Preoperative administration of Omega-3 fatty acids on postoperative pain and acute-phase reactants in patients undergoing Roux-en-Y gastric bypass: a randomized clinical trial

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Abstract:

Background: The term “Immunonutrition” (IMN) describes the enteral administration of certain substrates with a theoretical immunomodulating function. From all the elements conforming these IMN formulas, Omega-3 fatty acids (O3FA) are hypothesized to be the most important component for immunomodulation, with increased anti-inflammatory and antioxidant effect.

Patients and Methods: A prospective randomized clinical trial of all the patients undergoing laparoscopic Roux-en-Y gastric bypass was performed. Patients were randomly assigned into 2 groups: those patients receiving a preoperative balanced energy high-protein formula (Control Group) and those ones who received the same preoperative nutritional formula enriched with O3FA (Experimental Group). In both groups, there was a restriction to 900 Kcal/day. Nutritional intervention started 10 days before surgery and was maintained up to 8 hours before the surgical act. Preoperative weight loss, postoperative pain, complications and acute phase reactants were investigated.

Results: 40 patients were included in the study, 20 in each group. Preoperative excess weight loss (EWL) with the prescribed treatment was 10.6 $\pm$ 7.7% in Control Group and 14.1 $\pm$ 5.8% in the Experimental Group (p=0.024). Mean postoperative pain was 25 $\pm$ 9.2 mm in Control group and 10,9 $\pm$ 4,4mm in Experimental Group (p=0.015). CRP determined 24 hours after surgery was significantly lower in the Experimental Group than in the Control Group. There were not significant differences in complications, mortality or readmission rates between groups.

Conclusions: The use of a nutritional supplement enriched with O3FA is associated with a greater preoperative weight loss, reduced postoperative pain and decreased postoperative levels of C reactive protein.

Key words:

Omega-3 fatty acids; Immunonutrition; Sleeve Gastrectomy; Postoperative pain; C reactive protein; Preoperative excess weight loss

Introduction:

Most bariatric surgery groups establish dietary restrictions to a total caloric intake of less than 1000 kcal per day during a period between 2 and 8 weeks before surgery. The objective of this measure is to maximize the reduction of weight preoperatively, which has demonstrated to be beneficial. This weight loss is helpful for the surgeon, since a reduction of hepatomegalia secondary to steatosis is achieved. Nutritional formulas may be superior to regular diets because compliance is better controlled and lower energy intake is more likely to be accomplished[1]. Moreover, many nutritional formulas present a high protein content, essential for the process of postoperative healing, mainly in those patients who present hypoproteinemia despite their morbidly obese condition[1,2].

The term "Immunonutrition" (IMN) describes the enteral administration of certain substrates (omega-3 fatty acids (O3FA), arginine, glutamine, nucleotides and antioxidants) with an eventual immunomodulating function. Animal and human studies have suggested that the individual components might have beneficial effects on immune function. The reported evidence of IMN in surgical patients has been mostly focused on oncologic pathologies, reporting reductions in postoperative morbidity rates[3,4]. A previous study of our group showed that the preoperative administration of IMN was associated with a greater preoperative weight loss, and lower postoperative pain and acute-phase reactants, in patients undergoing laparoscopic sleeve gastrectomy as bariatric procedure[5].

Of all the elements conforming these IMN formulas, O3FA are hypothesized to be the most important component of immunomodulation, with increased anti-inflammatory and antioxidant effect[6].

The main outcome of this study was to evaluate the isolated effect of O3FA on analytical acute-phase reactants, in patients undergoing Roux-en-Y gastric bypass (RYGB) as bariatric technique. Secondary outcomes were preoperative weight loss, and postoperative pain and complications.

Patients and Methods:

A prospective double-blinded randomized clinical trial of the patients undergoing laparoscopic RYGB between February and September 2016 was performed. Inclusion criteria were body mass index (BMI) >40 Kg/m^2 or BMI > 35 Kg/m^2 with the presence of comorbidities associated to obesity, patients undergoing a laparoscopic RYGB as bariatric procedure, age older than 18 years and willing to participate in the study and giving their written consent. Exclusion criteria were patients undergoing other bariatric techniques, or undergoing any other surgical procedure added to the bariatric surgery, inability to understand the nature and purpose of the study and / or to accept written participation in the study, and impossibility to comply with pre-established clinical follow-up. Excepting these inclusion and exclusion criteria, there was no other selection process before deciding who should be considered eligible for the study.

