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Applying Opioid Free Anesthesia (Ofa) In Combination with Enhanced Recovery Anesthesia (Eras) In Bariatric-Metabolic Surgery: Evaluation at One Year Follow-Up with A Propensity Score

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Abstract

Since its introduction, laparoscopic bariatric metabolic surgery (BMS) has witnessed a consistant decrease in complications. Recently, enhanced recovery after surgery (ERAS) and opioid free (OFA) protocols have been developed separately to further improve outcomes.

To assess the surgical outcomes after ERAS in combination with OFA (ERAS+OFA) in BMS.

High volume bariatric metabolic center in Belgium.

A retrospective observational study comparing by propensity score matching the outcomes of our center (ERAS+OFA) with the outcomes of an Italian center of excellence adhering to opioid sparing, but not opioid free ERAS (ERAS-OFA). Primary endpoints were: length of hospital stay, number of readmissions and complications including leaks and bleedings. Secondary endpoints were: the number and severity of complications as evaluated by the Clavien-Dindo score.

Over a 12-month period, 341 consecutive patients treated according to ERAS+OFA in our center, were compared to 109 according to ERAS-OFA in the Italian center. Propensity matching resulted in comparable groups. Primary and secondary endpoints showed no significant difference between the 2 groups.

Our study shows no statistically significant difference in BMS outcomes between ERAS+OFA compared to ERAS- OFA

Keywords: *Opium free anesthesia (OFA), opium sparing anesthesia (OSA), enhanced recovery after surgery (ERAS), bariatric metabolic surgery (BMS)*

Introduction

According to the World Health Organization (1), obesity and morbid obesity are currently the leading non-infectious diseases on the planet. Surgery has proven to be the only effective treatment for this scourge until now (2). In the search to improve the surgical treatment, modern approaches have been adopted such as the laparoscopic technique. In order to enhance outcomes within the laparoscopic approach, as of 2015, new guidelines specifically addressing anaesthesia were established (3). Importantly, the current guidelines purposely include the minimization or avoidance of opioids. The "opioid crisis" although the term originated in the United

States, is now a wordwide phenomenon (4-5). Of note, patients suffering from obesity are significantly more at risk for pulmonary conditions such as sleep apnea syndrome and its inherent cardiometabolic consequences that could be enhanced by use of opioids. (6-7).

In order to address the specific issue of secondary effects of the per-operative opioid use especially in bariatric-metabolic surgery (BMS), opioid free anesthesia (OFA) techniques were recently developed (8-9). In our unit we attempted to implement both goals, i.e. enhanced recovery (ERAS) and OFA in a new protocol that was in accordance with the recommendations of the GRACE association (10) (Groupe de Réhabilitation Améliorée après ChirurgiE), the French speaking organization for the development of ERAS

Materials and Methods

The current observational study covers the prospectively collected data of all consecutive bariatric patients benfitinf from OFA in an ERAS protocol over a 1-year period (from March 1, 2019 to February 28, 2020). The clinical setting is a high-volume (>1000 cases/year) tertiary metabolic-bariatric center in Belgium. All patients included were treated by a fixed team consisting of one anesthesiologist (MC) specialized in ERAS, one experienced bariatric surgeon (ACD), as well as a fully trained assisting surgeon, an experienced scrub nurse and an operating room nurse. The control group consisted of patients treated by a well-respected specialized team from Italy that implements ERAS but not OFA and whose data were published in a leading, peer-reviewed journal (16).

Patient selection and preoperative management

Eligibility criteria for BMS are in accordance with the 1991 NIH consensus statement. Consequently, patient's Body Mass Index (BMI) must exceed the value of 40 kg/m^2 or 35 kg/m^2 in case of previous BMS or when in association with well-defined comorbidities, including treated type 2 diabetes (T2DM), defined by a glycated hemoglobin (HbA1c) >6.5%, arterial hypertension (AHT) (blood pressure exceeding 140/90 mmHg before treatment), necessitating at least 3 anti-hypertensive agents or obstructive sleep apnea syndrome (OSAS)with an apneic frequency exceeding 5 episodes per hour.

Preoperatively, every patient must follow a standardized clinical pathway, displayed in table 1.

