Ingestion of glutamine and maltodextrin two hours preoperatively improves insulin sensitivity after surgery: a randomized, double blind, controlled trial

Ingestão de glutamina e maltodextrina duas horas no pré-operatório imediato melhora a sensibilidade à insulina pós-operatória: estudo aleatório, duplo-cego e controlado

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ABSTRACT

Objective: *To investigate whether the abbreviation of preoperative fasting with a drink containing glutamine and maltodextrin improves organic response to surgical trauma.* ***Methods***: *Thirty-six female patients adult (18-62 years) candidates for elective laparoscopic cholecystectomy were randomly divided into three groups: conventional fasting (fasting group), and two groups receiving two different diets, eight hours (400ml) and two hours before induction of anesthesia (200ml): carbohydrate (CHO) group (12.5% maltodextrin) and the glutamine (GLN) group (12.5% maltodextrin and 40 and 10g of glutamine, respectively). Blood samples were collected pre and postoperatively.* ***Results***: *Twenty-eight patients completed the study. No pulmonary complication occurred. Gastric residual volume was similar between groups (p = 0.95). Postoperatively, all patients from the fasting group had abnormal glucose (> 110mg/dl), this abnormality being of 50% when compared to the CHO group (p = 0.14), and of 22.2% when compared to the GLN group (p = 0.01). All patients who had the fasting period shortened (CHO + GLN) had normal postoperative insulin, contrasting with 66.7% in the fasted group (p = 0.02). The abnormal sensitivity to insulin postoperatively rose from 32.1% to 46.4% of cases (p = 0.24), and it occurred in only 11.1% of patients in GLN group when compared to 55.5% in the fasting group (p = 0.02).* ***Conclusion***: *the abbreviation of preoperative fasting for two hours with maltodextrin and glutamine improves insulin sensitivity in patients undergoing elective laparoscopic cholecystectomy.*

Key words: *Fasting. Glutamine. Carbohydrates. Preoperative care. Insulin.*

INTRODUCTION

The past decades have witnessed efforts to adapt traditional perioperative conducts to the results obtained by investigations of high methodological quality. Paradigms such as the use of a nasogastric tube, bowel preparation, intravenous fluids and late oral nutrition have been challenged and changed. This is also the case of preoperative fasting[1-6].

Elective surgeries routinely keep the patient in overnight fast, "nothing by mouth" for six to eight hours until the induction of anesthesia. Their goal was to prevent pulmonary complications associated with vomiting and aspiration of gastric contents into the bronchial tree, known as the Mendelson's syndrome[7].

With the advent of evidence-based medicine, randomized prospective studies with level "A" evidence have repeatedly shown that reducing the time of preoperative fasting for just two hours, with the intake of clear liquids with carbohydrates (CHO), does not result in increased risk of bronchial aspiration of gastric contents associated with anesthesia[8-10]. Preoperative fasting adds a metabolic stress to surgical trauma and contributes to worsening of insulin resistance that is proportional to the magnitude of surgical trauma[11].

The decrease in insulin sensitivity in the postoperative period occurs as a result of the surgery and the prolonged preoperatively fasting. And that can result in hyperglycemia, increased length of stay, infectious complications, morbidity and mortality[12].

There is no more scientific basis that supports the conduct of preoperative fasting of "nothing by mouth" for candidates for elective operations until the beginning of anesthesia[1-10].

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The ingestion of carbohydrate drink in the immediate preoperative period is associated with improved insulin sensitivity, which, in turn, improves the metabolic response to surgical trauma, shortens hospitalization time and may result in clinical benefits such as reduction of nausea, vomiting, hunger, thirst, anxiety, possibly accelerating postoperative recovery[1-16].

With the advantages of abbreviation of preoperative fasting for two hours, the interest in associating one immune-modulating drug, glutamine (gln), in a formula containing 12.5% maltodextrin.

The use of gln in surgical patients is associated with lower rates of infectious complications in the postoperative hospitalization time. Moreover, it may improve nitrogen balance[17,18].

