Impact of implementation of an Enhanced Recovery After Surgery (ERAS) program in laparoscopic Roux-en-Y gastric bypass: A prospective randomized clinical trial

Abstract:

Background: The essence of Enhanced Recovery After Surgery (ERAS) programs is the multimodal approach and many authors have demonstrated safety and feasibility in fast track bariatric surgery.

Objectives: The aim of this study was to evaluate the postoperative pain after the implementation of an ERAS protocol in Roux-en-Y gastric bypass (RYGB) and to compare it with the application of a standard care protocol.

Setting: University Hospital Rey Juan Carlos, Madrid, Spain

Methods: A prospective randomized clinical trial of all the patients undergoing RYGB was performed. Patients were randomized into 2 groups: those patients following an ERAS program (ERAS) and those patients following a Standard Care protocol (SC). Postoperative pain, nausea or vomiting, morbidity, mortality, hospital stay and analytical acute phase reactants 24h after surgery were evaluated.

Results: 180 patients were included in the study, 90 in each group. Postoperative pain (16 vs 37mm; $p<0.001$), nausea or vomiting (8.9% vs 2.2%;$p=0.0498$) and hospital stay (1.7 vs 2.8 days; $p<0.001$) were significantly lower in the ERAS group. There were no significant differences in complications, mortality and readmission rates. White blood cell count, serum fibrinogen and C reactive protein levels were significantly lower in the ERAS group 24h after surgery.

Conclusion: The implementation of an ERAS protocol was associated with lower postoperative pain, reduced incidence of postoperative nausea or vomiting, lower levels of acute phase reactants and earlier hospital discharge. Complications, reinterventions, mortality and readmission rates were similar to that obtained following a standard care protocol.

Key words: Enhanced Recovery After Surgery; ERAS; Fast track; Roux-en-Y gastric bypass; Postoperative pain; Nausea; Vomiting

Introduction:

Recent improvements in the perioperative care of bariatric patients, optimization of the operative techniques, improvements in equipment and the standardization of bariatric surgery programs have all resulted in decreased morbidity and mortality from bariatric surgery. Laparoscopic bariatric procedures are being performed with increasing frequency, being laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) the most common operations[1].

Given the rising prevalence of obesity and its related diseases, and the resultant increased economic burden associated with their management, the current challenge is to increase the cost-effectiveness and efficiency of bariatric surgery, whilst maintaining the current low associated morbidity in this complicated group of patients [1,2]. Operative time, staff and hospital stay are costly and scarce, and cannot be issued indefinitely. Ideally, better logistics and use of resources could increase both production and quality of care[3].

Fast track care, also known as Enhanced Recovery After Surgery (ERAS), was developed by Kehlet in 1997. ERAS protocols are well-documented logistic programs in colorectal surgery, demonstrating that an "evidence-based" approach of perioperative care leads to faster recovery and shorter hospital stay, with improved patients´ well-being. Although the contents of different fast track programs vary, common factors include the use of minimal invasive surgical techniques, the introduction of short-acting anesthetic agents, optimal pain and anti-emetic control and aggressive postoperative rehabilitation, including early oral nutrition and ambulation. The rationale is to reduce the body´s perioperative stress response and to induce early restoration of vital organ function, leading to a quicker recovery of the patient[4-6].

The essence of these programs is the multimodal approach, and many authors have demonstrated safety and feasibility in fast track bariatric surgery. All these papers describe the implementation of an ERAS program and compare it with a historic cohort[7-11]. Up to our knowledge, this will be the first prospective randomized clinical trial comparing the implementation of an ERAS program versus the application of a standard care protocol. Given that ERAS programs are focused of improving patients´ well-being after surgery, one of the main parameters in assessing this fact, as an objective parameter, is postoperative pain. Thus, the main aim of this study was to evaluate the postoperative pain after the implementation of an ERAS protocol in Roux-en-Y gastric bypass (RYGB) and to compare it with the application of a standard care protocol.

Patients and Methods:

A prospective randomized clinical trial of all the patients undergoing RYGB was performed between March 2016 and December 2017. All the patients planned to undergo a RYGB during this period agreed to participate in the study and to be randomized. 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. Exclusion criteria were patients undergoing other bariatric techniques, severe underlying cardiovascular diseases, chronic renal failure, hepatic dysfunction, previous foregut surgery and patients with any contraindication for bariatric surgery.