Perioperative anesthetic protocols are thus different in +OFA and –OFA group. Preoperative management of the patient and work-up, surgical technique and postoperative application of the ERAS items were however similar and comparable in both groups.

Thromboprophylaxis is started the evening before surgery and consists of a subcutaneous injection of Low Molecular Weight Heparin (LMWH) (Enoxaparine dosage -40 mg versus 60 mg- adjusted to history and patient weight). LMWH thromboprophylaxis is continued for 10 days postoperatively (11).

In accordance with guidelines, preoperative fasting has been reduced to 6 hours for solids and 2 hours for clear liquids (12-13). Apple juice (400 ml night before surgery and 2 hours before surgery) provide carbohydrate. The carbohydrate load is not given if the patient is diabetic.

Premedication does not include anxiolytic agents.

Patients received pre-warming in the induction room by pulsed hot air cushion (Bair-Hugger°,3M, Saint Paul, MN, USA) (14)

Before transfer to the operating room (OR) the patient is visually confirmed for identification purposes by the GRACE nurse for an ultimate clinical and administrative (identification) assessment. The rehabilitation nurse constitutes the final link between the OR team and the extra-OR personnel.

During their positioning in the OR typically in the so-called French position (patient's legs in abduction, surgeon between the legs), the patients benefit from pre-oxygenation, (OFA protocol table 3a). Ventilation settings include a tidal volume of 6-8 ml/kg Ideal Body Weight (IBW) and a positive end-expiratory pressure (PEEP) value of 10 cm H2O. Respiratory frequency is set at 10-16 depending on end-tidal CO2.

Surgical technique

Pneumoperitoneum was initiated by Veress technique. The first trocar was placed in the left upper quadrant with a 30-degree 10 mm optics (Storz°, Tuttlingen, Germany). Further trocar placement (usually 4 in number, including two 5 mm and two 12 mm bladeless trocars) was preceded by local infiltration of ropivacaine 0.75% in all skin incisions, with the injection site ascertained by visual control. A fifth trocar (5 mm) was added to allow additional retraction as needed.

Insufflation was uniformly set at a pressure of 12 mm Hg or lower as permitted by the actual visual space.

Table 1: preoperative clinical pathway for all patients according to the GRACE protocol

GRACE: Groupe de Réhabilitation Améliorée après ChirurgiE

GI : Gastro-Intestinal

Appointment scheduled (telephone or e-mail)	**Practical details provided by mail. Personal contact with coordinating nurse**
First office-appointment with surgeon and GRACE Nurse	• general informations- documentation • history and physical (H+P) • work up explained • tobacco/alcohol stop imposed • general dietary guidelines presented
Work up (scheduled by coordinating nurse)	• polysomnography if indicated by H+P • upper GI endoscopy (all patients) • abdominal echography (US) (all patients) • exhaustive blood work (all patients) • psychologist's evaluation (all patients except when under treatment by own psychologist) • dietician evaluation and preparation. Evidence provided of past dietary efforts • nutritionist evaluation • internist evaluation (endocrinologist when possible issues suspected, cardiologist when indicated, general internist all others) • Barium swallow if deemed necessary by any work-up member
Multidisciplinary consultation	Work up outcomes reviewed for each case by senior team member (JH). Type of procedure proposed and documented in records
Second appointment with surgeon	Second check of work up outcomes. □If indication for surgery, intervention booked. Type of procedure decided. Cholecystectomy proposed if lithiasis on US. Consent form submitted to patient □If no indication for surgery or issues precluding surgery, non-surgical pathway scheduled
Immediate preparation for surgery	• 2 weeks of strict protein diet • alcohol and tobacco stop reinforced

Table 2: perioperative GRACE guidelines

GRACE: Groupe de Réhabilitation Améliorée après ChirurgiE

Bair Hugger° 3M, Saint Paul, MN, USA

Patient Info/patient education patient
No preoperative anxiolytics
Limited fasting
Immediate preoperative carbohydrates intake
Antibiotic prophylaxis
Hypothermia prevention (Bair Hugger°)
Surgical approach
Multimodal peroperative analgesia
Intravenous fluids optimization
Postoperatory Nausea-Vomiting prevention
No Drain
Intermittent pneumatic calf compression
Intravenous steroids
No nasogastric tube
No indwelling urinary catheter
Multimodal postoperative analgesia
Early (<Day 2) drain removal (if present)
Thromboprophylaxis
Mobilization before 24 hrs
Oral refeeding before 24 hrs

Perioperatively, patients are treated according to the GRACE guidelines (Table 2) and the OFA (Table 3a) (our unit) or Opioid Sparing (OSA) protocol (Table 3b) (control group).