The gln, in particular, attenuates insulin resistance[19], improves its peripheral sensitivity, with consequent reduction of hyperglycemia, favors increased availability of glucose[20] and also directly stimulates insulin production by the pancreatic beta cells [21].

The objective of this study was to investigate the effects of abbreviation of preoperative fasting for two hours on insulin sensitivity, with the ingestion of a liquid formula containing maltodextrin and glutamine, in patients undergoing elective laparoscopic cholecystectomy.

METHODS

This was a prospective, randomized, controlled, double blind trial with 43 adult patients. Data were collected between October 2008 and October 2010. The study was approved by the Ethics and Research Committee of the Júlio Müller University Hospital in Cuiabá, Mato Grosso State – MT, Brazil (no. 0468/09). All patients signed an informed consent form. The study included patients who met the following inclusion criteria: female; aged 18 to 65 years; diagnosis of chronic cholelithiasis; candidate for elective laparoscopic cholecystectomy; body mass index (BMI, kg/m2) between e" 18 and d" 29.9 kg/m^2; and an ASA score (American Society of Anesthesiologist) I or II. We excluded patients who did not adhere to the protocol at any stage of the study and who displayed: acute cholecystitis or cholangitis found during surgery; need for additional surgery; operating time longer than two hours; diagnosis of diabetes mellitus (fasting glucose> 110mg/dl); gastroesophageal reflux disease confirmed by endoscopy; and gastroparesis or routine use of prokinetic agents.

The protocol included three dietary intervention groups: fasting (Fasting), carbohydrate group (CHO) and glutamine (GLN) groups. For the group Fasting, we adopted the routine conventional fasting for eight hours the night before the operation. The CHO group received a liquid formula containing 12.5% maltodextrin, (NidexÒ, Nestlé, São Paulo, Brazil) being 50g in the first administration (T1) and 25g in the second (T2); the GLN group also received the maltodextrin, 50g (T1) and 25g (T2), though with added free glutamin (Resource glutaminÒ, Nestlé, São Paulo, Brazil), 40g in the first administration (T1) and 10g in the second (T2). Patients able to participate in the study were oriented with respect to the times of dilution and swallowing the contents of the vials by means of an explanatory printout. The first take of 400ml (T1) occurred at 23 hours (eight hours before induction of anesthesia) and the second take of 200ml (T2) occurred at five o'clock in the morning (two hours before induction of anesthesia). Ten hours after surgery, all patients received a liquid diet (liquefied soup, juice, gelatin, water).

As perioperative and anesthesia protocol, the patients were instructed to wake up at 04h30min in the morning and follow the procedures described in the previously delivered orientation. All patients were operated by the same team of surgeons and anesthetists at seven o'clock. We opted for balanced general anesthesia (alfentanil, 300mg/kg; propofol 2.5 mg/kg and atracurium 0.5 mg/kg, maintained with sevoflurane 5%) without epidural blockade. During anesthesia, only 0.9% saline solution and/or simple Ringer were infused through a peripheral vein. All patients received a dose of 1.0g of cefazolin or cephalothin at induction. In the first minutes that followed orotracheal intubation, a nasogastric tube (NGT) of 20F was inserted and connected to suction to determine the gastric residual volume (GRV). The aspiration of the GRV by the anesthetist was performed with aid of a 20ml syringe. The location of the NGT was evaluated by auscultation with a stethoscope placed in the epigastric region followed by injection of 10 to 20 cc of air. After positioning the gastric NGT, the GRV was aspirated, measured and recorded. In the postoperative period, we prescribed 2.0 g cefazolin, 10mg dexamethasone, 100mg ketoprofen, dipyrone 2.0 g; antiemetics were not routinely prescribed (in risk cases due to the increase of nausea and vomiting, we prescribed droperidol 0,.5 to 1.0 ml or metoclopramide 10mg).

