Basic nutritional investigation

Shrinking preoperative fast time with maltodextrin and protein hydrolysate in gastrointestinal resections due to cancer

Paula Alves Pexe-Machado R.D., M.Sc. a, Benedito Dario de Oliveira R.N. a, Diana Borges Dock-Nascimento R.D., Ph.D. b, Jose Eduardo de Aguiar-Nascimento M.D., Ph.D. a,*

a Department of Surgery, Julio Muller University Hospital, Federal University of Mato Grosso, Cuiabá, Brazil
b Department of Food and Nutrition, Federal University of Mato Grosso, Cuiabá, Brazil

ARTICLE INFO

Objective: Prolonged preoperative fasting increases postoperative hospital length of stay and current evidence recommends patients drink a carbohydrate-based liquid drink 2 h before surgery. The aim of this study was to investigate whether the addition of hydrolyzed protein to a carbohydrate-based drink would reduce both the inflammatory response and hospital length of stay.

Methods: We evaluated 22 patients of both sexes, undergoing gastrointestinal resection due to cancer. Patients were randomized into two groups: control group (n = 12; 6–8 h fast) and the intervention group (n = 10; fasted to solids for 6 h; and given a beverage containing 11% pea protein hydrolysate and 85% carbohydrates (79% maltodextrin and 21% sucrose), 400 mL the night before and 200 mL 3 h before surgery. Blood samples were collected the morning before surgery and on postoperative day 2.

Results: Overall mortality was 4.5% (one case, control group). The duration of postoperative hospital stay was twofold longer in the control group (P = 0.04). A significant increase of serum C-reactive protein/albumin ratio was observed in controls compared with the intervention group (P = 0.04).

Conclusion: The abbreviation of preoperative fasting time to 3 h using a solution containing carbohydrates and hydrolyzed pea proteins reduces the acute-phase inflammatory response and decreases the postoperative length of stay in patients undergoing major surgery for a malignancy.

* Corresponding author. Tel.: +556536237065; fax: +556536234020.
E-mail address: aguiar@terra.com.br (J. E. de Aguiar-Nascimento).

© 2013 Elsevier Inc. Open access under the Elsevier OA license.

Introduction

Perioperative care has been the subject of a number of studies in the past decade. The benefits of 6 to 8 h of preoperative fasting in order to reduce the risk for pulmonary aspiration of gastric content recently has been questioned in various studies [1,2]. Despite this, the “nothing by mouth after midnight” routine is still prescribed by many surgeons and anesthesiologists due to outdated concepts and paradigms [3]. Additionally, conventional fasting often is prolonged when surgery is delayed. Hence, the actual duration of the preoperative fast can be excessively long, lasting from 10 to 16 h [2,3]. This may impair patients’ recovery because the systemic response to surgical trauma is increased by the prolonged period of fasting.

The acute-phase inflammatory response to major abdominal surgeries is mediated by acute-phase proteins released by the liver. These proteins increase or decrease within hours after the trauma and may help to predict postoperative complications [4,5]. In this context, the Prognostic Inflammatory and Nutritional Index (PINI) proposed by Ingenbleek and Carpenter has been used to predict the risk for morbidity and mortality [6]. The PINI integrates two positive (C-reactive protein [CRP] and α-1-acid glycoprotein [α-1-GA]) and two negative (albumin and pre-albumin) acute-phase proteins. Studies have shown that formulas using acute-phase proteins, such as the CRP/albumin ratio, also may predict risks for hospitalized patients [7,8].

Beverages containing carbohydrates were evaluated and recommended to abbreviate preoperative fasting [9,10]. Recently, formulas containing either protein or amino acid
additions to a carbohydrate-enriched drink have been proposed. These new formulas may improve postoperative muscle strength [11] and reduce fatigue, anxiety, and discomfort [12] as well as lower the endocrine-metabolic response to trauma [13,14]. The addition of glutamine to these drinks improved the inflammatory response and nitrogen balance after laparoscopic cholecystectomy in one study [15] and the hepatic and mitochondrial metabolic response in two other recent studies [16,17].

However, the aforementioned studies were restricted to patients who underwent laparoscopic cholecystectomy. We questioned whether the abbreviation of preoperative fasting would improve the inflammatory response and other clinical outcomes after major surgery. Therefore, the aim of this study was to investigate whether shortening the preoperative fast using a solution containing carbohydrates and hydrolyzed proteins alters the acute-phase response and clinical outcomes of elective major operations of the digestive tract.