The sample size calculation was based on historical data of our institution, of postoperative C reactive protein (CRP) determined 24 hours after surgery in patients receiving a preoperative balanced energy high-protein formula (3.3 mg/dl) and an expected reduction of 50% of the CRP values in the experimental group (nutritional formula enriched with O3FA). At 80% power and a significance level of p=0.05, it was calculated that 20 patients were required in each arm of the study.

Patients were randomly assigned using a random-number table into 2 groups: those patients receiving a preoperative balanced energy high-protein formula (Fresubin Protein Energy Drink, Fresenius Kabi, Germany) (Control Group) and those ones who received the same preoperative nutritional formula enriched with O3FA (Supportan Drink, Fresenius Kabi, Germany) (Experimental Group) (CONSORT flow diagram).

Methodology:

The formula selected for each patient, depending on the randomization, was started 10 days before surgery and maintained up to 8 hours before the surgical act. The composition of the 2 formulas is shown in Table 1. The patients receiving the nutritional formulas were warned that apart from the formula they could only intake water or sweetened infusions (no sugar-added, no caloric). The flavors, available for both nutritional formulas, were chocolate, vanilla, cappuccino, strawberry and tropical fruits. Dietary compliance was evaluated by means of a food diary that the patients filled. A dietitian, who was in permanent contact with the patients, evaluated the food diary. The caloric intake has not been adjusted per Kg; 900 Kcal/day were uniformly prescribed. The patients must drink 3 cartons per day, each carton with a volume of 200 ml (caloric value of the supplement 1.5 Kcal/ml). Protein and O3FA content of each supplement is shown in Table 1.

Preoperative Evaluation

A multidisciplinary team, including surgeons, endocrinologists, dietitians, anesthesiologists and psychiatrists, performed a combined medical, nutritional, and endocrinological work-up to evaluate potential surgical candidates. Preoperative complementary test were abdominal ultrasound, upper gastrointestinal endoscopy,

polysomnography, and analytical parameters of the nutritional status. Psychiatrists assessed interviews to evaluate the implication of the patient in following a correct diet during the postoperative course.

Surgical Technique

5 ports will be placed in right hypochondrium (12 mm), left hypochondrium (12 mm), epigastrium (11 mm), subxyphoideal space (11 mm), and left flank (5 mm). Pneumoperitoneum pressure was set to 12 mmHg. A 6-cm long gastric pouch was performed, calibrating it with a 36-Fr bougie, with a linear stapler (Echelon Flex, Johnson&Johnson, USA). A 60-cm biliary limb and a 150-cm alimentary limb were performed. Both anastomoses were performed with linear stapler (Echelon Flex, Johnson&Johnson, USA), calibrating the gastrojejunal anastomosis to 2 cm. Mesenteric defects were not closed in any of the cases. The integrity of the anastomoses and staple lines was checked with intraoperative methylene blue dye; postoperative tests were not used.

Postoperative analgesia:

Intravenous analgesia included Metamizole 2g/8h and Acetaminophen 1g/8h, alternating every 4 hours, during the first 24 hours. The second postoperative day, the patient began with oral analgesia, alternating Metamizole 575mg/8h with Acetaminophen 1g/8h every 4 hours. The patients were discharged with analgesic recommendations of Acetaminophen 1g/8h during 4 days.

Port-sites infiltration was performed with 30 ml of Bupivacaine 0.25%, applying 6 ml under the aponeurotic layer in each port.

Morphine 3mg was established as rescue treatment when VAS values overcame 50 mm.

Dietary patterns after surgery

The first phase after surgery consisted in the administration of clear liquids for 2-3 days, followed by completely low-fat and protein-enriched (50 g/day) liquid diet for 2-4 weeks. Soft or ground diet, including very soft protein-rich foods, such as egg, low-calorie cheese, and lean meats, such as chicken, or fish is recommended 2-4 weeks after hospital discharge. Normal diet may be started within 8 weeks from surgery.

