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Randomised Controlled Trial

Evaluation of carbohydrate loading on clinical results and metabolic responses in patients undergoing laparoscopic cholecystectomy☆,☆☆

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A R T I C L E I N F O

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A B S T R A C T

Objective: Insulin resistance is associated with a number of postoperative complication and delays recovery. Carbohydrate rich drinks given preoperatively may decrease these deleterious effects. This study evaluated the clinical effects of a preoperative carbohydrate loading in patients undergoing laparoscopic cholecystectomy.
Methods: In this a randomized clinical trial conducted at (XXX) Medical Center located, patients undergoing elective cholecystectomy were included. Patients were randomly divided into fasting and dextrose-receiving groups. The outcomes of this study are the pain, pre- and postoperative blood sugar, fasting blood sugar, insulin, cortisol, albumin, CRP (c-reactive protein), and wound conditions such as wound infection and the amount of fluid discharge from the drain. The data was statistically analyzed using SPSS v22.
Results: Patients who received carbohydrates before surgery experienced less pain on the day after surgery (P-value <0.05). Insulin resistance, CRP, CRP to albumin ratio and cortisol levels were significantly reduced in dextrose group (P-value <0.05) However, difference in glucose levels and albumin was not significant in the two groups.
Conclusion: The present results show that although carbohydrate loading is associated with reduced postoperative pain and reduction in inflammatory factors along with insulin resistance.

1. Introduction

Surgery is a highly stressful event on the body's metabolic process that can also trigger immune response of the body. In this process, the stress leads to the production of catecholamines, and proinflammatory compounds, metabolic changes include disruption of glycogen metabolism and changes in heart rate and vasoconstriction. Simultaneous activation of the hypothalamic-anterior pituitary-adrenal medulla leads to the release of cortisol, which leads to a reciprocal response in the form of the release of proteins and fatty acids, immunosuppression, and decreased activity of anabolic hormones such as insulin and testosterone [1–3].

Based on the above evidence, nutritional preparation has two conflicting views among experts: one of these views practices in short-term starvation indicating that this improves some metabolic responses and prevents damage to organs such as the liver [4–6]. In contrast, another view practices preoperative carbohydrate loading improves the metabolic response to injury by altering the immune response [4,7].

Insulin resistance during the surgery leads to increased inflammation, organ dysfunction and mortality [8–10]. Because a limited number of studies have investigated the effect of oral intake of preoperative liquid carbohydrates on stress hormones and insulin resistance after laparoscopic cholecystectomy [11,12], in this study, we intend to investigate the effectiveness of preoperative carbohydrate loading on postoperative complications as well as the level of inflammatory factors.

2. Methods

In this randomized control trial patients who were candidates for elective cholecystectomy were enrolled from June 2020 to December

☆ This clinical trial was carried out in Iran at the center of clinical trial registered with a special registration code: **IRCT20200629047952N1**☆☆ This study was approved by the Research Ethics Board of Alborz University of Medical Sciences (**IR.ABZUMS.REC.1400.035).**

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2020. Written consent was obtained from all the patients before entering the study.

This clinical trial was carried out in (XXX).

Patients undergoing elective surgery, with no previous history of surgery, aged 18 to 70 were included in the study. Patient with body mass index below 20 and above 30, received previous treatment of colorectal disease, malignant disease, increased gastric content aspiration, any disorder requiring emergency surgical intervention, history of metabolic diseases such as diabetes, inflammatory bowel disease, and unwilling to participate in the study were excluded from the study.

Demographic characteristics of each participant were recorded in the relevant forms along with a history of comorbidities and medications if used. The participants were randomly divided between the two treatment groups. Group A received standard preoperative fasting and group B underwent glucose loading as follows: 12.5% solution of 800 cc in the evening before surgery and then a solution of 400 cc 2–4 h before surgery. The duration of surgery, postoperative findings such as the amount of fluid drained, and surgical site infection were recorded for all the patients. Blood glucose levels of patients before surgery and in recovery and the difference between the two in each group, as well as the degree of pain were measured based on the visual index VAS at 6 h, 12 h, 18 h and 24 postoperative hours. In terms of insulin resistance, fasting blood sugar (FBS), insulin and cortisol levels and the patient's inflammatory findings, such as albumin, c-reactive protein (CRP), CRP to albumin ratio were also recorded.