The sample size calculation was based on postoperative pain 24 hours after surgery, as measured by Visual Analogic Scale (VAS), ranging from 0 mm (absence of pain) to 100

mm (unbearable pain). Historic data at our center revealed a median postoperative pain 24 hours after RYGB of 30 mm. This value was proposed for the Control Group, and an expected reduction of 15 mm in the postoperative pain quantification was hypothesized in the Experimental Group. Changes between 13 and 16 mm in the postoperative pain score, as measured by VAS, are widely accepted as clinically relevant[12]. At 80 % power and a significance level of $p < 0.05$, it was calculated that 90 patients were required in each arm of the study.

Patients were randomized using a computerized simple randomization scheme in a 1:1 ratio into 2 groups: those patients following an ERAS program (ERAS) and those patients following a Standard Care protocol (SC). The study was blinded to the outcome evaluators.

Preoperative Evaluation

In both groups, a multidisciplinary team, including surgeons, endocrinologists, anesthesiologists and psychiatrists, performed a combined medical, nutritional, and endocrinological work-up to evaluate potential surgical candidates. Preoperative assessment included abdominal ultrasound, upper gastrointestinal endoscopy, polysomnography, and analytical evaluation of the nutritional status.

ERAS protocol:

The Spanish National ERAS protocol, developed and approved by the ERAS-Spain group (GERM), and validated in a pilot multi-center study, was followed in the ERAS group[13].

The Spanish National ERAS protocol for bariatric surgery is described in Table 1.

Preoperatively, nutritional formulas were prescribed to obtain an advisable preoperative weight loss of at least a 10% of the patient´s weight. The patients were informed that this weight loss was beneficial[14] and might allow a better recovery within the ERAS protocol. During surgery, goal directed fluids were administrated and hypothermia avoided. Central vein and bladder catheters were not used.

The protocol used for the management of postoperative nauseas or vomits (PONV) followed the consensus recommendations on the management of postoperative nausea and vomiting by the Society for Ambulatory Anesthesia[15]. All patients undergoing bariatric surgery were considered as patients at high risk of incidence of PONV. In both groups a triple antiemetic prophylaxis was applied, including Dexametasone during the anesthetic induction, and Droperidol and Ondansetron at the end of the surgery. Propofol was used as a hypnotic. The main difference between ERAS protocol and Standard Care was that, in ERAS patients, intra and postoperative opioid analgesia was minimized. The nursing staff recorded every 6 hours the presence or absence of PONV. If PONV occurred, postoperatively Metoclopramide 10 mg iv was used as treatment.

In the ERAS protocol, intra-abdominal drains and nasogastric tubes were not used. Early mobilization was practiced and oral fluids administered 6 hours after surgery.

Multimodal analgesia consisted in an intraoperative subaponeurotic port-site infiltration with bupivacaine 0.25%, applying 2 ml in each port. Postoperative analgesia included

Metamizole 2g/8h and Acetaminophen 1g/8h, alternating every 4 hours. When postoperative pain, as measured by VAS, overcame 50 mm at any moment in the postoperative course, 5mg of subcutaneous morphine was administrated.

The patients were completely informed about all the steps of the ERAS protocol, including the need of a preoperative weight loss, a preoperative fasting period of only 6 hours for solids and 2 hours for liquids, and early postoperative oral intake and mobilization. They were also informed that, if no complications appear, they would be probably discharged 1-2 days after surgery, always when pain was controlled with oral analgesia, full deambulation was achieved and the patient accepted it. It was explained to the patients that this early discharge is a safe act, that they would receive a telephone call from the nursing staff to monitor their status and that they should attend to the Outpatient Clinic two weeks after surgery for medical examination and analytical control. They also received nutritional education for the postoperative course by the dietitian, and nursing education for wound care and physical activity.

Patients were discharged following the criteria established by the protocol.

The Standard Care protocol is described in Table 2.

Variables:

The recorded variables include demographic data, comorbidities, anthropometric measures, morbidity, mortality, hospital stay and readmission. Specific items related with the ERAS program (Preoperative weight loss, intraoperative opiod-free analgesia,

postoperative nausea or vomiting, early oral intake and early mobilization) were also assessed.

Primary efficacy endpoint was postoperative pain score, as measured by VAS 24 h after surgery. Secondary efficacy endpoint was Morphine needs during the first 24 hours postoperatively.

Postoperative pain and nausea or vomiting, during the first 24h after surgery, were assessed by a nurse blinded to the applied protocol. Hospital discharge was decided by a surgeon blinded to the treatment, whose decision was based on the common discharge criteria in both protocols.

A Checklist was fulfilled by a not-blinded staff, marking each item performed. This staff did not participate in the decision making with the patient or inform to the blinded outcome evaluators.

Analytical acute phase reactants (White blood cell count, C reactive protein and Fibrinogen) were evaluated 24 hours after surgery.

