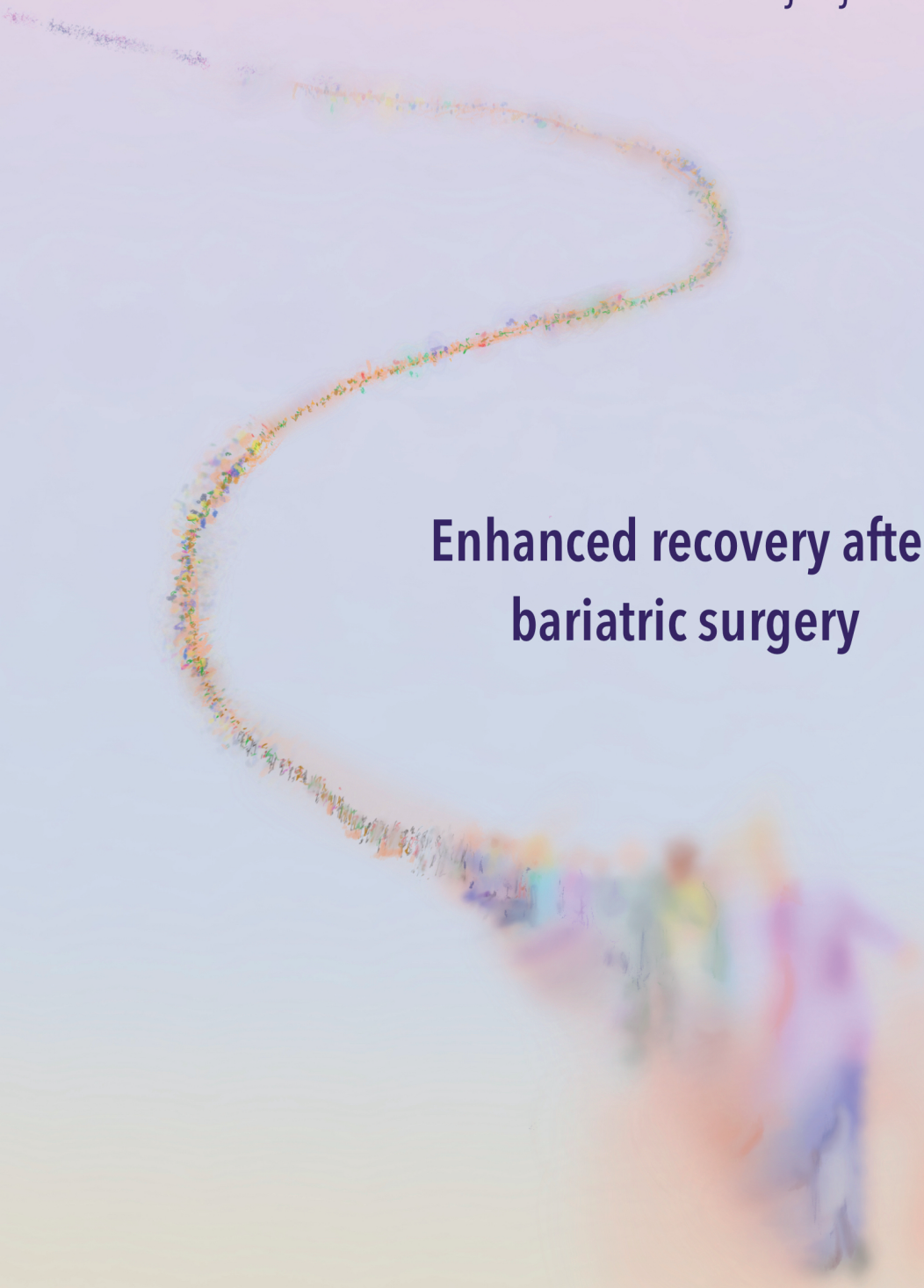
Marjolijn Leeman

Enhanced recovery after bariatric surgery



Enhanced recovery after bariatric surgery

Marjolijn Leeman

ISBN: 978-94-6361-466-5
Design cover by Mandy Bergman
Lay-out and printing by Optima Grafische Communicatie (www.ogc.nl)

Enhanced recovery after bariatric surgery
Continue evaluatie en verbetering van het fast-track protocol

Enhanced Recovery after Bariatric Surgery
Continuous evaluation and improvement of the fast-track protocol