Variables:

The investigated clinical variables were age, gender, comorbidities, basal BMI, preoperative excess weight loss (EWL), postoperative complications, surgical site infection (SSI), hospital stay and readmissions. Complications were examined over a 30-days postoperative period. Pain quantification, as measured by Visual Analogic Scale (VAS), was determined 24 hours after surgery; pain measurement ranged from 0mm (absence of pain) to 100mm (unbearable pain). Morphine needs during the first postoperative day were recorded. Analytical determination of acute phase reactants (CRP, fibrinogen, white blood cell count) was obtained 24 hours after surgery. Dietary compliance was quantified as the percentage of cartons consumed from all the cartons prescribed. Adverse events related with the intake of the supplements were assessed.

Incisional SSI was defined as the presence of a purulent discharge from any of the surgical wounds and confirmed with microbiological culture. Incisional SSI was

188 determined by an epidemiology nurse blinded to the treatment groups. Infection
189 surveillance was extended for 30 days following discharge. Organ-space SSI was
190 defined as the presence of a fluid collection at a contrast-enhanced CT scan in a
191 symptomatic patient, presenting with fever, tachycardia, abdominal pain or septic status.
192 The evidence of oral contrast extravasation at CT scan was considered a leak rather than
193 an organ-space SSI. The diagnosis of organ-space SSI and leak was determined by a
194 radiologist blinded to the treatment groups.

195

196 **Statistical analysis:**

197 Patients presenting postoperative complications were excluded from the analysis, as
198 they could represent a bias in the laboratory data. Thus, an analysis per protocol was
199 performed.

200 Statistical analysis was performed with the statistical software SPSS 19.0 for Windows.
201 Quantitative variables that followed a normal distribution were defined by the mean and
202 standard deviation. For non-Gaussian variables, the median and range were used.
203 Qualitative variables were defined by number and percentage of cases.

204 Comparison of variables was performed with t-Student test (Mann-Whitney test in non-
205 Gaussian variables). Comparison of qualitative variables was performed with the Chi-
206 square test; in those cases with fewer than 5 observations in the cell, the Fisher exact
207 probability method was used. $P< 0.05$ was regarded as significant.

208 The study was approved by the local ethics committee and informed consent was
209 obtained from all the patients.

Results:

A total of 40 patients were included in the study, 20 in each group. The sample consisted in 25 females and 15 males with a mean age of 45.9 ± 10 years (range 26-64 years) and a preoperative BMI of 41.3 ± 4.2 Kg/m^2. The distribution of age, gender, BMI and comorbidities between groups is showed in Table 2.

Mean operative time was 83.2 ± 22.7 minutes, without significant differences between groups. Postoperative complications rate was 2.5%, consisting in one gastro-jejunal leak in the Control Group, requiring reoperation, suture of the perforation, lavage and drain placement adjacent to the gastro-jejunal anastomosis. This patient recovered uneventfully after the reoperation and was discharged the 7th day after surgery. There were no cases of incisional or organ-space SSI in any of the groups.

Preoperative EWL with the prescribed treatment was 10.6 ± 7.7% in Control Group and 14.1 ± 5.8% in the Experimental Group (p=0.024). Total weight loss was 4 ± 2.7% in Control Group and 5.3 ± 3.2% in the Experimental Group (p=0.041).

Excluding the patient, who presented a postoperative complication, mean postoperative pain, as measured by VAS, was 25 ± 9.2 mm in Control group and 10,9 ± 4,4mm in Experimental Group (p=0.015). No patients required morphine rescue in any of the groups.

Laboratory data are shown in Table 3. CRP determined 24 hours after surgery was significantly lower in the Experimental Group than in the Control one. There were not significant differences in the other acute phase reactants between groups.

Median hospital stay was 2 days in both groups (Non significant). There were no readmissions in any of the groups.

Dietary compliance was 100% for both groups receiving nutritional formulas. There were no adverse events related with any of the nutritional supplements.

