting before operation can improve the immune function after operation, reduce the level of inflammatory response, and increase cell-mediated specific immunity. In 2006, the GERDIEN [16] team studied the effects of preoperative oral CHO-rich liquid diet on postoperative immune function. Compared with the routine water deprivation group before operation, the oral CHO floating diet group did not a decrease in HLA-DR, and the body's fluid balance in this group was not significantly disturbed. This shows that preoperative oral administration of CHOs can avoid the subsequent immune response and reduce the occurrence of infectious complications. However, another study by Mathur showed that CRP and IL-6 levels had no effect on systemic inflammation in patients undergoing major abdominal surgery [17]. Therefore, the authors consider that there is no evidence that the CHO load is essential to reduce surgical stress response. Tran [18] found that the levels of IL-6 and CRP were not affected by the preoperative use of CHO during coronary artery bypass grafting and spinal surgery.

The analysis of the present study showed that, in terms of the overall trend, compared with the routine fasted water group, the levels of inflammatory markers of the oral water placebo and CHO groups were lower, with an apparent decrease in the CHO group. Compared with the routine fasted water group, the CHO group showed a decrease in TNF on the first, third, and seventh day after the operation, a decrease in IL-6 on the first and sixth day after the operation, and a decrease in IL-8 on the first day after the operation. The reduction in TNF and IL-8 levels on the first and seventh day after the operation indicated that the CHO and water groups had a significant advantage in terms of reduction in postoperative inflammatory markers. CHO administration decreased TNF only on the third day after the operation when compared with the oral water group; thus, it may not have much advantage in terms of reduction in the levels of inflammatory markers. In other words, taking a certain amount of liquid before operation,
regardless of whether it is CHO or sweet water or other clear liquid, has a similar effect on postoperative inflammatory markers. Su Qian is an energy-rich carbohydrate drink, while placebo water is an energy-free clear liquid; the difference between these two drinks is that their sugar and energy content is 1 and 0, respectively. Sugar and energy may not play an important role in regulating the levels of inflammatory markers, and the intake of a certain amount of liquid before operation may play a decisive role in postoperative outcome. Compared with routine water deprivation, the intake of a certain amount of liquid before operation can significantly reduce the level of inflammatory markers in the body. Although the IL-6, IL-8, and TNF levels showed significant differences among the three groups, no difference was noted in the indices of cellular immunity and the incidence of postoperative infection among the three groups; thus, no clinical significance of CHO administration could be established. Because several factors affect the incidence of postoperative infection, the present study suggests that preoperative use of liquid may not be a key factor for reducing postoperative infection incidence.

After multivariate analysis, it was found that age, BMI, operation time and grouping were the independent risk factors for the increase of postoperative IL-6 of Day7, that means that the older the age leads the higher BMI and the longer operation time, and the grouping were the independent risk factors for the increase of IL-6 7 days after operation. The IL-6 of CHO, Placebo and Fasted increased in turn at 7 days after operation, which were 7.9 ±6.27 pg/ml, 18.29 ±19.95 pg/ml, 27.49 ±33.83 pg/ml, respectively. It is suggested that preoperative administration of CHO or placebo can inhibit the increase of IL-6 to some extent, and the effect of CHO is better than that of placebo.

Several studies [19-20] have shown that preoperative administration of CHO can significantly reduce preoperative hunger and anxiety, and does not affect gastric volume. The present study found that the preoperative administration of fluid, either CHO or clear liquid, can significantly improve thirst and hunger scores in the early morning (usually 90 to 120 min after drinking the liquid in the morning) when compared with conventional water deprivation. A similar effect was observed for the comfort parameters on the operation day. Furthermore, perhaps drinking liquid, not necessarily CHO, can significantly improve patient comfort.

The time of getting out of bed is affected by many factors such as medical staff education, renewal of medical cognition, patients’ fear of getting out of bed, and postoperative pain. The independent standing time after surgery for the CHO and water groups for patients who got out of bed after the operation was shorter than that for the routine water deprivation group; this was a surprising result in this study. This finding shows that the intake of liquid before operation can actually lead to better clinical outcome of patients. CHO, however, had no real advantage over the oral placebo water.

