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Original Article

Insulin Resistance Improvement After Cardiac Surgery by Preoperative Carbohydrate Loading: A Randomized Controlled Trial

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ABSTRACT

Background: The idea of preoperative overnight fasting was challenged and verified to have no benefits compared with drinking clear liquids up until 2 hours before surgery. In this study, we explored the possible effects of preoperative oral carbohydrate loading (OCL) on insulin resistance and the clinical outcomes of patients undergoing cardiac surgery.

Methods: Totally, 260 patients were recruited and allocated randomly to intervention (n=130) and control (n=130) groups. The intervention group received 250 mL of an oral carbohydrate fluid containing 25 g of glucose, and the control group received standard care. Insulin resistance, glycemic indices, and clinical outcomes were assessed before and after surgery.

Results: Totally, 107 patients in the intervention group and 103 in the control group completed the study and were, thus, included in the final analysis. Preoperative OCL 2 hours before surgery improved postoperative fasting blood sugar and clinical outcomes after cardiac surgery including thirst, hunger, anxiety, pain, the length of stay in the hospital, and the length of stay in the ICU (all *P*s<0.05).

Conclusions: OCL administered preoperatively seems to be beneficial in improving the biochemical and clinical outcomes of patients undergoing cardiac surgery. Notably, preoperative OCL as a safe, simple, and cost-benefit approach is associated with no or negligible harm and, therefore, could be recommended in the setting of cardiac surgery, with careful attention to contraindications. ***(Iranian Heart Journal 2022; 23(3): 49-58)***

KEYWORDS: Preoperative fasting, Carbohydrate loading, Insulin resistance

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Surgery stress creates a condition of hyperglycemia and insulin resistance, related to increased postoperative morbidity and mortality.[1] Postoperative insulin resistance (PIR) is a feature of the postoperative metabolic response to surgical injury, resulting in increased glucose release and hyperglycemia through a reduced insulin-stimulated glucose uptake in skeletal muscle and adipose tissue.[2] PIR happens most frequently on the day after surgery and lasts for weeks after uncomplicated elective cardiac operations. Hence, it has been considered a factor of clinical importance after surgery.[3] The degree of PIR is considered to be an independent factor determining the length of hospital stay after surgery.[4]

Patients undergoing cardiac surgery experience an inflammatory response with potentially high complication rates. The mechanisms that cause PIR are not well known. It seems that the secretion of stress hormones (adrenaline, cortisol, and glucagon) and defective transmission of GLUT-4,[5] the carrier protein of intracellular glucose regulated by insulin and inflammatory mediators, are the main factors. It has been shown that tumor necrosis factor α (TNF-α) is associated with increased PIR.[6] Additionally, the rate of PIR is related to the IL-6 concentration.[7] Several studies have evaluated C-reactive protein (CRP) as a primary marker for major complications after surgery and focused on CRP as the main indicator of postoperative complications.[8,9]

Fasting before surgery stimulates a catabolic condition that contributes to the development of insulin resistance.[10] In addition to surgical catabolic effects and inflammatory factors, various studies have demonstrated that fasting from the night before surgery increases metabolic stress in patients.[11] Preoperative oral carbohydrate loading (OCL) reduces the grade of whole-body PIR, improves and maintains whole-body protein balance and muscle function, and attenuates the reduction of the insulin suppressive effect on endogenous glucose release.[12,13]

Elements of enhanced recovery after surgery (ERAS) such as oral hyperosmolar glucose drinks could ameliorate surgical stress and would be well suited for patients undergoing cardiac surgery. Further, since the grade of PIR is directly related to the extent of surgery,[14] patients undergoing major cardiac surgery may serve as an appropriate model to study the effects of preoperative OCL after surgical stress.

Therefore, we conducted the present study to evaluate the impact of OCL in patients undergoing cardiac surgery. The primary hypothesis is that the adoption of OCL in patients undergoing cardiac surgery reduces hospitalization.