Table 3a: OFA (Opioid Free Anesthesia) protocol

IBW: Ideal body weight

TBW: Total body weight

Induction	Dexmedetomidine 0,5 mg /kg Magnesium 3 g Ketamine 25 mg Lidocaine 1,5 mg/kg Propofol 2 mg/kg Rocuronium 0,5mg/kg Methylprednisolone 125 mg Diclofenac 75 mg Paracetamol 1g
Maintenance	Sevorane as required
Emergence	Suggamadex 4mg/kg IBW + 4mg/kg 40%(TBW-IBW)

Table 3b: OSA (Opioid Sparing Anesthesia) protocol

Induction	Dexamethasone 8 mg IV Propofol 2 mg/kg Ketamine 0,5 mg/kg Remifentanil in TCI (Minto Model) using as target the Effector Site Concentration equal to 2 ng / mL Rocuronium (dose calculated on "lean body weight")
Maintenance	Desflurane: O2 (MAC 0.9, ~~Vt~~ Tv 8 mL / Kg, PEEP 8 -10 cmH2O, ~~Vt~~ Tv adequate to maintain Et CO2 35-45 mmHg) Remifentanil concentration based on haemodynamic response. Morphine 5 mg 30-60 minutes before the end of the procedure Ondansetron 8 mg i.v. ~~in the end~~ at completion of surgery
Emergence	Decurarizing mixture composed of atropine and neostigmine (1 mg, 2.5 mg) until reaching Tr> 0.9 Sugammadex in selected cases.

TCI: target-controlled infusion

MAC: mean alveolar concentration

PEEP: Positive End-Expiratory Pressure

Tv: tidal volume

Et: end-tidal

IBW: Ideal body weight

Tr: train of four ratio

TBW: Total body weight

In gastric bypass specific surgical technical characteristics included a small gastric pouch staple-tailored as guided by a 38 French endogastric tube, a hand sewn latero-lateral gastro-enteral anastomosis, a 70 cm alimentary and a 90 cm biliopancreatic limb with a stapled jejuno-jejunal (J-J) anastomosis (using white load, J&J, Cincinnati, OH, USA) and manual closure of the introduction site. The mesenteric defects (J-J and Petersen's) were closed by running suture of 3-0 non-resorbable barbed wire suture (V-lock). In case of documented cholecystolithiasis and provided the patient had given consent, cholecystectomy was performed. Skin closure was performed with skin staples.

In sleeve gastrectomy specific characteristics included the use of a 34 French orogastric tutor tube, preservation of the distal 6 cm of the stomach as well as the angle of His, the staple line staying some 2 cm lateral to the latter. Greater curvature devascularization was ensured by Harmonic scalpel (Ultracision, J&J) and additional hemostasis as required was obtained by titanium clips (Ligaclips). Of note, no staple line reinforcement was performed. In case of documented cholecystolithiasis and when the patient had given consent, cholecystectomy was performed. The gastric specimen was retrieved by enlarging the left upper quadrant incision as needed.

After completion of the surgical procedure, neuromuscular block was antagonized by sugammadex (4 mg/kg IBW+ 4 mg/kg (40%(TBW-IBW)) (15) and emesis prophylaxis by ondansetron 4 mg.

Of note, no indwelling catheters were used (nasogastric and/or urinary). In addition, intraperitoneal drains were avoided and only used at the surgeon's discretion for cases where hemorrhagic or fistular complications were feared.

Our patients were extubated on the table before their transfer to the recovery room. Routine immediate postoperative monitoring included electrocardiogram (EC), transcutaneous O_2 saturation and non-invasive blood pressure measurement. Further oxygenation was ensured via high-volume mask or endonasal tube as needed. Additional analgesia was provided by piritramide as required (Visual Analog Scale VAS>4/10).