Some studies [21] have identified that the preoperative CHO load is associated only with a small reduction in the time of hospital stay, and has no effect on the incidence of complications. In China, the length of hospital stay is affected by many factors; therefore, the postoperative time of hospital stay was not included as a clinical outcome of this study. Compared with the Veenhof [15] team study, this study added a group of placebo water control; compared with the Mathur [17] team study, this study added a
group of blank controls. The present study showed that CHO and placebo water had the same advantage in reducing the levels of inflammatory markers, but there was no significant difference in postoperative infection incidence among the three groups. The present study has some limitations. The sample size was small, and the level of inflammatory markers was not necessarily positively correlated with the infection incidence. The effects of CHO or clear liquid on inflammatory markers and clinical outcomes in elderly patients who undergo major surgery thus need to be further studied.

**Conclusions:**

Compared with conventional water deprivation, the intake of CHO and oral water before operation can reduce the levels of IL-6, IL-8, and TNF in elderly patients with open radical resection of prostate cancer; improve the comfort of patients before operation; and shorten the independent standing time after surgery. Compared with placebo, CHO had no significant advantage in regulating the levels of inflammatory markers and improving clinical outcomes.

**Abbreviations**

CHO  
Carbohydrate  
ASA  
American Society of Anesthesiologists  
ERAS  
recovery after surgery  
IR  
insulin resistance  
LOS  
length of stay  
BMI  
body mass index  
IL  
levels of interleukin  
TNF  
tumor necrosis factor  
CRP  
C-reactive protein  
VAS  
visual analogue scale  
HLA-DR  
leukocyte antigen DR

**Declarations**
**Ethics approval and consent to participate:** All procedures performed in studies involving human participants were in accordance with the ethical standards of Shanghai Tenth People's Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This manuscript reporting adheres to CONSORT guidelines.

**Consent for publication:** Not applicable.

**Availability of data and material:** All data and materials obtained in this research are true and effective.

**Competing interests:** The authors declare that they have no conflict of interest.

**Funding:** This study was funded by the Shanghai Science Committee Foundation (grant number 19411967700) and Natural Science Foundation of China (grant number 81472389, 81672549). Funders support the experiment.

**Authors’ contributions:** ZH completed the preliminary design of the trial, participated in the full implementation of the trial and prepared the manuscript. JL was responsible for collecting the clinical data of the trial and collating and analyzing it. WCM was responsible for the mapping work. Mr. FW was responsible for supervising the full implementation of the trial and reviewing the trial. Results and manuscripts, all authors have read and approved the manuscript.

**Acknowledgement:** I would like to thank SHL, WTZ etc. who have not obtained the qualification of authors for their contributions to the preliminary planning part of this research. At the same time, I would like to thank Mr. FW again for his supervision and guidance on this research, and for the corresponding financial support.

**References**

[1] Bilku DK, Dennison AR, Hall TC, Metcalfe M. Role of preoperative carbohydrate loading: a systematic review. Ann R Coll Surg Engl. 2014 Jan;96(1):15-22.

[2] Weimann A, Braga M, Harsanyi L, Laviano A, Ljunngqvist O, Soeters P; DGEM, Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH; ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr. 2006; 25:224-244.

[3] Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, Gan TJ, Kennedy RH, Ljunngqvist O, Lobo DN, Miller T, Radtke FF, Ruiz Garces T, Schricker T, Scott MJ, Thacker JK, Ytreb LM, Carli. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand, 2016, 60(3):289-334.

[4] Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg, 2002, 183(6): 630-641.
[5] Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammargvist F, Almstrom C, Lindh A, Thorell A, Ljungqvist O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001 Nov;93(5):1344-50.

[6] Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis 2006; 8:563–569.

[7] Dilmen OK, Yentur E, Tunali Y, Balci H, Bahar M. Does preoperative oral carbohydrate treatment reduce the postoperative surgical stress response in lumbar disc surgery? Clin Neurol Neurosurg. 2017 Feb; 153:82-86.