Statistics:

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

Comparison of variables was performed with a Student's t test (Mann-Whitney test in non-Gaussian variables). Comparison of qualitative variables was performed with the

Chi-square test; in those cases with fewer than 5 observations in the cell the Fisher exact probability method was used. $P< 0.05$ was regarded as significant.

The study was approved by the local Ethics Committee of the participant centers.

Clinicaltrial.gov Identifier: NCT03212573

Results:

A total of 180 patients were included in the study, 90 in each group. There were no significant differences in age, gender, BMI and comorbidities between groups (Table 3).

Mean initial weight was 124.3 $\pm$ 23.9 Kg in ERAS and 121.7 $\pm$ 22.8 Kg in SC (NS). Mean BMI was 45.1 $\pm$ 6 Kg/m^2 in ERAS and 44.7 $\pm$ 7.1 Kg/m^2 in SC (NS).

Conversion rate was 0% in both groups. Postoperative nausea or vomiting rates were 8.9% in the Standard Care group and 2.2% in the ERAS group (OR 3.81; CI95%(1.21-14.65), p=0.0498). Complications rate was 2.2% in both groups. In Standard Care group complications were one gastro-jejunal anastomotic leak and one intraperitoneal bleeding secondary to a spleen laceration. In the ERAS group, there were one jejuno-jejunal leak and one upper digestive bleeding. Reoperations rate was 2.2% in Standard Care group and 1.1% in the ERAS group (NS). There was no mortality in any of the groups.

Mean hospital stay was 2.8 $\pm$ 3.1 days (median 3 days; range 2-19 days) in Standard Care group and 1.7 $\pm$ 1.8 days (median 2 days; range 1-11 days) in ERAS group ($p<0.001$). Readmissions rate was 2.2% in the Standard Care group; one case was secondary to prolonged postoperative vomits and the other because of fever of unknown origin). There were no readmissions in the ERAS group (Table 4).

Mean postoperative pain, as measured by Visual Analogic Scale 24 hours after surgery, was 16 ± 12 mm in ERAS and 37 ± 28 mm in SC ($p< 0.001$). Postoperative morphine needs rate was 2.2% in ERAS group and 11.1% in the Standard Care group (OR 6.72; CI95%(2.1-23.5);p=0.009); in all the patients requiring it, only one rescue dose of subcutaneous 5mg was necessary.

Specific items related with the ERAS program:

Preoperative weight loss in the ERAS group was 12.3 ± 4.8 Kg (Total weight loss 10.8%) and in the Standard Care group 5.2 ± 4.1 (Total weight loss 4.6%) (p=0.016). However, the recommended preoperative weight loss of at least 10% of total body weight was achieved only in 55.5% of the patients.

Intraoperative opiod-free analgesia could be reached in 91.1% of the cases in the ERAS group.

Early oral intake (6 hours after surgery) could be achieved in 91.1% of the cases and early mobilization (6 hours after surgery) in 94.4% of the patients.

Analytical acute phase reactants 24 hours after surgery:

Postoperative levels of C reactive protein (CRP), fibrinogen and white blood cell count are shown in Table 5. CRP levels, fibrinogen and White Blood Cell count were significantly lower in the ERAS group.

Discussion:

Actually, the reported evidence about ERAS protocols is based on individual programs developed at single institutions and comparing prospective ERAS cohorts with historic ones[8-11,13]. Up to our knowledge, this is the first prospective randomized clinical study comparing an ERAS program with a standard care protocol in bariatric surgery. The main outcome analyzed in this study was the postoperative pain after ERAS program vs standard care protocol. One of the main aims of ERAS protocols are the improvement of patients´ well-being and an optimal postoperative pain control is an essential part of it. Our results reflect that, following the ERAS program, a significantly better control can be obtained and the requirements of morphine rescues can be reduced.

Following ERAS protocols, the body´s perioperative stress response related to the surgical act is diminished, so long the items included in the protocol overall tend to an immunomodulation, reducing the immune stress response and finally leading to less tissue damage, inflammation and lower postoperative pain[16]. In an effort to reduce the postsurgical pain, ERAS protocols include multimodal analgesia, which involves the use of two or more drugs with different mechanisms of action in an effort to maximize analgesic efficacy while reducing the risk and severity of adverse events. Moreover, these protocols defend the use of opioid-free analgesia, as opioids contribute to increase nausea and vomiting, postoperative ileus and delay in deambulation[17]. This was also confirmed in our results, as the patients in the ERAS group presented significantly lower postoperative nausea and vomiting, despite in both groups triple prophylaxis was applied. This was probably secondary to the intraoperative opioid-free analgesia, which could be reached in most of the patients from the ERAS group, and to the minimal

postoperative morphine needs. Altogether, these led to a correct oral intake of fluids and ambulation after the first 6 postoperative hours, in more than 90% of the cases.