**Material and methods**

This was a randomized, single-blinded, clinical study carried out at the Julio Muller University Hospital (Mato Grosso State, Brazil). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the hospital Research Ethics Committee registered under number 723/CEP-HUJM/09. Written informed consent was obtained from all patients. The study was registered in ClinicalTrials.gov under the number NCT01563965. External monitoring of the study was carried out by the Research Ethics Committee of the Julio Muller Hospital.

Inclusion criteria included adults ages 18 to 65 y old, both sexes, and candidates for an elective laparotomy for gastrointestinal (GI) malignancies such as subtotal gastrectomy, left or right colectomy, and anterior resection of the rectum. Exclusion criteria were having diabetes mellitus, chronic kidney failure, chronic liver disease, serum bilirubin >2 mg/dL, body mass index (BMI) > 35 kg/m², American Anesthesiologists Association score >3, gastroesophageal reflux, gastroparesis, or intestinal obstruction. Patients with any non-compliance with the study protocol, who had associated operations, who experienced severe intraoperative complications (any type of shock, cardiac arrest, or coagulations problems), or those who experienced prolonged (>6 h) operative time also were excluded.

On admission to the hospital, patients were randomized into two groups, an intervention group and a control group, using random numbers issued by a computer program (www.graphpad.com). For the randomization, the precepts of the CONSORT flow diagram were followed [18]. The intervention group received 400 mL (on the evening before surgery) and 200 mL (3 h before surgery) of a solution containing 11% protein (hydrolyzed pea protein) and 89% carbohydrates (79% maltodextrin and 21% sucrose) and 0% lipids (Providextra, Fresenius Kabi, Sao Paulo, Brazil). The control group received a conventional 6- to 8-h preoperative fast. All the patients were fasted for solids for at least 6 h before surgery.

On the day before the surgery and on postoperative day (POD) 2 blood samples were collected for glucose, insulin, triglycerides, albumin, prealbumin, CRP, and α-1-GA assays. The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) equation was used as proposed by Matthews et al [19] to assess insulin resistance according to the formula: HOMA-IR = insulin (µU/mL) x glucose (mg/dL)/405. Inflammatory activity was assessed with the PINI = CRP.
(mg/L) × α-1-GA (mg/L) albumin (g/L) × prealbumin (mg/L) and the CRP/albumin ratio [8].

Except for the conventional fast of 6- to 8-h preoperative fast in control groups, all patients received the ACEVO protocol, which consisted of perioperative nutrition, preoperative information, no bowel preparation, reduced intravenous (IV) fluids, early postoperative feeding, abdominal drains or nasogastric tube only when necessary and early postoperative mobilization [20,21]. Nutritional status was assessed by BMI and subjective global assessment [22]. Patients considered malnourished or to be at nutritional risk received oral nutrition supplements or enteral feedings for 7 to 10 d before surgery. Preoperative mechanical bowel preparation was not prescribed. Patients received general anesthesia alone or with epidural. A dose of 2 g of IV cefoxitin was given 1 h before the surgical procedure and was repeated when the surgery lasted for ≥4 h. Hydration with 2000 mL to 2500 mL of Ringer’s lactate was prescribed for 24 h postoperatively. Postoperative feeding was programmed to begin the next day. Analgesics included dipyrone (500 mg IV every 6 h) and ketorolac (30 mg IV every 8 h). A single dose of 10 mg IV dexamethasone was injected before the end of anesthesia and metoclopramide was prescribed 10 mg IV every 6 h until POD 2. Patients were encouraged to stay out of bed for 4 h on day 1 and gradually increase this to 6 to 8 h by POD 3. Discharge was conditional on the following: no pain or good pain control with oral analgesics, good bowel motility and intake of solid foods, no IV fluids, and willingness to go home.

The primary outcome variable was the postoperative hospital length of stay (LOS). Other end points included infectious morbidity, insulin resistance assessed by HOMA-IR, and the aforementioned biochemical indexes or markers of inflammation.