Discussion:

The Italian group of Braga et al has determined a reduction in postoperative complications, mainly surgical-site infections, but also reduction in the hospital stay and sanitary costs in many oncologic surgeries[7-11]. However, these studies have been criticized, because of the unacceptably high surgical-site infections and leak rates reported in the control groups. On the other hand, Klek et al could not demonstrate any benefit of IMN, compared with high protein supplements, in patients undergoing colorectal surgery, in terms of postoperative complications, mortality or hospital stay[12]. However, 2 recent meta-analysis including 21 and 19 clinical trials, respectively, and each one including more than 2000 patients, concluded that IMN reduces postoperative infectious complications and, thereby, the hospital stay, but they failed to demonstrate a reduction in mortality[3,4].

Though all the isolated components of IMN have demonstrated important antioxidant functions, immune-modulating effects and promotion of tissue repair and wound healing[13-16], O3FA eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) are possibly the most important elements of all. O3FA compete with arachidonic acid (omega-6) and participate in the synthesis of prostaglandins, leukotrienes, thromboxanes and prostacyclins[6,17]. The addition of EPA and DHA to enteral nutritional products results in a reduction of proinflammatory mediators, decreasing the generation of free radicals. Consequently, O3FA are considered immune-modulating agents,

reducing the postoperative inflammatory response to surgical aggression, and decreasing the release of proinflammatory mediators[6].

In our study, we could demonstrate this effect in the significantly lower levels of CRP among the patients who received O3FA addition, in comparison with the patients receiving only high protein formulas. Clinically, the anti-inflammatory effect can be represented as a reduction in the postoperative pain, as we have observed in our patients who received O3FA. Previous studies of our group have demonstrated that postoperative pain correlates with acute phase reactant levels in patients undergoing bariatric surgery[18] and in patients undergoing laparoscopic cholecystectomy.[19] Though CRP is a relatively weak marker of inflammation, it is easy to be clinically evaluated, as it is an available parameter in a routine blood analysis. Surgery stimulates a series of hormonal and metabolic changes that constitute the stress response. It has been shown that stress response is associated with the postoperative pain feeling[20]. Proinflammatory parameters, such as Interleukin-6 (IL-6) and TNF-α, have been involved in the response to the surgical aggression, and IL-6 promotes the CRP synthesis in the liver[21].

Itariu et al published in 2012 a study, analyzing the effect of the administration of long-chain n3- polyunsaturated fatty acids (EPA and DHA), during a period of 8 weeks, in morbidly obese patients before undergoing bariatric surgery, on inflammatory gene expressions in visceral and subcutaneous fat. They observed that, in patients receiving EPA and DHA, the inflammatory genes expression and the circulating levels of IL-6 were reduced[22].

Ianelly et al evaluated the effect of a preoperative 4-weeks supplementation with omega-3 polyunsaturated fatty acids on the liver volume, determining a 20% reduction of the volume of the left hepatic lobe. These authors did not attribute the

decrease of the liver volume to weight loss, as they did not establish any preoperative dietary restriction for these patients[23]. Abidin et al examined liver volume by MRI and body weight of bariatric candidates after 4 weeks of preoperative treatment with a very low calorie diet (VLCD) or with 2000 mg/day omega 3, without dietary restriction, and concluded that O3FA supplementation (without dietary restriction) and VLCD have the same effect in reducing liver volume and body weight[24].

We have observed that the preoperative EWL achieved in the O3FA Group is higher than that observed in the Control Group, despite the caloric intake is similar. It is widely known that self-reported food intake in obese subjects is inaccurate due to under-reporting[25]. Despite all the patients were warned that, apart from the formula, they could only intake water or no-caloric infusions, probably if they feel hungry during the day, they would have eaten some regular meal, without telling the dietitian. Omega-3 polyunsaturated fatty acids have effects on the central nervous system. Specifically EPA and DHA have shown positive results in animal and human studies in the prevention and treatment of obesity[26]. Given their effects on many pathways involved in obesity, and specifically in the endocannabinoid and mesocorticolimbic pathways, it has been shown that EPA and DHA supplementation might reduce the reward associated with food, thereby reducing the appetite and food intake[26]. This could be a possible explanation for the greater EWL in the patients receiving O3FA, but we cannot obtain certainty, so long most morbidly obese patients systematically under-report what they really eat. Anyway, in the previous study of our group, which evaluated the effect of IMN on sleeve gastrectomy, mean preoperative EWL in the patients receiving IMN was 15.3% versus 12.3% in those patients receiving hypocaloric hyperproteic supplements. Despite these results did not achieve statistical significance, greater preoperative weight loss with IMN tend to be observed[5]. In this previous study, IMN included arginine,

glutamine and nucleic acids, apart from O3FA, so that the supplements used are not comparable to that used in the present project. Further studies must be conducted to confirm if O3FA are responsible of this greater weight loss.