The primary outcome variable was insulin sensitivity, calculated by the test Quicki (quantitative insulin sensitivity check index: $1 / (\mathrm{Log}_{10}\ \mathrm{insulin} + \mathrm{Log}_{10}\ \mathrm{glucose})$[22]. We considered a normal insulin sensitivity when the Quicki test values were greater than 0.35. Dosages of blood glucose (mg/dl; enzymatic method) and insulin (IU/ml; electrochemiluminescence method) were performed to calculate the Quicki test pre and postoperatively. Blood samples were collected at two different times: immediately before induction of anesthesia (preoperative) and at the tenth hour after surgery, before the release of the liquid diet. Patients were instructed not to ingest any food or liquid before the second blood collection. For the analysis of perioperative serum glucose we considered normal blood values below 110mg/dl; and for perioperative insulin, below 24.9 U/ml. The GRV was also evaluated between the three groups.

The sample size was calculated according to previous studies by our group[23,24]. It was estimated that a minimum of nine patients per group is sufficient to meet 60% reduction in sensitivity to insulin calculated by Quicki with a power of 70% (â error) and alpha error of 0.05%[25]. The chi-square or Fisher tests were used for analysis of categorical variables. All continuous variables were initially analyzed by the Levene test to verify homogeneity, then the Kolmogorov-Smirnov test to determine normality. For continuous data, we applied a repeated measures ANOVA for evaluation of intra-group and between-groups difference, followed by the Tukey test, when significant, to ascertain where was the statistical difference. We established a limit of 5% statistical significance (p d” 0.05). Results were expressed as mean, followed by the standard mean error (EMR), or median and range, as appropriate.

RESULTS

The flowchart of inclusion, exclusion and randomization of patients studied is shown in figure 1. Of the 43 eligible patients, 15 were excluded and 28 remained for analysis (n = 9 fasting group, n = 10 CHO group and n = 9 glutamine group) with a median age of 42 (18-62) years. All patients included in the study ingested the entire volume of liquid formulas prescribed but the fasting group, which remained in conventional preoperative fasting. There was no event of aspiration or regurgitation of gastric contents manifest by clinical signs and symptoms during anesthetic induction, or at any other time of the study. Also, there were no postoperative deaths or complications. All patients were discharged from hospital 12 or 24 hours after the operation.

The median gastric residual volume (GRV) was 6ml, and varied between zero and 20ml. The comparison