Routine postoperative analgesia consisted of paracetamol 1g/6h, diclofenac 75 mg every 12 hours for a maximum of 48 hours. Patient-controlled anesthesia (PCA) pump with piritramide (set at 1mg/7 min maximum) was allowed for 24 hours. Intravenous fluids consisted of an ionic balanced solution (Ringer's lactate) enriched by 3 grams of Magnesium, 150 micrograms of clonidine and 200 mg of lidocaine for the first 24 hours.

Sips of water were allowed, and patients encouraged to get up and ambulate as soon as they returned to the ward.

Analysis of our patient cohort was possible on the basis of 2 prospectively kept data bases, i.e., the GRACE data-base, which includes length of hospital stay and complications, and the surgeon's (AC) personal database, which includes type of surgery and comorbidities.

The aim of the current study was to demonstrate the non inferiority of the ERAS + OFA approach in comparison to a non-OFA ERAS protocol.

Primary endpoints were: length of hospital stay, number of readmissions and complications including leaks and bleedings. Secondary endpoints were: the number and severity of complications as evaluated by the Clavien-Dindo score (22).

A propensity score-matched analysis was carried out to compare our endpoints with those of a control cohort, treated as mentioned in accordance with the ERAS but not the OFA protocol.

Statistical analysis

In order to compare ERAS + OFA with ERAS – OFA a propensity score-matching was performed. This statistical approach negated the effects of selected covariates in order to obtain equalized groups on the selected covariates and test the effect of the treatment group on outcomes of interest.

Propensity scores were performed on the two groups, one implementing opioid sparing anesthesia (OSA, the Italian cohort), the other implementing opioid free anesthesia (OFA, our cohort). After 15 multiple imputations of the datasets using the **mice** R package, the **CBPS** R package was used to perform the propensity score, estimating an Average Treatment Effect (ATE), using covariate balancing and requesting an exact match. An absolute standardized difference less than 10-15% was considered to support the assumption of balance between the groups because it is not affected by the sample size, unlike P-values, and it may be used to compare the relative balance of variables measured in different units. The mean and standard deviation obtained after matching were used for continuous variables, and the percentage for categorical variables. After the propensity score the **survey** R package (R Core Team, 2019,version 3.6.2.)was used to perform logistic regressions for binary outcome variables and linear regressions for continuous outcomes, which included the treatment group effect, the weight resulting from the matching and variables present in the propensity score in order to obtain a doubly-robust estimator to correct the possible imbalance between the covariates and produce an unbiased treatment effect (The **survey** R package includes the Huber-White corrected standard errors, which maintains the standard errors unbiased even under heterogeneity of the residuals).

Before interpreting the results, a Bonferonni correction was applied to the p-value. Thus the p-value of 0.05 was divided by the number of comparisons (i.e.10) which resulted in a significance limit of 0.005. Therefore, variables for which the p-value was under 0.005 were considered significantly different.

Results

Within the one-year period, 341 consecutive patients were treated as outlined in « Methods ».

Table 4 shows the degree of adherence to the GRACE protocol.

Table 4: degree of implementation of the GRACE guidelines in our patient cohort

PREOPERATIVE	
Patient information/ education	100%
No anxiolytic premedication	100%

Limited fasting	100%
Carbohydrates loading (if indicated)	98,83%
PEROPERATIVE	
Antibiotic prophylaxis	100%
Hypothermia prevention	100%
Laparoscopy	100%
Multimodal analgesia	100%
Intravenous fluid optimisation	100%
Nausea-vomiting prevention	100%
No abdominal drainage	93%
Intermittent pneumatic calf compression	0%
Corticoids	100%
No nasogastric tube	100%
No urinary catheter	100%
POSTOPERATIVE	
Postoperative multimodal analgesia	100%
Early(<2days) drain removal (if present)	91,6%
Thromboprophylaxis	100%
Early mobilisation (<24h postoperative)	100%
Early alimentation (<24h postoperative	100%

GRACE : Groupe de Réhabilitation Améliorée après ChirurgiE

Table 5: shows the equivalence of the ERAS+OFA and the ERAS-OFA on the set of chosen covariates: all absolute standard differences (ASD) are equal or close to 0.