METHODS

Subjects

A total of 270 patients who underwent cardiac surgery were evaluated for eligibility between April 2019 and August 2019 in this prospective randomized controlled clinical trial. Before participation, patients received information about the study, including details of the treatment procedure. Ten patients were excluded after the initial assessment; hence, 260 eligible patients were randomized. Permuted block randomization was used with a block size of 2 and an allocation ratio of 1:1. Fifty patients were excluded from the study after randomization due to canceled operations. Of the remaining patients, 107 patients received OCL (the OCL group), and 103 patients received conventional standard care (the control group). Informed consent for participation in the study was obtained from each subject. The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center (approval number: IR.RHC.REC.1397.042) and was registered on IRCT.ir (identity number: IRCT20200114046131N1). The study was carried out in accordance with the

Declaration of Helsinki of the World Medical Association.

Procedures

Patients were included if they were at least 18 years of age, had a body mass index (BMI) of 18.5 to 30 kg/m^2, and were scheduled to undergo elective heart surgery. The exclusion criteria consisted of emergent surgery, New York Heart Association (NYHA) functional class IV, a history of stroke; creatinine levels exceeding 1.2 mg/dL, abnormal liver function tests (eg, a decreased synthesis of liver proteins), endocrine diseases (eg, thyroid and adrenal diseases), severe mental disorders, a history of alcohol and drug abuse, and patient refusal.

Study Design and Clinical Pathway

The OCL and control groups were studied in a randomized controlled clinical trial at Rajaie Cardiovascular Medical and Research Center, Iran.

Preoperative

The OCL group received education and psychological counseling conducted by trained personnel. The OCL group followed a diet prescribed by a dietitian to standardize the caloric intake at 7 pm the night before the surgery. The nil per os time was reduced from the conventional 12 hours to 6 hours with light meals. Fasting started after 12 pm (6 hours of fasting). On the day of surgery, 2 hours before the operation, the OCL group received 250 mL of an oral carbohydrate solution containing 25 g of glucose.

The control group followed a diet prescribed by a dietitian to standardize the caloric intake at 7 pm the night before the surgery. The nil per os time was about 12 hours. The control group patients did not receive any beverages.

Postoperative

Postoperatively, the patients in both groups received intravenous patient-controlled analgesia according to the hospital's protocol. Ondansetron was used to reduce the risk of postoperative nausea and vomiting. In the OCL group, oral fluids were commenced within 6 hours of extubation, and a full diet was started on the first day after extubation in the intensive care unit (ICU).

Outcomes

The primary outcome was the duration of hospitalization, while the secondary outcomes were insulin resistance and feeding tolerance. The length of hospital stay was recorded. In addition, pain scores at rest postoperatively, as well as nausea and vomiting, were collected from individual case report forms. Insulin resistance and insulin sensitivity were measured a day after surgery, and both HOMA-IR = [fasting insulin (μU/ml)] × [fasting glucose (mmol/l)]/22.5 and QUICKI = 1/ [log (fasting insulin (μU/mL) + log (fasting glucose, mg/dL)] methods were used. Furthermore, the function of β cells was assessed as 20 × fasting insulin (μU /ml)/fasting glucose (mmol/mL) – 3.5.

Sampling and Analysis

In the preoperative period, blood samples were obtained before surgery. After the operation, blood samples were taken a day after the patient's arrival at the ICU. Blood glucose was measured immediately upon collection and after the rapid centrifugation of the arterial blood samples to 14000 rpm using the enzyme-linked immunosorbent assay (ELISA) kit. Serum insulin was sampled after the operation and analyzed using a commercial ELISA kit. All the serum samples were permitted to clot, while the plasma samples were immediately centrifuged at 4 °C at 2010*g* for 10 minutes. All the samples were stored in a −20 °C freezer for later batch analysis.

Assessment of Self-Reported Discomfort

The patients rated their sense of pain on a visual analog scale (VAS).[15] Self-reported discomfort as rated by the patients on the VAS (0, none or extremely light; 10, extremely severe) was evaluated by the investigator.