Sampling was done randomly from the study population that included inclusion criteria and no exclusion criteria. The sample size was obtained with 95% confidence interval, 0.05 error coefficient and 80% strength using Cochran's sample size determination formula of 90 people.

Due to the patient's knowledge of the type of intervention performed, it was not possible to blind the patient. However, the results of the study were evaluated by a physician who was unaware of the type of intervention. To hide the random allocation process, the treatment sequence card was written in order, then the cards were placed in sealed envelopes. On each envelope, a random 10-digit code is written without order and frame, which was the relevant patient identification number, and only the design methodologist was aware of the relevant code. When the physician declared a patient eligible, the secretary provided the envelope to the physician and the treatment was performed according to the type mentioned in the envelope.

The collected data were analyzed by SPSS software (IBM, IL, Chicago, USA) and *t*-test and A NOVA was used to compare the data. P-value less than 5% was considered significant.

This study was approved by the Research Ethics Board of (XXX).

Unique identifying number is: researchregistry7810.

The methods were stated in accordance with CONSORT criteria [13].

3. Results

Of 95 patients, 24 (25.3%) were male and 71 (74.7%) were female. The frequency of men and women in the study was not statistically significant, $p = 0.44$. The number of participating in group A and group B was not statistically significant, $p = 0.99$ (45 vs 50 patients).

The mean duration of operation was in group A and B was 35.38 ± 14.41 and 31.80 ± 13.95 min, respectively. The difference in the duration of operation among the two groups was not statistically significant, $p = 0.22$. Reported values, mean and deviation from the criterion of patients' pain in 4 time periods, 6 h postoperatively, 12 h postoperatively, 18 h postoperatively and 24 h postoperatively in each of the receiving and non-receiving groups Dextrose intake by follow-up time is shown in Table 1.

The mean VAS in group A and B at 6th postoperative hour was 8.24 ± 1.89 and 6.66 ± 2.66, respectively. The difference in pain scores this amount in all patients, 2.15 ± 7.41. There was a significant difference in pain between the two groups 6 h after surgery, $p < 0.05$.

Table 1
The amount of pain in each group by follow-up time.

Checked hours	Groups	Numbers	Mean ± SD
6 Hours after surgery	Do not receive dextrose	45	8.24 ± 1.897
	Get dextrose	50	6.66 ± 2.115
	Total	95	7.42 ± 2.156
12 Hours after surgery	Do not receive dextrose	45	7.24 ± 1.990
	Get dextrose	50	5.58 ± 2.322
	Total	95	6.37 ± 2.316
18 Hours after surgery	Do not receive dextrose	45	6.51 ± 2.361
	Get dextrose	50	4.02 ± 2.075
	Total	95	5.20 ± 2.533
24 Hours after surgery	Do not receive dextrose	45	4.93 ± 2.799
	Get dextrose	50	3.08 ± 2.284
	Total	95	3.96 ± 2.693

The mean pain score after 12 h of the surgery in group A and B was 7.24 ± 1.99 and 5.58 ± 2.32, which was also statistically significant, $p < 0.05$. These differences were statistically significant at 18 and 24 h after the surgery, $p < 0.05$, Table 1.

18 patients (18.9%) developed surgical site infection, of which 5 (10%) were in the group A and 13 (28.9%) in the group B. The two group were significantly different in terms of surgical site infection, $p < 0.05$. The mean amount of fluid drained was 47.71 ± 32.22 in group A and 33.64 ± 17.80 in group B, which was not statistically significant, Table 2.