Table 5: Propensity score matching for demographic data, type of surgery and time of surgery.

	Before Matching			**After Matching**		
	Opioid sparing anesthesia (n=109)	Opioid free anesthesia (n=341)	ASD	Opioid sparing anesthesia (n=109)	Opioid free anesthesia (n=341)	ASD
Age	46.35 (10.81)	39.22 (11.53)	63.80%	42.65 (10.72)	42.65 (12.2)	0.00%
Weight (kg)	120.88 (22.82)	107.41 (15.69)	68.74%	112.06 (19.27)	112.06 (18.81)	0.00%
Size (cm)	167.54 (11.45)	166.03 (8.54)	14.90%	165.95 (10.92)	165.95 (8.81)	0.00%
BMI (kg/m^2)	42.54 (5.67)	38.86 (3.84)	75.88%	40.45 (5.05)	40.45 (4.96)	0.00%
Gender (M)	33.03%	20.23%	29.25%	30.27%	30.27%	0.00%
Surgery (Bypass)	55.96%	71.55%	32.87%	60.58%	60.58%	0.00%
Redo	7.34%	12.61%	17.66%	11.16%	11.16%	0.00%
OSAS	25.69%	53.37%	59.04%	38.38%	38.38%	0.00%
AHT	44.95%	17.60%	61.76%	15.06%	15.06%	0.00%
Diabetes	57.80%	11.73%	110.53%	27.48%	27.48%	0.00%
Dyslipidemia	66.97%	10.26%	143.28%	30.85%	30.85%	0.00%

ASD (absolute standard difference) is 0.00%.

Continuous variables are provided as means (standard deviation).

Categorical variables are provided in percentages

BMI: Body Mass Index

M: Male gender

SAOS: Obstructive Sleep Apnea Syndrome

AHT: arterial hypertension

Primary and secondary outcomes are shown for both cohorts after propensity matching and are displayed in table 6.

Table 6: Primary and secondary outcomes in the 2 cohorts after propensity matching

Variable	Opioid sparing anesthesia (n=109)	Opioid free anesthesia (n=341)	Adjusted -p value
Length of stay post-operative (days ± standard deviation)	1.53 ± 1.47	1.98 ± 1.09	0.02909787
Readmission before day 30	11.75%	1.08%	0.04085563
Complications	18.62%	4.50%	0.03062211
Leak	0.46%	0.87%	0.4869467
Bleeding	1.82%	3.63%	0.4917543
Clavien Dindo – 1	9.02%	0.20%	0.001529068
Clavien Dindo – 2	1.05%	3.62%	0.1386721
Clavien Dindo – 3a	7.70%	0%	<0.001
Clavien Dindo – 3b	0.86%	0.43%	0.439485
Clavien Dindo – 4a	0%	0.44%	<0.001

Table 6. Primary and secondary outcomes in the 2 cohorts after propensity matching (opioid free anesthesia is the local cohort, opioid sparing anesthesia is the Italian cohort). A Bonferonni correction was applied to the p-value. Because 10 comparisons were performed, the p-value 0.05 was divided by the number of comparisons (10) resulting in a p-value = 0.005. Therefore, variables for which the p-value is under 0.005 are significantly different.

Significant differences were found as follows: a higher rate of Clavien Dindo 1 (any deviation from the normal postoperative course), and Clavien Dindo 3a (intervention not under general anesthesia), but a lower rate of Clavien Dindo 4a (single organ dysfunction) for patients of the ERAS-OFA compared to the ERAS+OFA group.

Discussion

ERAS protocols have been successfully implemented in a significant number of specialisms, such as colorectal surgery, breast disease conditions and many more. Definite advantages of the protocol encompass hospital stay, organ dysfunction and postoperative recovery. Not surprisingly, BMS characteristics fit ERAS requirements quite well in terms of numbers of patients and similarities across clinical pathways.