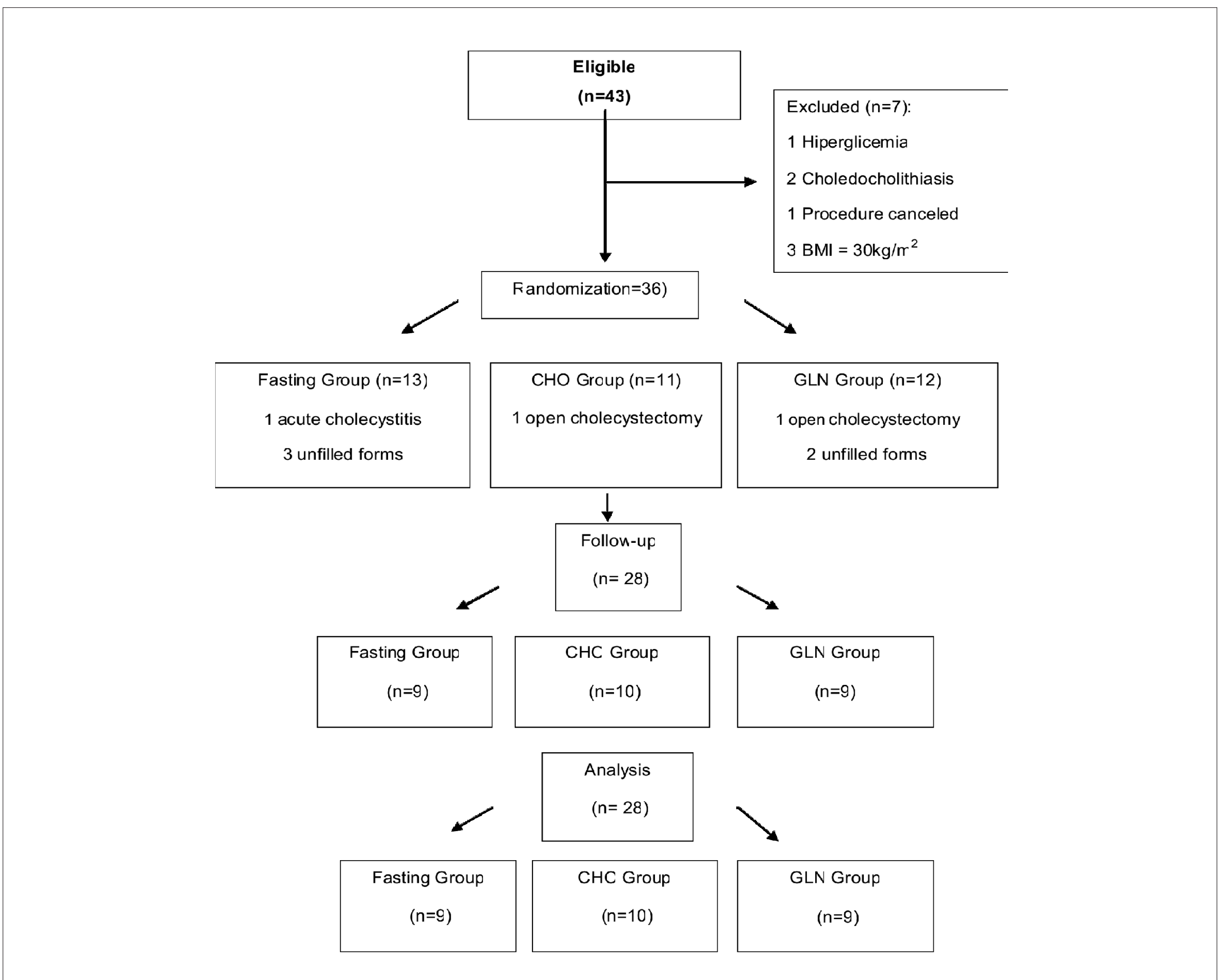

Figure 1 - *Flowchart of inclusion, exclusion and randomization of studied patients.*

between the three groups showed no difference in values of GRV (p = 0.95) between the fasting group (median = 3.0 ml [0-20]), CHO (median = 7.0 [0-10]) and GLN (median = 5ml [0-15]). The results of GRV are shown in figure 2.

As a premise for inclusion in the study, all patients (n = 28) had normal blood glucose in the outpatient consultation that preceded the operation. In the induction measurement blood glucose levels remained unchanged, no case above 110mg/dl being recorded (Table 1). However, ten hours after the operation, 53.6% (n = 15) began to show blood glucose above 110mg/dl. When comparing groups, all patients in the fasting group had abnormal blood glucose (> 110mg/dl), this abnormality being displayed in 50% of the CHO group (p = 0.14), and only in 22.2% in GLN group (p = 0.01).

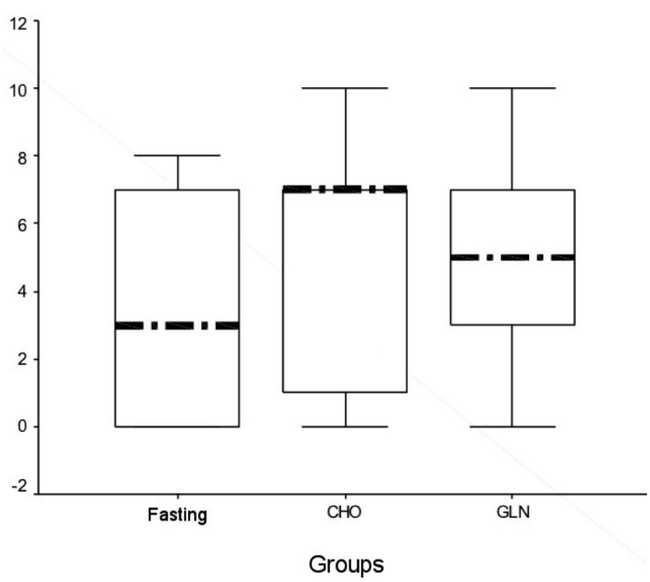

Figure 2 - *Distribution of gastric residual volume in the three groups of patients studied. Data represent median, interquartile range and variation. One-way ANOVA statistical test followed by Tukey test (p = 0.95).*

There were no cases of elevated serum insulin in the GLN group. At induction, only one case in the fasting group and two cases in the CHO group had higher insulin levels (p> 0.05). Postoperatively, all patients receiving drink two hours before induction (CHO + GLN group) had normal serum insulin (<24.9 U / ml), whereas 33.3% (n = 3) of cases operated on conventional fasting had elevated serum insulin (p = 0.02). There was no statistical difference when the three groups were compared.