Blood glucose level before and after surgery was 96.71 ± 22.22 and 141.2 ± 23.15 in group A and 122.56 ± 22.98 and 161 ± 28.33, respectively. Comparison of overall blood glucose levels between pre- and postoperative groups was not statistically significant ($p = 0.129$). But these were significantly different in each group are significant ($p < 0.005$)(Table 3).

Fasting blood sugar among patients in group A and B was 89.44 ± 17.22 and 94.94 ± 14.14, respectively, which was not statistically significant, $p = 0.091$. Blood insulin levels in group A and B was 19.44 ± 7.56 and 22.74 ± 7.94, respectively. The difference between the two groups in A and B in terms of insulin levels was significantly different, $p = 0.042$(Fig. 1).

Cortisol and CRP levels in group A and B were also significantly different, $p < 0.001$ (34.64 ± 15.28 vs 23.52 ± 10.94) and (40.16 ± 26.5 vs 22.62 ± 12.82), respectively (Figs. 2 and 3). However, the mean albumin levels were not significantly different in two groups, $p = 0.58$. The ratio of CRP to albumin was 1.18 ± 0.79 and 5.82 ± 3.65 in group A and B, respectively. This difference was statistically significant, $p < 0.001$(Fig. 4).

4. Discussion

Fasting of patients before surgery is a traditional method to protect the patient from aspiration of gastric contents during general anesthesia, which leads to decreased hepatic glycogen, increased glycogenosis and insulin resistance [14,15]. This is followed by insulin resistance, which increases gluconeogenesis [16]. Hypothesis of patients' need for fasting during the night before surgery, for the first time in the year 1994 was challenged by Luzhang Wist et al., on patients undergoing open cholecystectomy [17]. The study found that postoperative insulin resistance

Table 2
The incidence of infection in postoperative wounds.

Wound infection		Do not receive dextrose	Get dextrose	Total
	Yes	13(28.9%)	5(10.0%)	18(18.9%)
	No	32(71.1%)	45(90.0%)	77(81.1%)
Total		45(100%)	50 (100.0%)	95(100.0%) (100.0%)

Table 3
Blood sugar level before surgery and in recovery.

	Groups	Numbers	Mean ± SD	Standard Error
Blood sugar before surgery	Do not receive dextrose	45	96.71 ± 22.22	3.31
	Get dextrose	50	122.56 ± 22.98	3.25
Blood sugar recovery	Do not receive dextrose	45	141.20 ± 23.15	3.45
	Get dextrose	50	161.10 ± 28.32	4.0
Differences in blood sugar before surgery and recovery	Do not receive dextrose	45	4.48 ± 32.62	4.86
	Get dextrose	50	38.54 ± 21.59	3.053

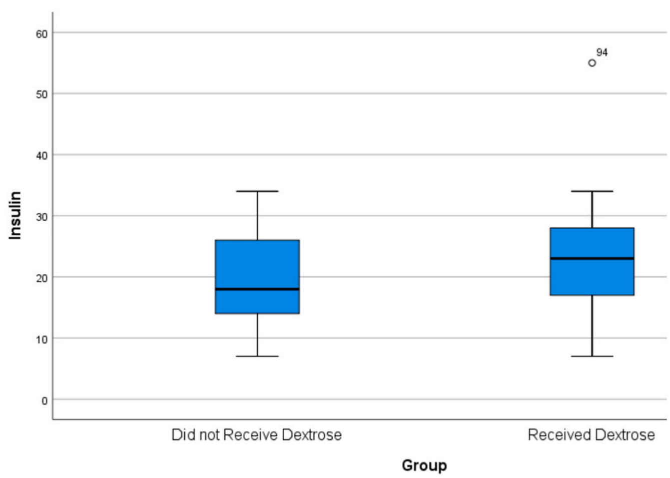

Fig. 1. Insulin levels.