A good postoperative pain control and a correct oral intake of fluids within the first hours after surgery imply a patient´s perception of better quality of life and improve the satisfaction with the procedure. In our opinion, these are the basis for a significantly shorter length of stay in the ERAS patients, and not just the patient´s expectation of early discharge. Mean hospital stay in our ERAS group was 1.7 days versus 2.8 days in the SC group. Several groups report hospital stays lower than 24 hours and some authors even defend that bariatric surgery can become a day case surgery[18]. In our ERAS group, hospital discharge 24 hours after surgery was possible in some patients. However, this is not a routine practice in our group, as we still fear the appearance of complications far from a sanitary institution that might end in a fatal outcome for the patient. The systematic review performed by Elliott et al[1] concluded that there was no sufficient evidence to promote such an early discharge based on fast track protocols.

Our results also show that there were no significant differences in morbidity and mortality between those patients following the ERAS protocol and those ones receiving a standard care. Moreover, the morbidity and mortality rates after following our ERAS protocol, were similar to those reported by other groups following fast-track protocols[6-11] and similar to the actual evidence available in literature for bariatric surgery[19,20].

Similarly to postoperative pain, analytical acute phase reactants are also a reflection of the body´s perioperative stress response to the surgical act. We observed significantly lower levels of CRP, fibrinogen and WBC count 24 hours after surgery in the ERAS group. As previously mentioned, the measures included in ERAS programs (short pre

and postoperative fasting period, goal-directed fluids administration, multimodal analgesia,…) tend to an immunomodulation, reducing the immune stress response[16].

Preoperative weight loss has not been clearly associated in the literature with a reduction in the surgical risk. However, weight loss is globally considered beneficial and most groups recommend a preoperative weight loss before undergoing any bariatric approach. Weight loss achieves a reduction in liver steatosis and liver size, the latter implying less technical difficulties during the surgical act in many cases[16]. Moreover, obesity is considered a pro-inflammatory disorder and preoperative weight loss has demonstrated to reduce serum cytokines and acute phase reactants. Many groups defend the use of low-calorie diets to achieve a significant weight loss several weeks before surgery. A previous study of our group showed that preoperative weight loss could be better achieved with nutritional formulas, rather than with hypocaloric diet, and this greater weight loss was associated with a reduction in CRP[21]. The decrease in the proinflammatory status, associated with weight loss, might also have a certain immunomodulating effect, reducing the postoperative inflammatory response to surgical damage and finally leading to a better recovery after surgery.

The objective of the intraoperative fluid administration is to maintain an adequate circulatory volume, avoiding a volume overload. The administration of fluids based on the patients´ weight tends to be higher than the necessary one and this is especially relevant in morbidly obese patients. Goal-directed fluid administration has been associated with a reduction in postoperative complications, mortality and hospital stay. Excessive volume administration determines a fluid extravasation to the bowel wall, to the lungs and to the lower limbs, leading to postoperative ileus, pulmonary edema and atelectasis, and lower limbs edemas, affecting oral intake and ambulation[22]. A recently

published study demonstrated that goal-directed fluid therapy reduces postoperative nausea and vomiting, postoperative pain, analytical acute phase reactants and hospital stay in morbidly obese patients undergoing bariatric surgery[23].

Finally, opiod-free anesthesia (OFA) is also involved in a better postoperative recovery after surgery. Little has been published about its use in bariatric surgery, but the actual evidence demonstrates that OFA reduces postoperative nausea and vomiting and allows an early oral intake in a greater amount of patients[24,25].

ERAS protocols in colorectal surgery have been widely implemented in many hospitals. The benefits obtained with them led to the development of similar protocols in other surgeries, like bariatric surgery. The results of the present study, demonstrating the safety of the protocol (similar morbidity and mortality) and the improvement of postoperative course (lower postoperative pain, nausea and vomiting) may help to the implementation of ERAS protocols in bariatric surgery world-wide. One of the main strengths of this study is the follow-up rate of 100%. Patients lost to follow-up often represent a limitation for the extrapolation of the results obtained, to general practice. However, the follow-up of all of our patients increases the reproducibility of our results and reflects the ease of adherence and collaboration of the bariatric patient with the implementation of ERAS protocols.

Conclusion:

The implementation of an ERAS protocol was associated with lower postoperative pain, reduced incidence of postoperative nausea or vomiting, lower levels of acute phase

reactants and earlier hospital discharge. Complications, reintervention, mortality and readmission rates were similar to that achieved with a standard care protocol.

Disclosure of interest:

The authors report no conflicts of interest.

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