Statistical Analysis

Data analysis was performed using the SPSS software, version 21. A *P* value of less than 0.05 was considered statistically significant. The frequency distribution, the mean ± the standard deviation, and the median (the interquartile range) were reported based on the type of variable. The normality of the data was evaluated using the Kolmogorov–Smirnov test or histogram charts. The χ^2 test or the Fisher exact test was utilized to compare qualitative variables. For the comparison of the mean of the quantitative variables between the groups, the Student *t* test (in the case of normally distributed data) was employed. The comparison of the mean values of the quantitative variables was performed by modifying confounding factors via repeated measurement or generalized estimating equations tests. The relationship between the outcomes was calculated using the Pearson correlation. Finally, ANCOVA models were used to eliminate the effect of confounders. The sample size was calculated based on the primary outcome, an α of 0.05, and a β of 0.01.[16]

RESULTS

Among the 260 cardiac surgery candidates who participated in the current trial, 23 patients were excluded from the intervention group and 27 patients from the control group (due to surgery cancellations) (Fig. 1). Finally, analyses were conducted on 210 patients: 107 in the OCL group and 103 in the control group. There were no significant differences between the 2 groups in terms of age, sex, body weight, height, BMI, left ventricular function, the NHYA functional class, and the type of cardiac surgery (all *P*s>0.05) (Table 1).

The glycemic indices of the participants on the first day after the cardiac surgery showed that the OCL protocol improved fasting blood sugar significantly (*P*<0.05), whereas the other parameters, including insulin, HOMA-IR, HOMA-β, and QUICKI, did not change significantly in the intervention group compared with the control group (all *P*s>0.05) (Table 2).

The results concerning the correlation between insulin resistance markers, including HOMA-IR and HOMA-B, and the length of stay at the ICU (h) and the length of stay in the hospital (d) showed a positive and significant correlation between the ICU length of stay and the markers of insulin resistance (all *P*s<0.05) (Table 3).

The data regarding postoperative discomfort are presented in Table 4 and Figure 2. The patients who received the OCL protocol had fewer complaints than the control group regarding thirst, hunger, anxiety, and pain (all *P*s<0.05). Nonetheless, there was no significant difference in nausea and vomiting (all *P*s>0.05).

The clinical characteristics of the participants in the ICU are presented in Table 5. The intervention group experienced a shorter duration of hospitalization and length of stay in the ICU (all *P*s<0.05). Furthermore, the first meal after surgery was initiated sooner for the patients who received OCL (*P*<0.05).

Table 1: Characteristics of the studied patients

Variables	Control Group (n=103)	Intervention Group (n=107)	*P* values
Demographic Characteristics			
Age (y)	57.7±7.9	59.03±7.8	0.258[1]
Female/ sex	17 (16.5)	20 (18.7)	0.370[2]
Body weight (kg)	74.2±12.1	73.2±11.4	0.539[1]
Height (cm)	173.6±5.9	171.5±8.6	0.065[1]
BMI (kg/m^2)	24.6±3.8	24.8±3.4	0.684[1]
LV function (%)	47.1±4	47.9±4.7	0.164[1]
NHYA I I I I I	 69 (68.3) 32 (31.7)	 67 (67.7) 32 (32.3)	0.941[2]
Surgery type CABG Valve	 95 (92.2) 8 (7.8)	 98 (92.1) 9 (8.4)	0.832[2]

Data are presented as mean ± SE or count (%).
[1]Calculated using the independent samples *t* test
[2]Calculated using the χ^2 test or the Fisher exact test
P values<0.05 were considered statistically significant.

BMI, Body mass index; NHYA, New York Heart Association; CABG, Coronary artery bypass grafting

Table 2: Measurement of insulin resistance and sensitivity 1 day after surgery

Variables	Control Group (n=103)	Intervention Group (n=107)	*P* values
FBS (mg/dL)	134.9±29	125.8±26.1	0.002
Insulin (µU/mL)	24.7±7.9	21.4±4.7	0.218
HOMA-IR	7.9±2.7	7.2±3.8	0.532
HOMA-B	149.5±12.2	126.±10.4	0.215
Quicki	0.3±0.03	0.3±0.03	0.960

Data are presented as mean ± SE.
Calculated using the independent samples *t* test
P values<0.05 were considered statistically significant.