Definitions

The following definitions were used:

1. infection of the surgical incision site
   a) purulent drainage through the incision with or without laboratory confirmation or
   b) isolation of organism from the wound or incision tissue and concomitant presence of at least one of the following signs and symptoms: pain, hypersensitivity, edema, hyperemia, or fever;

2. intra-abdominal infection
   a) purulent fluid within a drain or
   b) isolation of organism from abdominal cavity tissue or secretion or
   c) abscess found during reoperation, histopathologic examination, or image scan;

3. urinary tract infection
   a) urine culture with 100 000 or more colony forming units (CFU)/mL with one or at most two bacterial species or
   b) when two of the following were present: fever, urinary urgency, increased urinary frequency, dysuria or suprapubic pain in addition to one of the following laboratory findings: pyuria, presence of nitrates in the urinary sediment, or positive bacteriocracy;

4. pneumonia: presence of new or progressive infiltrate, consolidation, cavi
tation, or pleural effusion on chest X-ray in addition to clinical manifestations [23].

Statistical methods

The sample size calculation was based on the presupposition that the mean postoperative hospital LOS in the intervention group would be 3 d less than that of the control group. Eight cases in each study branch were judged to be sufficient to ensure 80% power (β error) and 5% significance (α error). All continuous data were initially analyzed for homogeneity by the Levene test and for normality by the Kolmogorov-Smirnov test. Either the Student’s t test or the Mann-Whitney test was then applied accordingly. The repeated measures analysis of variance was used to compare the evolution of both the biochemical parameters and the inflammatory indexes from the preoperative to postoperative period and the Bonferroni test was used to compare the main effects. A significance level of 5% (P < 0.05) was used. The data were presented as a mean and SD or as a median and variance. All the calculations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows 11. 0.

Results

Thirty patients were eligible: 15 were randomly allocated to each group. Eight patients were excluded for different causes, and 10 patients remained in the intervention group and 12 in the control group. Figure 1 shows the flowchart of the study. The clinical aspects and demographic characteristics of the patients are shown in Table 1. All procedures were performed by qualified surgeons using open laparotomy. There were no anesthetic complications and no cases of aspiration or vomiting during induction of anesthesia. The overall mortality was 4.5% (one case in the control group). The overall morbidity was 40.9% (nine cases); infectious complications were the most frequent at 31.8% (seven cases). Infectious complications occurred in four cases (33.4%) in the control group and in three cases (30%) in the intervention group (P = 1.00). One patient in the control group developed pneumonia; there were two cases of intra-abdominal sepsis (due to anastomotic breakdown) and one case of wound infection in each of the groups. Two patients in the intervention group developed non-infectious complications (prolonged postoperative ileus and atrial fibrillation).

| Table 1 Clinical and demographic characteristics of the patients in the two groups |
|-----------------|-----------------|-----------------|------|
| Variable        | Control group   | Intervention group | P   |
| Sex             | Males (%)       | Females (%)      |      |
| Males (%)       | 6 (50)          | 7 (50)           |      |
| Females (%)     | 10 (50)         | 8 (40)           | 0.20 |
| Age (y) (mean ± SD) | 48 ± 12        | 49 ± 10          | 0.89 |
| Type of surgery | Subtotal gastrectomy (%) | 3 (25) | 2 (20) | Non-analyzed |
| Cholecdo-jejunosotomy (%) | 1 (8.4) | 0 (0) |      |
| Hemicolecction + anastomosis (%) | 4 (33.3) | 3 (30) |      |
| Anterior resection of the rectum (%) | 4 (33.3) | 5 (50) |      |
| Preoperative fast (min) | 754 ± 100 | 240 ± 50 | <0.001 |
| Type of anesthesia | General (%) | 8 (66.7) | 6 (60.0) | 1.00 |
| General (%) | 4 (33.3) | 4 (40.0) |      |
| Blockage (%) | 2 (16.6) | 2 (20.0) |      |
| Preoperative fast (min) | 240 ± 50 | 200 ± 50 |      |
| Subjective global assessment (N%) | A- normal (%) | 2 (16.6) | 1 (10) | 0.54 |
| B- mild malnutrition (%) | 3 (25) | 1 (10) |      |
| C- severe malnutrition (%) | 7 (58.3) | 8 (50) |      |
| Body mass index (kg/m²) | 24.4 ± 5.4 | 25.0 ± 3.9 | 0.79 |
| Percentage of body weight loss (mean±SD)* | 10 ± 8 | 16 ± 5 | 0.13 |
| American Society of Anesthesiologists score | 1 | 1 (10) | 0.25 |
| 2 | 6 (50) | 7 (70) |      |
| 3 | 1 (8.3) | 2 (20) |      |

* 9 controls; 7 intervention.