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 23 november 2020 om 15.30 uur

door

Marjolijn Leeman

geboren te Vlaardingen

PROMOTIECOMMISSIE:

Promotor:	prof.dr. C. Verhoef
Overige leden:	prof.dr. J.F. Lange prof.dr. J.W. Greve prof.dr. E.J. Hazebroek
Copromotor:	dr. M. Dunkelgrun

TABLE OF CONTENTS

1 General introduction and outline of the thesis

OBESITY

The mean body mass index (BMI) is rapidly increasing worldwide. In 2008, an estimated 1.46 billion adults were overweight (BMI ≥ 25 kg/m^2(1). In 2015, the Global Obesity Group estimated that 107.7 million children and 603.7 million adults worldwide were obese (BMI ≥ 30 kg/m^2)(2). In 2018, the Dutch National Institute of Public Health and the Environment published alarming rates of obesity in the Netherlands; 51.9% of the Dutch population was overweight and 11.9% was obese(3).

The general etiology of obesity is an imbalance between intake and usage of calories for a longer period of time. In the majority of cases, an unhealthy eating pattern and/or a limited physical activity pattern are involved(4). Regarding the eating pattern, wrong dietary choices including high-caloric meals, large portions, an irregular eating pattern, and little fruit and vegetable intake can contribute in weight gain. Regarding physical activity, spending little time on physical exercise, and a relatively high amount of sedentary and sleeping hours can lead to obesity(5, 6).

Excess weight leads to increased risks of several diseases, such as type 2 diabetes, hypertension, dyslipidemia, stroke, sleep apnea, infertility and certain types of cancer (Figure 1). In the current corona virus pandemic, obesity (48.3%) was present in many of the hospitalized or deceased COVID-19 patients(7). These potentially lethal comorbidities can fortunately be reversed by weight loss(8-10). However, losing weight can be challenging for the morbidly obese patient.

Different approaches can be used to reach substantial weight loss: surgical and non-surgical treatment. Non-surgical treatment includes lifestyle changes such as diet alterations and increasing physical activity. Lifestyle changes are often difficult to follow and, more importantly, to maintain in the longer term. Weight loss surgery however, has shown good results on the short term and in the longer term, and was shown to be superior to non-surgical treatment in weight loss and in inducing remission of obesity-related comorbidities(11, 12).

HISTORY OF METABOLIC SURGERY

In the 1950s, V. Henrikson of Norway was the first to report a procedure for morbid obesity, in which he performed a massive small bowel resection, leaving a “short bowel” with malabsorptive weight loss(13). Ever since, different types of procedures have been performed, ranging from jejuno-colic bypasses, to jejuno-ileal bypasses, and ileo-gastrostomies. In the beginning, all procedures were performed in open surgery. Nowadays, laparoscopy is the gold standard for metabolic surgery(14-16). Three types of procedures have shown excellent results and are therefore performed in the Franciscus Gasthuis & Vlietland, which are shown in Figure 2 and described below.

