RANDOMIZED CLINICAL TRIAL TO COMPARE THE EFFECTS OF PREOPERATIVE ORAL CARBOHYDRATE LOADING VERSUS PLACEBO ON INSULIN RESISTANCE AND CORTISOL LEVEL AFTER LAPAROSCOPIC CHOLECYSTECTOMY*

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Postoperative insulin resistance, used as a marker of stress response, is clearly an adverse event. It may induce postoperative hyperglycemia, which according to some authors can increase the risk of postoperative complications. One of the elements of modern perioperative care is preoperative administration of oral carbohydrate loading (CHO-loading), which shortens preoperative fasting and reduces insulin resistance.

The aim of the study is to establish the influence of CHO-loading on the level of insulin resistance and cortisol in patients undergoing elective laparoscopic cholecystectomy.

Material and methods. Patients were randomly allocated to one of 2 groups. The intervention group included 20 patients who received CHO-loading (400 ml Nutricia pre-op®) 2 hours prior surgery. The control group received a placebo (clear water). In every patient blood samples were taken 2 hours prior to surgery, immediately after surgery, and on the 1st postoperative day. Levels and changes in glucose, cortisol and insulin resistance were analyzed in both groups.

Results. Although there were differences in the levels of cortisol, insulin, and insulin resistance, no statistically significant differences were observed between groups in every measurement. The length of stay and postoperative complications were comparable in both groups.

Conclusions. We believe that CHO-loading is not clinically justified in case of laparoscopic cholecystectomy. No effect on the levels of glucose, insulin resistance and cortisol was observed. Even though such procedure is safe, in our opinion there is no clinical benefit from CHO-loading prior to laparoscopic cholecystectomy.

Key words: laparoscopic cholecystectomy, insulin resistance, preoperative carbohydrate loading, perioperative care
believed to increase the risk of postoperative complications (2-5). Another important factor of inducing insulin resistance is prolonged perioperative fasting; therefore, modern perioperative care is aiming to achieve maximal shortening of fasting before and after an operation. One of the elements of modern perioperative care, according to the Enhanced Recovery After Surgery protocol, is preoperative administration of oral carbohydrate loading (CHO-loading) (6, 7).

International anesthesiological societies have stated that the procedure is completely safe and does not increase the risk of complications related to general anesthesia (8, 9, 10). Even a single dose of CHO-loading decreases postoperative insulin resistance, reduces gluconeogenesis, glycogenolysis, and lipolysis, minimizes catabolism of muscle proteins, and enhances glucose accumulation in the liver in form of glycogen (11). This allows maintaining primary muscle strength and, according to some authors, positively influences the return of normal intestinal peristalsis (12, 13). It is recognized that the administration of such a preoperative drink has a metabolic significance in extensive abdominal operations, which are associated with substantial insulin resistance (13-16). On the other hand, little is known about the use of this intervention in operative procedures that involve smaller stress responses.

The aim of this study was to establish the influence of preoperative carbohydrate loading on the level of insulin resistance and cortisol in patients undergoing elective laparoscopic cholecystectomy.

METHODS AND MATERIAL

Patients undergoing elective laparoscopic cholecystectomy were recruited from November 2013 to February 2014. Randomization with an allocation ratio of 1:1 was performed by an independent researcher who was not involved in the treatment process. He used a computer number generator (www.random.org) that randomly generates sequences of numbers (odd numbers were allocated to the intervention group, even numbers to the control group). Group allocations were placed in sequentially numbered opaque sealed envelopes. After obtaining informed consent, patients were included into the study.

Neither the surgeon and investigator nor the patient was blinded to the treatment assignment. Intervention arm patients received 400 ml of an oral carbohydrate-rich solution (Nutricia Pre-op®) 2 hours prior to the operation. The control group included patients who received a placebo (clear water). The last solid meal was given to all patients the evening before the operation and oral fluids were stopped before 24:00 (midnight) on the day preceding the surgery.

Inclusion criteria were: elective laparoscopic cholecystectomy for cholelithiasis, operation starting between 8 and 9 AM, and informed consent of the patient. Patients operated on for acute cholecystitis and patients with conversion to open surgery were excluded from the study. Patients with diabetes mellitus, liver or kidney failure, patients treated with glucocorticosteroids or other drugs that could influence glucose, insulin, or cortisol levels were also excluded from the study. Aside from the intervention, all patients underwent identical preparation for surgery. None of them received pre-, intra-, or postoperative intravenous infusion of glucose or parenteral nutrition.

Perioperatively, patients received 1000–2500 ml of crystalloids. Anesthesiological techniques were identical in all cases. Surgery was performed in a typical manner with laparoscopic approach using 4 trocars.

Primary outcome measures were changes in insulin and cortisol levels, as well as insulin resistance assessed with HOMA-IR. To measure levels of glucose, insulin, and cortisol, blood samples were taken from every patient 2 hours prior to surgery (before preoperative CHO-loading was administered in intervention group), immediately after surgery, and at 8:00 AM on the 1st postoperative day. Levels and changes in glucose, cortisol, and insulin resistance were analyzed in both groups. To assess insulin resistance, we used the HOMA-IR index calculated according to the formula: HOMA-IR = blood glucose level (mg / dl) x blood insulin level (μU / ml) / 405. Secondary outcome measures were postoperative complications and length of stay.