Conclusions:

The use of nutritional supplements enriched with O3FA is associated with a greater preoperative weight loss, reduces postoperative pain and decreases postoperative levels of C reactive protein.

ClinicalTrials.gov Identifier: NCT03010280

Conflict of interests statement:

All authors declare that they have no conflict of interests in the preparation of this manuscript.

Statement of informed consent:

Informed consent was obtained from all individual participants included in the study.

Statement of human rights:

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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Average Nutritional Information Per 100 ml	**Fresubin Protein Energy Drink**	**Supportan**
Energetic value (Kcal)	150	150
Proteins (g)	10	10
Carbohydrates (g)	12.4	11.6
Fats (g) - **Saturated** - **Monounsaturated** - **Polyinsaturated** **EPA** **DHA**	6.7 - 0.6 - 4.9 - 1.2 **0** **0**	6.7 -2.8 -1.6 -2.3 **0.5** **0.21**
Fibre (g)	0	0
Calcium (mg)	205	203
Phosphorus (mg)	120	120
Potassium (mg)	130	128
Sodium (mg)	50	47.5
Chlorine (mg)	58	50
Iron (mg)	2.5	2.5
Zinc (mg)	2	2
Copper (µg)	375	375
Iodine (µg)	37.5	37.5
Selenium (µg)	13.5	13.5
Magnesium (mg)	28	26
Manganese (mg)	0.5	0.5
Fluoride (mg)	0.25	0.25
Molybdenum (µg)	18.8	18.8
Chrome (µg)	12.5	12.5
Vitamin A (µg)	150	150
Vitamin D (µg)	2.5	2.5
Vitamin E (mg)	3.75	3.75
Vitamin C (mg)	18.8	18.8
Vitamin B1 (mg)	0.3	0.3
Vitamin B2 (mg)	0.4	0.4
Vitamin B3 (mg)	3.75	3.75
Vitamin B6 (mg)	0.43	0.43
Vitamin B12 (µg)	0.75	0.75
Biotin (µg)	9.4	9.4
Pantotenic acid (µg)	1.5	1.5
Folic acid (µg)	62.5	62.5
Vitamin K (µg)	21	21
Coline (mg)	2.5	2.5
Osmolarity (mOsm/L)	380	385

Table 1: Nutrition information of the Nutritional formulas

	Fresubin Protein Energy Drink	Supportan	P
Age (years)	46.4 ± 12	45.5 ± 7.9	0.780
Females/males	12/8	13/7	0.744
BMI (Kg/m²)	41.7 ± 4.6	41.1 ± 3.9	0.666
T2DM	40%	30%	0.507
Hypertension	40%	45%	0.749
Dyslipidemia	40%	40%	1
SAHS	25%	30%	0.723

422 T2DM: Type 2 diabetes mellitus. SAHS: Sleep apnea-hypopnea syndrome

423 **Table 2: Distribution of age, gender, BMI and comorbidities between groups**

424

	Fresubin Protein Energy Drink	Supportan	P
POSTOPERATIVE VALUES			
C reactive protein (mg/dl)	0.94 ± 0.87	0.97 ± 0.96	**0.920**
Fibrinogen (mg(dl)	449.6 ± 96.6	442.6 ± 83.8	**0.814**
White blood cell count (WBC/mm³)	7540.4 ± 1235.2	7611.1 ± 998.6	**0.659**
POSTOPERATIVE VALUES			
C reactive protein (mg/dl)	7.36 ± 4.22	2.98 ± 1.1	**0.009**
Fibrinogen (mg(dl)	480.7 ± 70.2	473.7 ± 76.5	0.774
White blood cell count (WBC/mm³)	10473 ± 5428	9796 ± 3574	0.650

425 **Table 3: Distribution of postoperative laboratory data between groups**

426