HOMA-IR, Homeostasis model assessment for insulin resistance; HOMA-β, Homeostasis model assessment for β-cell function

Table 3: Relationship between insulin resistance and clinical outcomes

Variables	HOMA-IR	*P* values	HOMA-B	*P* values
ICU stay (h)	0.176	0.032[1]	0.331	<0.001[1]
Hospitalization (d)	-0.031	0.710[1]	0.162	0.053[1]

[1]Calculated using the Pearson correlation

P values<0.05 were considered statistically significant.
ICU, Intensive care unit; HOMA-β, Homeostasis model assessment for β-cell function

Table 4: Number of patients complaining of postoperative discomfort

Variables	Control Group (n=103)	Intervention Group (n=107)	p-values
Nausea First day (yes) Second day (yes) Third day (yes)	 24 (23.3) 12 (11.6) 3 (2.9)	 36 (33.6) 17 (15.9) 5 (4.7)	 0.138[2] 0.421[2] 0.377[2]
Vomiting First day (yes) Second day (yes) Third day (yes)	 34 (33) 15 (14.6) 3 (2.9)	 33 (30.8) 8 (7.5) 2 (1.9)	 0.627[2] 0.141[2] 0.680[2]
Pain score	5.6±1.3	4.8±1.4	0.001[1]

Data are presented as mean ± SE or count (%).

[1]Calculated using the independent-samples *t* test
[2]Calculated using the χ^2 test or the Fisher exact test
P values<0.05 were considered statistically significant.

Table 5: Clinical outcome of the patients

Variables	Control Group (n=103)	Intervention Group (n=107)	*P* values
Hospitalization (d)	16.8±3.7	12.6±2.3	<0.001[1]
Starting liquid (h)	10.5±2.1	7.4±1.4	<0.001[1]
Starting solid (h)	19.5±3.7	11.5±3.5	<0.001[1]

Data are presented as mean ± SE.
1Calculated using the Pearson correlation
P values<0.05 were considered statistically significant.