Fig. 2. Mean (SEM) postoperative length of stay in the two groups*, P = 0.04 (Mann-Whitney test).
Table 2
Changes in serum glucose, serum insulin, and HOMA-IR from preop to POD 2 in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 12)</th>
<th>Intervention group (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>POD 2</td>
<td></td>
</tr>
<tr>
<td>Serum glucose (mg/dL)</td>
<td>93 (26)</td>
<td>100 (37)</td>
<td></td>
</tr>
<tr>
<td>Serum insulin (mg/dL)</td>
<td>3.6 (2.8)</td>
<td>4.2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.92 (0.82)</td>
<td>1.25 (1.55)</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; CRP, C-reactive protein; PINI, Prognostic Inflammatory and Nutritional Index; POD, postoperative day; preop, preoperative Data are mean (SD). Repeated measures ANOVA. The within-groups interaction tests for all variables were not significant (P > 0.05).

Postoperative hospital stay

Figure 2 shows the postoperative hospital LOS in the two groups. A significant (P = 0.04) twofold longer hospital LOS was found in the control group (median 14 d, mean 15.6 d, range, 4–34 d) when compared with the intervention group (median 7 d, mean 8.1 d, range, 4–17 d). In non-complicated patients, there was a trend to a shorter postoperative LOS in the studied group (intervention group: median 6.5 d, mean 6.1 d, range, 4–8 d versus control group: median 9.5 d, mean 9.1 d, range, 4–15 d; P = 0.09). The same trend was observed in complicated patients (intervention group: median 10 d, mean 11 d, range, 7–17 d versus control group: median 24 d, mean 22.8 d, range, 8–34 d; P = 0.06).

Serum glucose, serum insulin, and HOMA-IR

Changes in serum glucose, serum insulin, and HOMA-IR are shown in Table 2. There was no significant difference between the two groups except that serum insulin was greater in the intervention group. Serum glucose increased from the preoperative period to POD 2 in both groups (P < 0.01).

Inflammatory markers

The changes in the acute-phase proteins and inflammatory indexes are shown in Table 3. Only serum prealbumin did not significantly change overtime. All other inflammatory markers changed from preoperative period to POD 2 in both groups. The control group showed a tendency toward a lower serum albumin than the intervention group. The CRP/albumin ratio was significantly greater in control group when compared with the intervention group (Fig. 3).

Discussion

The overall findings of this study showed that the intake of a beverage containing carbohydrate plus pea protein hydrolysate 3 h before the induction of anesthesia is both safe and associated with benefits to patients undergoing major surgery for GI malignancies. The main outcome of the present study was a significant decrease in the postoperative LOS associated with the abbreviation of preoperative fasting using this beverage. Additionally, the patients in the intervention group had a lower postoperative inflammatory reaction than the controls. These findings are quite relevant and suggest that the shortening of preoperative fast with pea protein hydrolysate in the carbohydrate-based drink in this subset of patients may be effective.

The abbreviation of preoperative fasting to 2 h with clear fluids or carbohydrate-enriched drinks is recommended by many anesthesiology societies [24–26]. However, the addition of either amino acids or hydrolyzed proteins to the carbohydrate-based beverages may confer postoperative benefits. Randomized studies reported that patients who drank this type of solution 2 h to 3 h before surgery lost less urinary nitrogen [15] and acquired greater muscle strength [11]. In agreement, our findings showed that this type of solution was associated with a reduced postoperative inflammatory response and a shortened postoperative hospital LOS after laparotomy for GI malignancies.