Statistical analysis was performed with Statsoft STATISTICA ver. 10 software. For sample size calculation, we assumed that a
20% increase in level of measured parameters represents a clinically relevant difference. To detect this, we calculated that 18 patients would be required in each treatment arm to give the study a power of 80%. Anticipating a 10% loss to complete the protocol, at least 20 patients per arm were required in the study. For qualitative variables, the chi-squared test was used. For quantitative variables assessment, when there was no normal distribution, the Mann-Whitney test was used. After confirmation of distribution of calculations, the t-test for independent variables was used. To compare ASA (American Society of Anesthesiologists) physical status, we used the Kolmogorov-Smirnov test for 2 samples. The local independent ethics committee approved the study.

A CONSORT diagram depicting the allocation of patients is presented in fig. 1. Of 58 patients, 46 met the inclusion criteria and were randomized. One patient in the intervention group and 2 in the control group were excluded due to intraoperative signs of cholecystitis or conversion. Another 3 patients were later excluded due to lack of all required biochemical measurements. The entire group consisted of 40 patients (25 females, 15 males), with a mean age of 54.35 years (range 27–74 years). The mean length of hospital stay (LOS) was 1.33 days (range 1–3 days) and mean operative time was 77.8 minutes (range 45–140 minutes). Demographic characteristics are summarized in tab. 1.

RESULTS

No statistically significant differences were observed between groups in sex, age, BMI, or ASA physical status. Mean operative time, complication rate, and the LOS in both groups were also similar (tab. 1).

All laboratory measurements are presented in tab. 2. Before surgery (1st measurement), mean glucose level was comparable between groups. Immediately after the operation, glucose levels increased in both groups, but the differences between groups were not statistically significant (p=0.069). At 24 hours after

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**Fig. 1. CONSORT diagram**
Preoperative Oral Carbohydrate on Insulin Resistance and Cortisol Level after Cholecystectomy

Table 1. Characteristics of patient groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (intervention)</th>
<th>Group 2 (control)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>12 (60%)</td>
<td>13 (65%)</td>
<td>p=0.744</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>8 (40%)</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>53.7 ± 15.29</td>
<td>55 ± 9.55</td>
<td>p=0.787</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>28.78 ± 4.85</td>
<td>28.76 ± 5.31</td>
<td>p=0.992</td>
</tr>
<tr>
<td>Mean operative time (min.)</td>
<td>78.25 ± 25.97</td>
<td>77.37 ± 21.50</td>
<td>p=0.988</td>
</tr>
<tr>
<td>Mean LOS (days)</td>
<td>1.35 ± 0.75</td>
<td>1.32 ± 0.58</td>
<td>p=0.819</td>
</tr>
<tr>
<td>ASA 1, n (%)</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>ASA 2, n (%)</td>
<td>13 (65%)</td>
<td>14 (70%)</td>
<td></td>
</tr>
<tr>
<td>ASA 3, n (%)</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

Complications

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (intervention)</th>
<th>Group 2 (control)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>1</td>
<td>2</td>
<td>p=0.998</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Overall n (%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI – Body Mass Index, LOS – Length of hospital stay, ASA – American Society of Anesthesiologists Physical Status

Table 2. Analysis of biochemical parameters

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (intervention)</th>
<th>Group 2 (control)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.28 ± 1.26</td>
<td>4.74 ± 0.76</td>
<td>p=0.323</td>
</tr>
<tr>
<td></td>
<td>5.94 ± 1.34</td>
<td>5.29 ± 1.24</td>
<td>p=0.069</td>
</tr>
<tr>
<td></td>
<td>6.04 ± 1.64</td>
<td>4.77 ± 1.57</td>
<td>p=0.019</td>
</tr>
<tr>
<td>Insulin (µIU/ml)</td>
<td>11.33 ± 4.75</td>
<td>9.62 ± 4.50</td>
<td>p=0.102</td>
</tr>
<tr>
<td></td>
<td>11.54 ± 6.11</td>
<td>17.26 ± 12.25</td>
<td>p=0.125</td>
</tr>
<tr>
<td></td>
<td>16.31 ± 8.55</td>
<td>18.47 ± 10.08</td>
<td>p=0.679</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.48 ± 0.65</td>
<td>1.23 ± 0.58</td>
<td>p=0.138</td>
</tr>
<tr>
<td></td>
<td>1.57 ± 0.87</td>
<td>2.07 ± 1.72</td>
<td>p=0.610</td>
</tr>
<tr>
<td></td>
<td>2.13 ± 0.89</td>
<td>1.80 ± 1.04</td>
<td>p=0.377</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>20.67 ± 8.15</td>
<td>16.23 ± 6.51</td>
<td>p=0.056</td>
</tr>
<tr>
<td></td>
<td>23.25 ± 13.55</td>
<td>25.10 ± 11.05</td>
<td>p=0.647</td>
</tr>
<tr>
<td></td>
<td>12.28 ± 9.91</td>
<td>9.54 ± 8.25</td>
<td>p=0.388</td>
</tr>
</tbody>
</table>

surgery (3rd measurement), the mean glucose level in group 1 was higher than in group 2 (p=0.019).