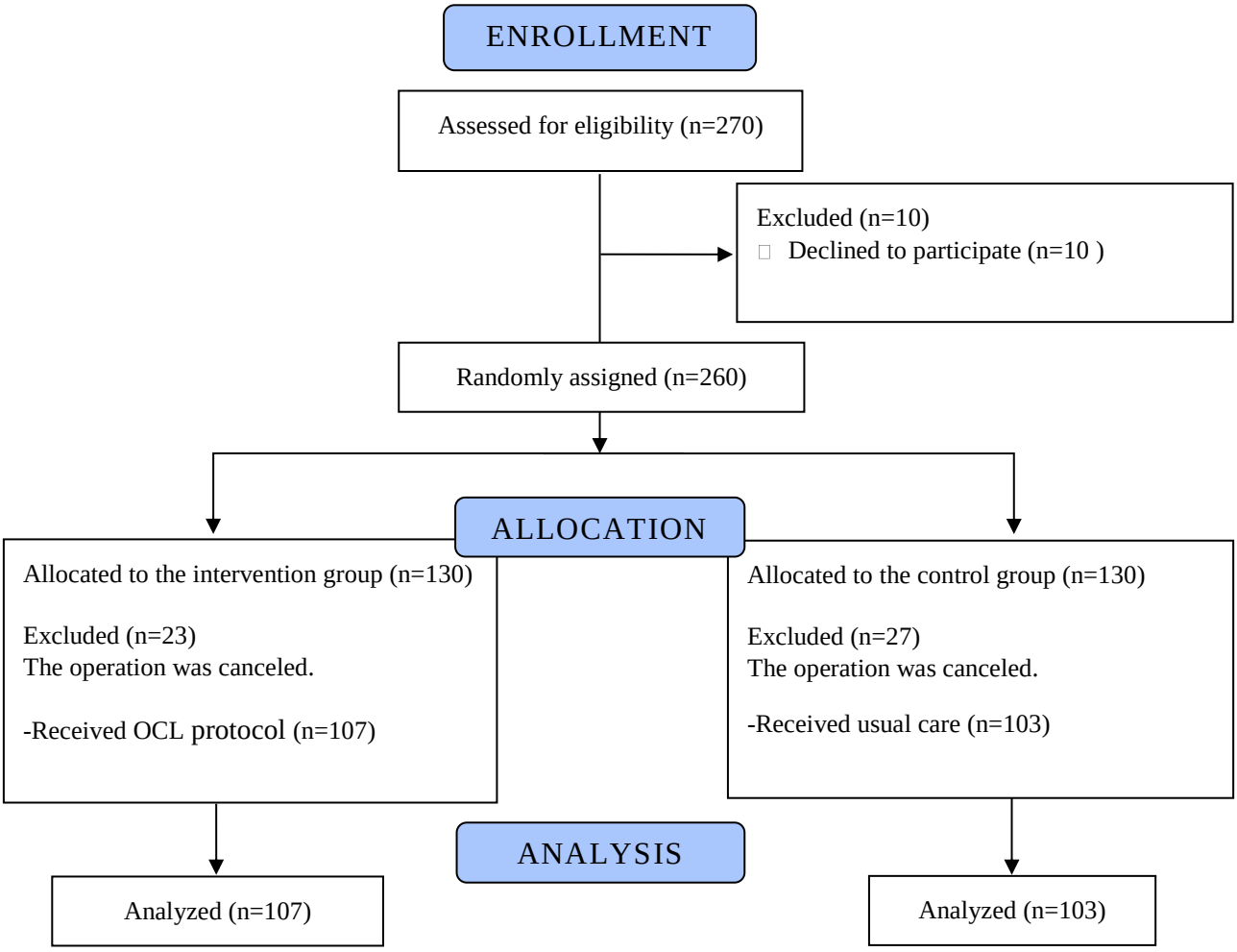

Figure 1: The image depicts the study's flow diagram.

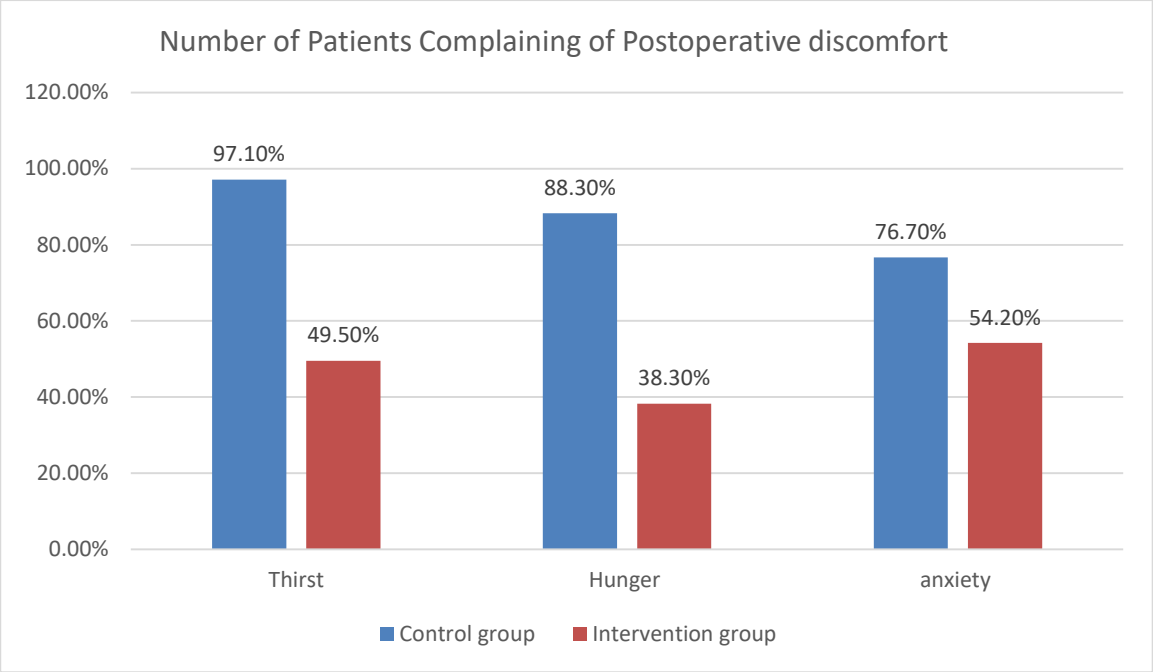

Figure 2: The image presents the number of patients complaining of postoperative discomfort, including thirst, hunger, and anxiety.