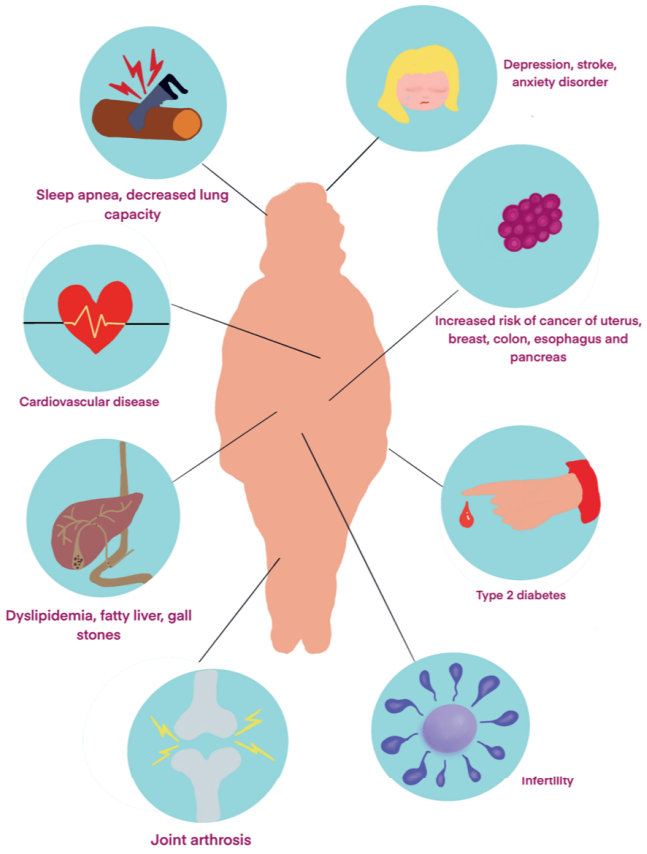


Figure 1: Health risks caused by obesity

The first is the laparoscopic Roux-en-Y gastric bypass (LRYGB), which is performed with the antecolic linear technique. A small 4 cm long pouch is calibrated over a 34 french boogie and 3 cm linear gastroenterostomy is realized. The measured biliopancreatic limb is 60 cm and the alimentary limb is 150 cm. The omentum can be divided at the surgeons' discretion. Both mesenteric defects are closed with clips to prevent internal herniation(17).

Secondly, the laparoscopic sleeve gastrectomy (LSG) is a procedure which is performed often. The greater curvature and the posterior stomach are fully mobilized, followed by stapling calibrated over a 34 french boogie, starting 2-3 cm's from the pylorus(18).

Thirdly, the mini gastric bypass-one anastomosis gastric bypass (MBG-OAGB) has been associated with good early and midterm results(19). In this procedure, the stomach is divided parallel to the lesser curvature using an oral calibration tube and is stapled up to the angle of His. The jejunal loop is brought up antecolic-antegastric, after which the stomach is anastomosed to the small bowel at this point using the linear stapler. The distal end of the gastric tube is anastomosed to the side of the small bowel(20).

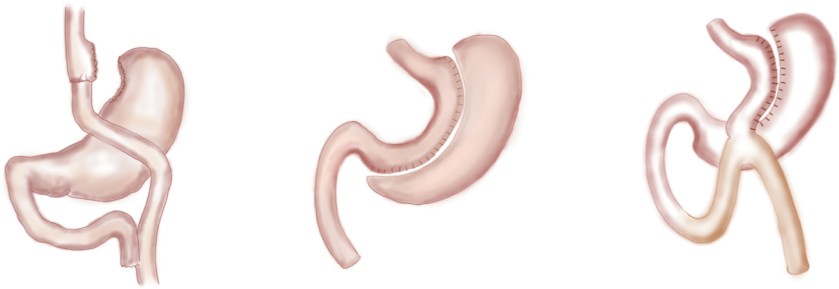


Figure 2: Roux-en-Y gastric bypass – Sleeve gastrectomy – Mini gastric bypass-one anastomosis gastric bypass

Before determining the type of surgery most suitable for a patient, the patient must be found eligible for metabolic surgery according to specific guidelines. According to the International Federation for Surgery of Obesity and Metabolic Diseases (IFSO) guidelines, metabolic surgery is indicated to patients in age groups from 18 to 65 years having the following characteristics: 1) BMI $\geq$ 40 kg/m^2, or 2) BMI 35-40 kg/m^2 with comorbidities in which surgically induced weight loss is expected to improve the disorder(21).
The patients who are found eligible for metabolic surgery have increased mortality risk as compared to the general population due to excess weight and co-morbidities (e.g., cardiovascular, type 2 diabetes)(22). As metabolic procedures are often high-risk procedures, perioperative care needs to be well-organized for it to result in a good outcome. Standardized care in the shape of perioperative protocols can lead to a safe, patient-friendly and efficient treatment path.

ENHANCED RECOVERY AFTER BARIATRIC SURGERY

To improve efficiency and cost-effectiveness in healthcare, Enhanced Recovery After Surgery (ERAS) protocols were developed for colorectal surgery in 1997(23). Ever since, several study groups have implemented a similar protocol for bariatric care. Eventually, official ERABS (Enhanced Recovery After Bariatric Surgery) guidelines were published in 2016. The three key points of the ERABS protocol are safety, patient-friendliness and efficiency in the perioperative phase. A multidisciplinary team, experienced in obesity management and metabolic surgery, is considered to be of great importance for a good treatment outcome.
In the Franciscus Gasthuis & Vlietland, an ERABS protocol was implemented in 2012. The implementation of this protocol has led to shorter procedural times and a decreased length of hospital stay, which could lead to more efficient and cost-effective bariatric care(24). The improvement in efficiency and cost-effectiveness are important outcomes, however, there is always room for further improvement. Continuous evaluation and revision of the ERABS protocol can help to improve patient care in bariatric surgery.