Preoperatively, 32.1% (n = 9) of the patients had abnormal sensitivity to insulin (three in the fasting group, five in the CHO group and one in the GLN group, p = 0.19). There was a nonsignificant increase in the group of patients with abnormal insulin sensitivity ten hours after surgery (46.4% of cases, p = 0.24). However, when comparing the frequency of cases with abnormal insulin sensitivity measured by the Quicki test, it was found that the GLN group showed only one (11.1%) case of abnormal sensitivity, while the fasting group had five (55.5%) (p = 0.02) (Table 2).

DISCUSSION

This study showed that intake of liquid formula with 12.5% of maltodextrin, enriched with glutamine (gln) was able to attenuate the organic response to routine laparoscopic cholecystectomy. The relevance of this study consists in adding free gln to the liquid formula with maltodextrin, already established in the literature for abbreviation of preoperative fasting for two hours.

The ingestion of formula with protein or gln associated with maltodextrin does not result in increased GRV, ensuring the safety of its intake up to two hours before induction of anesthesia[26,27]. It is noteworthy that the GRV was no different for patients who conventionally fasted foe eight hours or for the ones submitted to shortened preoperative fasting with gln and maltodextrin and pure maltodextrin. However, our study is the limited by gastric

Table 1 - Comparison of mean and mean standard error of the biochemical variables and insulin sensitivity determined by Quicki test at anesthesia induction and postoperatively ih the three groups.

	Group						
	Fasting		CHO		GLN		
Variables	Preop	Postop	Preop	Postop	Preop	Postop	p (intra-group)
Glucose (mg/dL)	81 ± 2	119 ± 4	76.5 ± 4	108 ± 7	77.1 ± 4	96.3 ± 7	< 0.01
Insulin (IU/mL)	12.0 ± 3.2	13.0 ± 3.6	18.6 ± 5.3	8.6 ± 1.4	8.0 ± 0.8	6.5 ± 0.7	0.08
Quicki Test	0.35 ± 0.02	0.33± 0.01	0.33± 0.01	0.35± 0.01	0.36± 0.04	0.36± 0.05	0.55

ANOVA for repeated measures. p> 0.05 for all comparisons between groups.
CHO: carbohydrate group
GLN: glutamine group
Pre-op: preoperative
Post-op: postoperative
Test QUICKI: quantitative insulin sensitivity check index

Table 2 - Sensitivity of insulin evaluated by the Quicki test in the three groups postoperatively.

Group	Quicki Test	
	Normal (>=0.35)N(%)	Abnormal (<0.35)N (%)
Fasting	4 (45.5)	5 (55.5)
CHO	7 (70)	3 (30)
GLN	8 (89.9)*	1 (11.1)

QUICKI Test: quantitative insulin sensitivity check index
CHO: carbohydrate group
GLN: glutamine group
** P = 0.02 vs. fasting group*

aspiration technique used to measure the GRV. Currently, the gold standard for this measure is considered to be the assessment of gastric emptying with radioisotope[28] or other imaging method, such as magnetic resonance[26].

Lobo et al. used magnetic resonance to assess gastric emptying and found that, with 300 to 400ml of beverage with 12.5% maltodextrin, it occured at 120 minutes, and when 15 grams of gln and antioxidants were added to the formula, the emptying occured in approximately 180 minutes[26].

Several studies with grade "A" evidence have shown that GRV returns to its baseline value after one hour of liquid ingestion (10-30ml)[8-10,13,14].

The risk of aspiration pneumonia, vomiting or regurgitation does not increase when comparing patients who remaining in total fasting the night before the operation to patients with shortened fasting for two hours before anesthesia induction[14,27,29].