[8] Zhang Y, Min J. Preoperative Carbohydrate Loading in Gynecological Patients Undergoing Combined Spinal and Epidural Anesthesia. J Invest Surg. 2019 Jan 15:1-9.

[9] Porcaro AB, de Luyk N, Corsi P, et al. Robotic assisted radical prostatectomy accelerates postoperative stress recovery: Final results of a contemporary prospective study assessing pathophysiology of cortisol peri-operative kinetics in prostate cancer surgery. Asian J Urol. 2016 Apr;3(2):88-95.

[10] Pędziwiatr M, Pisarska M, Matłok M, Major P, Kisielecki M, Wieradk M, Natkaniec M, Budzynski P, Rubinkiewicz M, Budzynski R. Randomized Clinical Trial To Compare The Effects Of Preoperative Oral Carbohydrate Loading Versus Placebo On Insulin Resistance And Cortisol Level After Laparoscopic Cholecystectomy. Pol Przegl Chir. 2015 Aug;87(8):402-8.

[11] Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammargvist F, Almstrom C, Lindh A, Thorell A, Ljungqvist O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001 Nov;93(5):1344-50.

[12] Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Cramer R, Duan S, Eiwegger T, Eljaszewicz A, Ferstl R, Garbani M, Globinska A, Hess L, Huitema C, Kubo T, Komlosi Z, Konieczna P, Kovacs N, Kucukesezer UC, Meyer N, Morita H, Olzhausen J, OMahony, Pezer M, Prati M. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016 Oct;138(4):984-1010.

[13] Wu FP, Sietses C, von Blomberg BM, van Leeuwen PA, Meijer S, Cuesta MA. Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients: a prospective randomized trial. Dis Colon Rectum, 2003, 46 (2): 147-155.

[14] Schwenk W, Jacobi C, Mansmann U, Böhm B, Müller JM. Inflammatory response after laparoscopic and conventional colorectal resections-results of a prospective randomized trial. Langenbecks Arch Surg, 2000, 385 (1): 2-9.

[15] Veenhof AA, Vlug MS, van der Pas MH, Sietses C, van der Peet DL, de Lange-de Klerk ES, Bonjer HJ, Bemelman WA, Cuesta MA. Surgical stress response and postoperative immune function after
laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Annals of Surgery, 2012;255 (2): 216-221.

[16] Melis GC, van Leeuwen PA, von Blomberg-van der Flier BM, Goedhart-Hiddinga AC, Uitdehaag BM, Strack van Schijndel RJ, Wuisman PI, van Bokhorst-de van der Schueren MA. A Carbohydrate-Rich Beverage Prior to Surgery Prevents Surgery-Induced Immunodepression. A Randomized Controlled Clinical Trial. JPEN J Parenter Enteral Nutr, 2006, 30(1):21-26.

[17] Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK, Merrie AE, Torrie JJ, Pugh F, Koea JB, Bissett IP, Parry BR. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. Br J Surg. 2010; 97:485-94.

[18] Tran S, Wolever TM, Errett LE, Ahn H, Mazer CD, Keith M. Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery. Anesth Analg. 2013 Aug;117(2):305-13.

[19] Çakar E, Yilmaz E, Çakar E, Baydur H. The Effect of Preoperative Oral Carbohydrate Solution Intake on Patient Comfort: A Randomized Controlled Study. J Perianesth Nurs. 2017 Dec;32(6):589-599.

[20] Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, Lindh A, Thorell A, Ljungqvist O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001 Nov;93(5):1344-50.

[21] Watt DG, McSorley ST, Horgan PG, McMillan DC. Enhanced Recovery After Surgery: Which Components, If Any, Impact on The Systemic Inflammatory Response Following Colorectal Surgery?: A Systematic Review. Medicine (Baltimore). 2015 Sep;94(36): e1286.