In their systematic review and meta-analysis on the ERAS protocol in BMS, Malczak et al. (17) found a shortened hospital stay without negative impact on morbidity. ERAS is also possible in BMS for bariatric patients with end stage renal failure (18)

Importantly, such new protocols additionally allow a multidisciplinary approach, and, consequently, for the patients, a closer adherence to the clinical pathways and ultimately better clinical and Patient reported Outcomes measures (PROMS) (19)

Along the same lines, a 2018 meta-analysis found less morbidity, shorter operative times and reduced hospital stays with the ERAS approach. (20)

Our study again confirms the outcomes linked with ERAS described in the literature so far. It additionally focuses on a new concept, i.e. opioid free anesthesia (OFA). So far, ERAS protocols encouraged the *reduced* peroperative use of opioid drugs to avoid their immediate postoperative side effects (respiratory depression, worsening of OSAS, urinary retention, ileus and postoperative somnolence)

The persisting peroperative use of morphine-based agents rests on their mitigating effect on cardiovascular stability and on the reduced need for hypnotic drugs during surgery.

Importantly, according to the International Association for the Study of Pain (IASP), the definition of pain is « an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage ». Consequently, the use of analgesic morphine drugs during general anesthesia may be questioned considering that, by definition, pain can only be experienced by a subject with conscious awareness. Accordingly, during surgery, opioid agents exert their action on nociceptive receptors only, hence achieving selective inhibition of the sympathetic nervous system. Moreover, potent synthetic morphine-like agents used peroperatively may create significant undesired secondary effects such as hyperalgesia and acute tolerance to opioids (21). Hyperalgesia is defined as the lowering of the threshold for pain experience. Acute tolerance to opioids implies the need for higher doses of the drug to obtain similar effects. As a consequence, a vicious circle is initiated with a markedly increased opioid need for adequate postoperative analgesia as well as the subsequent enhancement of side effects.

“Opioid free anesthesia” i.e. *total abstention* from the peroperative use of opioids was initiated as a concept to reduce the postoperative need for opioid analgesia and to avoid the side effects linked with their use.

Considering the potential dangers of the continued

use of opioids during anesthesia we started implementing OFA in combination with ERAS as of 2017. With the current work we aimed at documenting the possible benefits of the aforementioned combination after completion of the learning curve in our practice (i.e. after more than one year of practicing the approach). We instituted for a retrospective observational study after considering the difficulty in obtaining a randomized protocol that combines all multimodal aspects involved with OFA. In order to deal with the drawbacks inherent to a retrospective study, such as the substantial risk for selection bias, we performed a propensity score-matched analysis with the data from an experienced foreign team that recently published their outcomes in a peer-reviewed journal (16) and that kindly shared their analyzed outcomes with us .We decided to select the current approach rather than an analysis with historical data from our own center because the Italian center, compared to ours, implemented very similar surgical and resuscitative techniques except solely for an opioid sparing rather than an opioid free approach. Conversely, our data arise from a subunit that has remained constant in terms of team composition, and pre-, peri- and postoperative care dedicated to OFA. The current study demonstrates by statistical analysis that the ERA-OFA protocol provides comparable outcomes in terms of primary and secondary endpoints as set out in “methods”.

Whereas, to our knowledge, the current study is the first one aiming at evaluating the benefits of the combined use of ERAS and OFA protocols, important weak points remain. They include: first, the already mentioned retrospective observational aspect, and second, the lack in reporting the cohort’s quantity of opioids consumed, pain scores as well as the incidence of perioperative nausea and vomiting, which are obviously relevant parameters in this matter.

Conclusions

The implementation of an OFA protocol in an ERAS approach for bariatric-metabolic surgery appears feasible while providing similar outcomes as the opioid sparing ERAS protocol.

More research is needed in terms of postoperative opioid needs, occurrence of nausea and vomiting quality of rehabilitation as evaluated in accepted scaling systems such as QOR-40.

COMPLIANCE WITH ETHICAL STANDARDS

All the procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards

Conflict of Interest

The authors declare the following potential conflicts of interest:

Author 1 received honorarium as a speaker with Ethicon Endosurgery, MSD and Conmed

Author 2 is a consultant with Ethicon Endosurgery and with Medtronics.

Authors 3,4, 5 and 6 declare they have no conflict of interest

Author 7 received honorarium as a speaker with Ethicon Endosurgery, MSD and Conmed

Informed Consent Statement

Informed consent was obtained from all individual participants included in the study, according to Ethics Committee requirements.

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