Since the early studies with fasting abbreviation, no morbidity or adverse events were reported. This is confirmed by the observation of more than 2000 patients in clinical studies and over two million patients who had fasting shortened in clinical practice[30].

The results of our study indicate that the abbreviation of preoperative fasting with maltodextrin and glutamine-enriched water is safe and is associated with reduced organic response to surgical trauma by improving insulin sensitivity evaluated by QUICKI test.

In another study of our group, conducted with patients who underwent a protocol of fasting abbreviation with the same maltodextrin and gln, formula, the peripheral insulin resistance increased in the postoperative period only for the patients who remained in "nothing by mouth" fasting when compared to the CHO and GLN groups[31]. In this study all patients in conventional fasting had abnormal blood glucose after 10 hours of cholecystectomy and only the patients with fasting shortened with a drink enriched with glutamine or dextrose showed no associated abnormal insulin.

The combination of gln, maltodextrin and antioxidants can cause the plasma more physiological metabolism of glucose and insulin due to the increased insulin production and improvement of its sensitivity[32]. The gln can also modify the metabolism of glucose to be converted to arginine, improving insulin sensitivity[19] and increasing insulin secretion[33].

Our results showed that the conventional preoperative fasting reduced insulin sensitivity, even after a minimally invasive procedure, such as elective laparoscopic cholecystectomy. The sensitivity of insulin is reduced by 50%, even in uncomplicated cholecystectomies[34]. In kidney-pancreas double transplant patients, the Quicki test proved to be a reliable test to assess insulin sensitivity when compared to the euglycemic hyperinsulinemic clamp[35].

Thus, the results of this study contribute to adding new information to the perioperative nutritional treatment with short time of preoperative fasting for two hours and with the inclusion of gln to maltodextrin clear liquids.

The abbreviation of preoperative fasting for two hours, with the ingestion of liquid formula containing glutamine and maltodextrin is safe and improves insulin sensitivity in patients undergoing elective laparoscopic cholecystectomy.

R E S U M O

Objetivo: *investigar se a abreviação do jejum pré-operatório com uma bebida contendo glutamina e dextrinomaltose melhora a resposta orgânica ao trauma cirúrgico.* ***Métodos:*** *trinta e seis pacientes adultas, (18-62 anos) candidatas à colecistectomia videolaparoscópica eletiva foram aleatoriamente divididas em três grupos: grupo jejum convencional (grupo Jejum), ou em dois grupos para receber duas dietas diferentes, oito horas (400ml) e duas horas antes da indução anestésica (200ml): grupo carboidrato (12,5% de dextrinomaltose) e glutamina (12,5% de dextrinomaltose e, respectivamente, 40 e 10g de glutamina). As amostras de sangue foram coletadas no período pré e pós-operatório.* ***Resultados:*** *vinte e oito pacientes completaram o estudo. Nenhuma complicação pulmonar ocorreu durante o estudo. O volume residual gástrico foi similar entre os grupos (p=0,95). No pós-operatório, todas as pacientes do grupo jejum apresentaram glicemia anormal (>110mg/dl), sendo essa anormalidade 50% para o grupo CHO (p=0,14) e, apenas, 22,2% para o grupo GLN (p=0,01). No pós-operatório, todas as pacientes que abreviaram o jejum (grupo CHO*

+ GLN) apresentaram insulinemia normal, contrastando com 66,7% no grupo jejum (p=0,02). A sensibilidade anormal à insulina subiu no pós-operatório de 32,1% para 46,4% dos casos (p=0,24). A sensibilidade anormal à insulina, no pós-operatório, ocorreu em apenas 11,1% das pacientes do grupo GLN comparado com 55,5% do grupo jejum (p=0,02). ***Conclusão:*** *a abreviação do jejum pré-operatório para duas horas com glutamina e dextrinomaltose melhora a sensibilidade à insulina de pacientes submetidas à colecistectomia videolaparoscópica eletiva.*

Descritores: *Jejum. Glutamina. Carboidratos. Cuidados pré-operatórios. Insulina.*

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