The type of carbohydrate contained in the beverage we tested was a mixture of maltodextrin and sucrose. Maltodextrin is a sweet, easily digested carbohydrate made from cornstarch. It contains small chains of several dextrose molecules held together by very weak hydrogen bonds. Consequently, it is absorbed slower than sucrose and thus makes maltodextrin an excellent carbohydrate for preoperative drinks. The solution containing both maltodextrin and sucrose may better activate more transport mechanisms in the intestinal lumen and thereby facilitate faster energy uptake and hydration [27]. Adding hydrolyzed proteins to a carbohydrate-based drink was reported by Henriksen et al. They found a significant decrease in the activity of muscular glycogen synthase (a rate-limiting enzyme for glucose storage as glycogen) in patients who received preoperative hydrolyzed soy protein supplemented carbohydrate-rich drinks before undergoing major abdominal surgery. In accordance, other studies also found either clinical or metabolic benefits with either glutamine or whey protein supplemented carbohydrate-rich preoperative drinks [15,16]. Pea protein hydrolysate has rapid gastric emptying and is probably more effective than soybean hydrolysate. Pea protein hydrolysate plus carbohydrate induces both higher insulin and glucagon responses than soybean protein hydrolysate plus carbohydrate [28]. Additionally, pea protein hydrolysate may

Table 3
Changes in the inflammatory markers from preop to POD 2 in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 12)</th>
<th>Intervention group (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>POD 2</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>20.4 (26.6)</td>
<td>180.8 (62.0)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8 (0.7)</td>
<td>2.8 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Prealbumin (g/L)</td>
<td>0.25 (0.10)</td>
<td>0.22 (0.26)</td>
<td></td>
</tr>
<tr>
<td>s1-glycoprotein (mg/dL)</td>
<td>147.0 (112.4)</td>
<td>164.2 (59.3)</td>
<td></td>
</tr>
<tr>
<td>PINI</td>
<td>12.8 (31.8)</td>
<td>96.3 (112.5)</td>
<td></td>
</tr>
<tr>
<td>CRP/albumin ratio</td>
<td>6.9 (10.9)</td>
<td>64.9 (24.0)</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; CRP, C-reactive protein; PINI, Prognostic Inflammatory and Nutritional Index; POD, postoperative day; preop, preoperative Data are mean (SD). Repeated measures ANOVA. The within-groups interaction tests for all variables were not significant.
have antioxidant, anti-inflammatory, and immunomodulating properties that may confer benefits to the patient [29].

As expected, preoperative insulin levels were higher in the intervention group than in the control group patients, who had lower serum insulin levels in response to an overnight fast [11]. Serum glucose increased in both groups and was not different between patients who did or did not drink the energy-rich beverage. Insulin resistance, measured by the HOMA-IR test, was similar in the two groups. This finding differed from other studies reported by our group in which we found a significantly higher HOMA-IR in patients who received a carbohydrate-enriched drink 2 to 3 h before a less-aggressive operation such as laparoscopic cholecystectomy [8,15,30]. However, in our earlier studies, the HOMA-IR was evaluated 10 to 12 h after the operation. In the current study, blood samples were collected on POD 2 when patients were already receiving oral or enteral nutrition. This early initiation of postoperative feeding in the two treatment groups may explain their similar findings in this study.

CRP is a positive acute-phase protein and its level correlates well with inflammation intensity and may predict postoperative complications [4,5]. In contrast, a decrease of negative acute-phase proteins, such as albumin and prealbumin, is expected after trauma, due to the inhibition of their synthesis by proinflammatory cytokines [5]. Hypoalbuminemia however, is one of the suggested parameters to confirm preexisting malnutrition in surgical patients [31]. The serum albumin concentration frequently has been regarded as an indicator of nutritional status, although hypoalbuminemia may reflect an acute-phase protein response during inflammation mediated by cytokines [4]. Changes of serum proteins and electrolytes between the treatment groups may explain their similar findings in this study.

Fig. 3. Changes in serum CRP/albumin ratio in the two groups overtime 1.

Data are means and standard errors of the means. White bars = preoperative period, hatched bars = 2nd postoperative day.

*p < 0.05 versus preoperative period

† p = 0.04 versus intervention group

The shortening of the preoperative fast to 3 h using a drink containing carbohydrates and pea protein hydrolysate reduced both the acute-phase inflammatory response and the postoperative hospital LOS. Thus we concluded that the abbreviation of preoperative fasting with carbohydrates plus pea hydrolyzed protein not only is safe but also may enhance the recovery of patients who undergo major abdominal operations due to GI malignancies.

Acknowledgments

We thank BioMed Proofreading for the English copy editing of this manuscript. This study was funded by the CNPq—Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil.

References


American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 2011;114:1158–64.