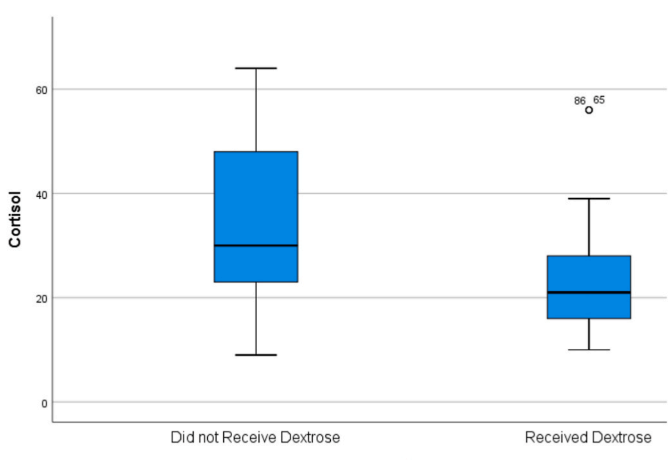

Fig. 2. Cortisol level.

was 50% lower in patients receiving intravenous glucose infusion. In addition, the hepatic glycogen content of patients receiving glucose infusion during surgery was 65% higher than that of fasting patients.

Vomiting, nausea and pain after surgery is one of the most common complications after surgery, the incidence of which varies from 20 to 30% in the general population and 70–80% in high-risk patients [18].

These symptoms have a significant impact on the patient's general

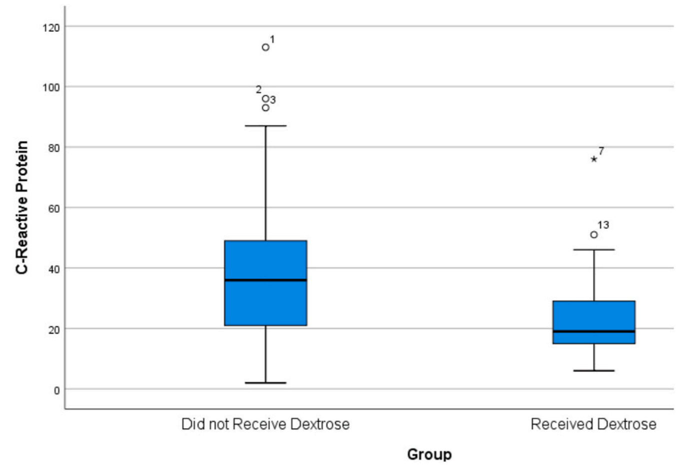

Fig. 3. Reactive protein C level.

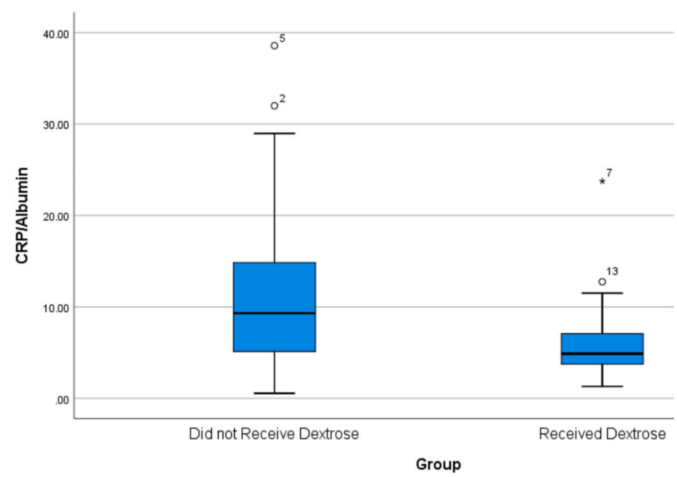

Fig. 4. Ratio of reactive protein to albumin.