Tables
|                                | CHO          | Placebo     | Fasted      | p value |
|--------------------------------|--------------|-------------|-------------|---------|
| Number of patients             | 28           | 30          | 32          |         |
| Age at surgery (years) Mean (min-max) | 71.79(65-81) | 70.25(65-81)| 72.44(58-83)| 0.286   |
| BMI (kg/m$^2$) Mean (min-max)  | 23.82(17.30-31.91) | 23.97(18.51-29.76) | 24.16(19.00-30.76) | 0.92    |
| Preoperative fasting blood glucose (mmol/L) Mean (min-max) | 4.8(3.9-6.9) | 5.1(4.0-9.1) | 0.748 |
| ASA grade (n/%)                |              |             |             |         |
| I                             | 5(18)        | 6(20)       | 6(19)       |         |
| II                            | 17(61)       | 18(60)      | 19(59)      |         |
| III                           | 6(21)        | 6(20)       | 7(22)       |         |
| OR Time (min) Mean (min-max)   | 178.8(105-330) | 158.5(100-330) | 169.5(90-285) | 0.416   |
| Blood loss (ml) Mean (min-max) | 189.29(50-500) | 225(100-900) | 201.56(50-500) | 0.628   |
| Intraoperative Fluid (ml) Mean (min-max) | 2078.57(1500-3500) | 1925(1250-2750) | 2007.81(1500-2750) | 0.136   |

Table 1: Patient demographics and surgical characteristics

Note: CHO = Carbohydrate, BMI = body mass index, ASA = American Society of Anesthesiologists, OR Time = Operative Time
## IL-6 (pg/ml)

| Day  | CHO Mean(SD) | Placebo Mean(SD) | Fasted Mean(SD) | CHO vs Placebo Mean difference(95% CI);p value | CHO vs Fasted Mean difference(95% CI);p value | Placebo vs Fasted Mean difference(95% CI);p value |
|------|--------------|------------------|-----------------|------------------------------------------------|-----------------------------------|--------------------------------------------|
| Day 0 | 9.6(18.29)   | 9.09(14.58)      | 17.1(33.58)     | 0.51(-14.32 to 15.35);0.945                     | -7.5(-21.1 to 6.09);0.275             | -8.0(-22.14 to 6.11);0.262               |
| Day 1 | 72.98(58.67) | 109.09(116.58)   | 134.6(81.28)    | -36.1(-86.48 to 14.27);0.157                  | -61.6(-107.62 to 15.61);0.009         | -25.5(-74.37 to 23.34);0.301            |
| Day 3 | 27.03(39.55) | 33.88(38.61)     | 33(58.92)       | -6.86(-33.75 to 20.03);0.613                  | -5.98(-31.79 to 19.83);0.646          | -0.8(-25.77 to 27.54);0.948             |
| Day 7 | 7.9(6.27)    | 18.29(19.95)     | 27.49(33.83)    | -10.39(-24.53 to 3.75);0.147                  | -19.59(-32.98 to -6.2);0.005          | -9.2(-22.59 to 4.19);0.175              |

## IL-8 (pg/ml)

| Day  | CHO Mean(SD) | Placebo Mean(SD) | Fasted Mean(SD) | CHO vs Placebo Mean difference(95% CI);p value | CHO vs Fasted Mean difference(95% CI);p value | Placebo vs Fasted Mean difference(95% CI);p value |
|------|--------------|------------------|-----------------|------------------------------------------------|-----------------------------------|--------------------------------------------|
| Day 0 | 179.23(305.38) | 181.03(376.86) | 197.96(233.26) | -1.81(-181.65 to 178.03);0.984                   | -18.73(-183.56 to 146.1);0.821       | -16.92(-188.17 to 154.32);0.844          |
| Day 1 | 253.29(444.17) | 406.38(665.09) | 851.78(1014.13)| -153.08(-601.84 to 295.67);0.499                | -598.49(-1008.32 to 188.66);0.005    | -445.4(-880.59 to 10.22);0.045           |
| Day 3 | 344.74(618.95) | 466.31(714.82) | 428.44(808.19) | -121.56(-532.1 to 288.97);0.557                 | -83.7(-477.77 to 310.36);0.673       | 37.86(-369.08 to 444.81);0.853           |
| Day 7 | 325.83(604.03) | 265.24(340.08) | 654.45(1027.1)| -121.56(-378.15 to 499.34);0.784               | -328.62(-744.05 to 86.81);0.119      | -389.21(-804.65 to 26.22);0.066         |