The mean insulin level in the first measurement in group 1 was comparable with group 2 (p=0.102). After surgery, we observed that insulin levels stayed at the level of 11.54 µIU/ml in group 1, whereas in group 2 it increased up to 17.26 µIU/ml, but it was not a statistically significant difference (p=0.125). There were also no differences between groups in the 3rd measurement of insulin level (p=0.679) (fig. 2).

HOMA-IR prior to intervention was also comparable in the analyzed groups (p=0.138). Right after surgery, we noted at the level of 1.57 in group 1 and in group 2 it reached the level of 2.07 (p=0.610). There were no differences in the 3rd measurement in the analyzed groups (p=0.377) (fig. 3).

There were also no differences in preoperative cortisol levels between groups (p=0.056). Although postoperative levels were higher in
both groups, we did not notice any significant difference between the intervention and control group (p=0.646). At 24 hours after surgery, mean cortisol levels were again lower than in the 2nd measurement (p=0.38821) (fig. 4).

The relation of blood cortisol right after surgery to cortisol level prior to operation (2nd measurement/1st measurement) and 24 hours after surgery to cortisol level prior to operation (3rd measurement/1st measurement) did not differ significantly in either group (p=0.161 and p=0.979, respectively, tab. 2).

During the study period, no adverse or unintended effects were noted in either study group.

**DISCUSSION**

In this randomized controlled trial we failed to demonstrate any influence of preoperative CHO-loading on postoperative glucose, insulin resistance, or cortisol levels in patients undergoing elective laparoscopic cholecystectomy. We also did not find any differences in clinical outcomes. According to some authors, oral administration of carbohydrate-rich fluid a few hours prior to the surgery has certain positive effects (12, 17, 18). However, one must ask how extensive the surgery must be for CHO-loading to have an important biochemical and clinical implications.

Our results are different from the reports of other studies. Ljungqvist found a significant difference between insulin resistance in intervention and control groups after laparoscopic cholecystectomy. However, he used a different measuring technique and a constant intravenous glucose administration was applied. Similarly to us, Faria used an HOMA-IR index. He also noticed significant difference between the 2 groups, but the measurements were performed 10 hours after surgery, unlike our double measurements right after and 24 hours after surgery (19). Observations of Vigano also showed a lower surgical stress reaction (lower insulin resistance and lower cortisol level) in comparison to the control group, but in his group, smaller operations (laparoscopic cholecystectomy and mastectomy), as well as major surgical procedures, were also included (gastrectomy, pancreatectomy, and hemicolectomy), which indirectly explains the results (20). Therefore, it seems that administration of carbohydrate-rich fluids can have a positive influence by decreasing hormonal responses to surgical stress. However, increased insulin resistance and cortisol levels after smaller operative procedures is minimal and has a short duration, which therefore requires a more sensitive measurement tool.

An even more important issue is the clinical benefits of CHO-loading. They were listed earlier in the article in the context of extensive surgeries (18, 21) – laparoscopic cholecystectomy is not one of these. Currently, surgeons regard this operation as an almost outpatient procedure. The mean length of hospital stay is 1-2 days. Return to normal everyday activities takes only several days. Moreover, this procedure, with the exception of very rare complications (eg, common bile duct injury), is not considered a high perioperative risk surgery (22, 23, 24).

Thus, the question may arise of whether the administration of carbohydrate-rich fluid can improve the postoperative recovery even more? Our study did not show an influence on complications rate or length of postoperative stay. Other authors also do not report any positive clinical outcomes (25, 26). Kaska and Hausel
suggested that CHO-loading can decrease preoperative thirst and anxiety level, which can theoretically justify its use in cholecystectomy (27, 28). In our hospital, patients are allowed to drink clear fluids up to 2 hours before surgery and all patients are counseled preoperatively about the operation and postoperative course. Many of them are admitted on the day of surgery. In our opinion, this may decrease anxiety and thirst without the necessity of CHO-loading.

Our study has certain limitations. First of all, due to the relatively small groups, there is a possibility of the study being underpowered. Insulin resistance was assessed by the HOMA-IR index, which is considered inappropriate by some authors in this setting because it measures basal (hepatic) insulin resistance, although it has been reported as an outcome by numerous other studies of carbohydrate loading (29). Moreover, there are other hormones affecting stress response, which we did not measure.

CONCLUSION

We believe that CHO-loading is not clinically justified in laparoscopic cholecystectomy. No effect on levels of glucose, insulin resistance, or cortisol were observed. Although the procedure is safe, in our opinion there is no clinical benefit from CHO-loading prior to laparoscopic cholecystectomy.

REFERENCES


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