DISCUSSION

To our knowledge, the present study is the first attempt among the Iranian population to investigate the effects of preoperative OCL on the outcome of patients undergoing cardiac surgery. Among patients after cardiac surgery, we found marked improvements in fasting blood sugar and clinical outcomes, including thirst, hunger, anxiety, pain, the length of hospital stay, and the length of stay in the ICU. These findings are in agreement with previous studies that document improved biochemical and clinical outcomes if OCL is done prior to cardiac surgery.[3, 17-19] Additionally, a meta-analysis by Kotfis et al[20] demonstrated that preoperative carbohydrate loading in individuals undergoing cardiac surgery could reduce the length of ICU stay by 50% and postoperative insulin requirement by 35%. Another meta-analysis reported a significant reduction in PIR and the length of hospital stay among patients undergoing major abdominal surgery.[21] In contrast to the above documents, a meta-analysis by Li et al[22] concluded that OCL did not improve the length of ICU and hospital stay or the incidence of postoperative nausea and vomiting. The nonsignificant findings regarding PIR can be explained. Firstly, we did not assess preoperative insulin resistance in the participants; thus, it is probable that they were not on the upper end of abnormal cut-points, which might reduce the chance of achieving significant changes in these features following the intervention. Secondly, we assessed insulin resistance using the values of basal glucose and insulin, which may not have been sensitive enough to sense changes in insulin resistance when compared with the clamp technique as the gold-standard method.

The idea of preoperative OCL is a part of a multidisciplinary approach to the perioperative management of surgical patients. Most available data regarding cardiac surgery are derived from the available literature on abdominal surgery

patients. Currently, there are several protocols for surgery patients, including the ACERTO (Acceleration of Total Postoperative Recovery) and ERAS.[23-25] Previous studies have reported that adherence to only a few parts of those protocols contributes to improved outcomes in surgical patients.[26,27]

The traditional approach of overnight fasting results in hepatic glycogen depletion, elevated gluconeogenesis, and insulin resistance, which was challenged by Ljungqvist et al[28] in 1994. The infusion of overnight intravenous glucose decreased insulin resistance by 50% and increased hepatic glycogen by 65%.[29] The improvement in β-cell function could be associated with a shorter duration of stay in the recovery and ICU units. Tran et al[1] reported that postoperative HOMA-β (as the β-cell function indicator) tended to be elevated in the OCL group (87% vs 47.5% in the control group).

Thirst before and after surgery has been proposed to be the main influential modulator of patient discomfort, followed by hunger and anxiety.[30] Furthermore, anxiety is associated with the degree of postoperative pain that an individual experiences. A higher degree of postoperative pain could minimize mobility and increase the need for analgesics and, consequently, longer hospital stays. Therefore, the reported reduced anxiety in the OCL group may provide an additional explanation for the reduction in the duration of hospital stay.[1,31]

Several limitations of this study are acknowledged. Firstly, we assessed insulin resistance using the values of basal glucose and insulin, which are not the gold-standard method. Secondly, glycemic indices were measured just after the surgery, which precluded us from interpreting the effects of OCL relative to the values before surgery. Additionally, this was a single-center study, which warrants further multicenter trials. Due to the nature of the present study, it was not possible to perform blinding completely; however, blinding was achieved in the ICU physicians, surgeons on the ward, personnel who collected the data, and the statisticians.

CONCLUSIONS

It could be concluded that OCL administered preoperatively seems to be beneficial in improving the biochemical and clinical outcomes of patients undergoing cardiac surgery. Notably, preoperative OCL as a safe, simple, and cost-benefit approach is associated with no or negligible harm and, therefore, could be recommended in the setting of cardiac surgery, with careful attention to contraindications. Further investigations are needed to elucidate the exact biochemical, physiological, and clinical mechanisms of preoperative OCL in individuals undergoing cardiac surgery.

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