## TNF (pg/ml)

| Day  | CHO Mean(SD) | Placebo Mean(SD) | Fasted Mean(SD) | CHO vs Placebo Mean difference(95% CI);p value | CHO vs Fasted Mean difference(95% CI);p value | Placebo vs Fasted Mean difference(95% CI);p value |
|------|--------------|------------------|-----------------|------------------------------------------------|-----------------------------------|--------------------------------------------|
| Day0 | 14(25.01)    | 13.83(15.14)     | 20.47(12.86)    | 0.17(-10.65 to 10.99);0.975                     | -6.46(-16.38 to 3.45);0.198          | -6.63(-16.94 to 3.67);0.204              |
| Day1 | 11.74(11.57) | 13.06(8.15)      | 24.06(17.07)    | -1.32(-9.11 to 6.46);0.736                     | -12.32(-19.43 to -5.21);0.001        | -11(-18.55 to -3.45);0.005              |
| Day3 | 9.64(8.88)   | 19.57(21.36)     | 21.39(13.7)     | -9.93(-18.61 to -1.25);0.026                   | -11.75(-20.08 to -3.42);0.006        | -1.82(-10.42 to 6.78);0.674             |
| Day7 | 9.59(8.58)   | 12.88(10.97)     | 19.77(13.88)    | -3.3(-10.19 to 3.59);0.343                     | -10.18(-16.76 to -3.6);0.003         | -6.88(-13.39 to -0.38);0.038           |
|                | CHO       | Placebo   | Fasted    | p value (CHO vs Fasted) | p value (Placebo vs Fasted) |
|----------------|-----------|-----------|-----------|-------------------------|----------------------------|
| **anxiety**    |           |           |           |                         |                            |
| Day 0          | 1.20(0-8) | 1.76(0-5) | 1.56(0-4) | 0.141                   | 0.338                      |
| Day of surgery | 0.95(0-4) | 1.68(0-5) | 1.22(0-8) | 0.838                   | 0.119                      |
| Day 1          | 0.86(0-7) | 0.63(0-5) | 0.66(0-4) | 0.603                   | 0.999                      |
| Day 3          | 0.27(0-2) | 0.16(0-2) | 0.5(0-5)  | 0.339                   | 0.365                      |
| **thirst**     |           |           |           |                         |                            |
| Day 0          | 1.70(0-6.5)| 1.42(0-5)| 2.38(0-5) | 0.451                   | 0.52                       |
| Day of surgery | 0.68(0-4) | 1.26(0-4) | 3.03(1-8.5)| <0.001                 | 0.001                      |
| Day 1          | 2.16(0-8) | 1.82(0-8) | 2.22(0-7) | 0.7                      | 0.335                      |
| Day 3          | 1.23(0-7) | 0.37(0-2) | 0.78(0-5) | 0.692                   | 0.306                      |
| **hunger**     |           |           |           |                         |                            |
| Day 0          | 0.93(0-3) | 0.39(0-4.5)| 0.95(0-4)| 0.934                   | 0.78                       |
| Day of surgery | 0.24(0-3) | 0.47(0-3) | 1.39(0-7) | 0.004                   | 0.01                       |
| Day 1          | 1.86(0-8) | 1.18(0-5) | 1.50(0-6) | 0.474                   | 0.886                      |
| Day 3          | 0.83(0-5.5)| 0.42(0-5)| 0.89(0-5)| 0.889                   | 0.439                      |
| **nausea**     |           |           |           |                         |                            |
| Day 0          | 0(0-0)    | 0.21(0-3) | 0(0-0)    | 0.999                   | 0.07                       |
| Day of surgery | 1.24(0-3) | 1.53(0-6) | 2(0-6)    | 0.666                   | 0.916                      |
| Day 1          | 0.54(0-5) | 1.84(0-6) | 1.33(0-3) | 0.828                   | 0.758                      |
| Day 3          | 0.57(0-5) | 0.05(0-1) | 0.06(0-3) | 0.138                   | 0.585                      |
| **fatigue**    |           |           |           |                         |                            |
| Day 0          | 1.09(1-2) | 1.04(1-2) | 1(0-2)    | 0.125                   | 0.563                      |
| Day of surgery | 2.18(0-6) | 2.47(1-6) | 2.41(0-6) | 0.553                   | 0.979                      |
|          | Grip Strength |
|----------|---------------|
|          | Index%        |
| **Day 0**|               |
|          | 44.67(29.04-  |
|          | 67.74)        |
|          | 46.86(33.38-  |
|          | 67.69)        |
|          | 44.07(30.71-  |
|          | 62.27)        |
|          | 0.211         |
|          | 0.588         |
| **Day of surgery** |           |
|          | 38.38(26.22-  |
|          | 68.06)        |
|          | 41.45(32.77-  |
|          | 57.50)        |
|          | 41.29(25.88-  |
|          | 57.88)        |
|          | 0.57          |
|          | 0.475         |
| **Day 1** |               |
|          | 39.15(27.57-  |
|          | 65.97)        |
|          | 42.14(24.80-  |
|          | 63.23)        |
|          | 43.00(30.88-  |
|          | 61.21)        |
|          | 0.968         |
|          | 0.567         |
| **Day 3** |               |
|          | 42.41(29.73-  |
|          | 66.13)        |
|          | 44.11(25.13-  |
|          | 63.13)        |
|          | 44.08(28.86-  |
|          | 64.85)        |
|          | 0.496         |
|          | 0.691         |