condition, quality of life, as well as the increase in the cost of health care due to the increased length of hospital stay. Despite efforts to date, there are not many treatment options for controlling these symptoms. However, a randomized controlled trial including 120 patients undergoing laparoscopic cholecystectomy showed that preoperative carbohydrate loading is an effective way to reduce PONV and reduce postoperative pain in 24 postoperative hours [19]. The results of the present study show that preoperative administration of dextrose solution significantly reduces postoperative pain and production of inflammatory markers. The two possible explanations for this are that it may be because the stress of surgery along with fasting intensifies the catabolic state of patients, increases insulin resistance and thus delays recovery, which with carbohydrate loading reduces the overall stress response after surgery, which is seen as the reduction in pain. It may also improve the general condition of patients by reducing nausea, vomiting, thirst and lack of energy after surgery.

However, a previous study by Bisgaard et al., showed that preoperative carbohydrate loading did not improve any of the clinical outcomes after laparoscopic cholecystectomy. No improvement in fatigue, appetite, pain, and nausea and vomiting compared with patients who underwent fasting was reported in the study [20]. These results contrasted with studies showing that preoperative carbohydrate intake was clinically beneficial and should be used as standard treatment in elective surgery patients [17,21,22]. It also reduced postoperative insulin resistance in patients [17,23]. Changes induced by surgical stress and the catabolism process ultimately overshadow insulin resistance at least the day after surgery but may persist for several days [17]. However, because laparoscopic cholecystectomy is a minimally invasive surgery, insulin resistance (15–20% one day after surgery) is considerable [24], compared to elective hip surgery or open abdominal surgery (30–60% of the first day after surgery [25–27].

In an experimental study by Ljungvist [17] that examined preoperative glucose infusion compared to preoperative fasting in 68 patients, preoperative glucose infusion appeared to reduce the postoperative metabolic stress response and insulin resistance. Consumption of 12.5% carbohydrates increases the whole-body sensitivity to insulin by almost 50%. Insulin sensitivity also decreases by about 15–20% even after minimally invasive procedures such as laparoscopic cholecystectomy [28]. Animal studies have shown that the response to a particular injury depends on the animal's metabolic status at the time of injury. This indicates that carbohydrate loading is a clear advantage of surgery over fasting [29]. The results of the study by Gomus et al., showed that preoperative oral carbohydrate intake had no effect on blood glucose ($p < 0.05$) but reduced insulin resistance at 24 h postoperatively and serum cortisol levels [30]. Network meta-analysis showed that carbohydrate loading has minimum effect on hospital stay compared to fasting whereas incurs no benefits compared to placebo and water [31].

The findings of our study are limited to small sample size and does not evaluate other postoperative outcomes like nausea and vomiting. Therefore, further studies in future with greater sample size and other type of surgeries are recommended.

7. Conclusion

The results of this study showed that loading carbohydrates before cholecystectomy surgery reduces pain and the rate of infection in surgical wounds. Also, although there is no significant difference between pre-surgery and post-surgery blood sugar levels between the two groups but considering the significant reduction in insulin and cortisol levels in the dextrose group, it can be said that carbohydrate loading reduces insulin resistance. Also, in the study of inflammatory criteria, although the amount of albumin did not differ significantly between the two groups, but CRP and CRP to albumin ratio showed significant difference. Preoperative carbohydrate loading seems to put the patient in a better metabolic state and catabolism responses are less pronounced in patients.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Sources of funding

No funding was secured for this study.

Author contribution

Dr. Mahdi Tavalaee: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Ehsan Beigi and Dr. Alireza Shirzadi: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Ali Karbalaeikhani and Dr. Izadmehr Ahmadinejad: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Registration of research studies

Name of the registry: This study was approved by the Research Ethics Board of Alborz University of Medical Sciences.

Unique Identifying number or registration ID: **IRCT20200629047952N1.**

Hyperlink to the registration (must be publicly accessible):

Guarantor

Dr. Mahdi Tavalaee.

Consent

Not applicable.

Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication

Informed consent was obtained from each participant.

Availability of data and materials

All relevant data and materials are provided with in manuscript.

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Provenance and peer review

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Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

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