Table 3
| Variable                  | CHO Mean(min-max) | Placebo Mean(min-max) | Fasted Mean(min-max) | CHO vs Placebo Mean difference(95% CI);p value | CHO vs Fasted Mean difference(95% CI);p value | Placebo vs Fasted Mean difference(95% CI);p value |
|---------------------------|-------------------|-----------------------|----------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                           | 26.46(7.5-24.70) | 25.02(1.5-24.70)     | -1.76(-11.19 to 7.66);0.711 | -0.32(-9.30 to 8.65);0.943                    | 1.44(-7.91 to 10.79);0.76                    |
| Time to first anal exhaust(h) | 28.71(12-28.57) | 39.21(15-24.70)     | -1.37(-10.15 to 9.88);0.978 | -10.64(-20.03 to -1.25);0.027                | -10.50(-20.29 to -0.712);0.036              |
| Independent standing time after surgery (h) | 26.46(7.5-24.70) | 25.02(1.5-24.70)     | -3.93(-4.56 to 3.78);0.851 | -1.97(-5.87 to 1.92);0.316                   | -1.58(-5.69 to 2.53);0.446                  |
| Time to intake of water(h)   | 27.94(12-27.94) | 34.82(8-34.82)      | -6.88(-16.50 to 2.73);0.158 | -6.65(-15.72 to 2.40);0.147                 | 0.22(-9.68 to 9.24);0.963                   |
| Time to intake of oral diet(h) |                       |                       |                       |                                               |                                               |                                               |
| number of infection patient | 4                  | 4                     | 3                     | 0.916;0.554;0.623                              |                                               |                                               |
|                         | 2                  | 2                     | 3                     | 0.943;0.755;0.696                              |                                               |                                               |
|                         | 0                  | 0                     | 0                     | 0                                               |                                               |                                               |

Table 4

| Variable             | HR    | 95% CI range   | p value |
|----------------------|-------|----------------|---------|
| Age                  | 1.275 | 1.064-1.527    | 0.008   |
| BMI                  | 1.303 | 1.012-1.677    | 0.040   |
| Operation Time       | 1.017 | 1.002-1.033    | 0.031   |
| Group                | 3.018 | 1.166-7.809    | 0.023   |
| Blood Loss           | 0.996 | 0.989-1.003    | 0.217   |
| Intraoperative Fluid | 1.000 | 0.998-1.002    | 0.896   |

Table 5: Multivariate analysis of risk factors for elevated IL-6 7 days post-operation

HR: hazard ratio; CI: confidence interval

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Figures

Figure 1

Illustration of the experimental design
Figure 2

Experimental flow chart

![Experimental flow chart diagram]
Figure 3

Changes of postoperative inflammatory factors including IL-8, IL-6, TNFα in different groups