OUTLINE OF THE THESIS

The present thesis focuses on metabolic surgery in a fast-track setting. The first aim, which is described in part I of this thesis, was to evaluate and change the protocols used in metabolic surgery, and herewith improve the surgical treatment of morbid obesity. We focused on patient experience of the procedure and admission, pain scores, and the prevention and early diagnosis of complications. Part II of this thesis describes the second aim: to evaluate the outcomes after metabolic surgery in a fast-track setting. In this part, we focused on vascular changes within one year after surgery, nutritional deficiencies and sweet-eating behavior. This thesis does not include long-term results of metabolic surgery.

In part I of this thesis, **Chapter 2** reports the morbidity-related outcomes of patients undergoing bariatric surgery within our clinic over the years, in which the ERABS protocol is continuously being evaluated and optimized. In **Chapter 3**, the influence of the operator's level of experience on patient outcome in fast-track bariatric surgery is analyzed. **Chapter 4** describes the results of a randomized pilot study to determine the feasibility, safety and tolerability of low-pressure pneumoperitoneum and deep neuromuscular blockade to reduce postoperative pain. In **Chapter 5**, the optimal thromboprophylaxis management for bariatric patients following a fast-track protocol is reported. **Chapter 6** describes the trial protocol of a double-blinded placebo-controlled randomized trial, which aims to investigate whether peroperative administration of tranexamic acid reduces the peroperative and postoperative hemorrhage rates in laparoscopic sleeve gastrectomy. In **Chapter 7**, the predictive value of the neutrophil-to-lymphocyte ratio on early postoperative major complications in metabolic surgery is investigated. Part II of this thesis starts with **Chapter 8**, which reports the effects of bariatric surgery on the structural and functional arterial changes after one year of follow up. In **Chapter 9**, the outcomes are reported of a randomized controlled trial investigation the optimal length of the limbs of a LRYGB. **Chapter 10** investigates the predictive value of the preoperative DSEQ on postoperative weight loss after LRYGB and LSG.

REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet (London, England). 2011;377(9765):557-67.
2. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. The New England journal of medicine. 2017;377(1):13-27.
3. Lengte en gewicht van personen, ondergewicht en overgewicht; vanaf 1981. Statline, CBS. 2018.
4. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Annals of nutrition & metabolism. 2015;66 Suppl 2:7-12.
5. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl 4:S164-92.
6. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obesity facts. 2015;8(6):402-24.
7. Samuels JD. Obesity and severe COVID-19 disease: a strong association. Obesity (Silver Spring, Md). 2020.
8. Jonker FHW, van Houten VAA, Wijngaarden LH, Klaassen RA, de Smet A, Niezen A, et al. Age-Related Effects of Bariatric Surgery on Early Atherosclerosis and Cardiovascular Risk Reduction. Obesity surgery. 2018;28(4):1040-6.
9. Hatoum IJ, Blackstone R, Hunter TD, Francis DM, Steinbuch M, Harris JL, et al. Clinical Factors Associated With Remission of Obesity-Related Comorbidities After Bariatric Surgery. JAMA surgery. 2016;151(2):130-7.
10. Cooiman MI, Aarts EO, Janssen IMC, Hazebroek EJ, Berends FJ. Weight Loss, Remission of Comorbidities, and Quality of Life After Bariatric Surgery in Young Adult Patients. Obesity surgery. 2019;29(6):1851-7.
11. Arterburn D, Bogart A, Coleman KJ, Haneuse S, Selby JV, Sherwood NE, et al. Comparative effectiveness of bariatric surgery vs. nonsurgical treatment of type 2 diabetes among severely obese adults. Obesity research & clinical practice. 2013;7(4):e258-68.
12. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. The Cochrane database of systematic reviews. 2014(8):Cd003641.
13. Deitel M. Handbook of obesity surgery : current concepts and therapy of morbid obesity and related disease. Toronto: FD-Communications Inc.; 2010.
14. Lujan JA, Frutos MD, Hernandez Q, Liron R, Cuenca JR, Valero G, et al. Laparoscopic versus open gastric bypass in the treatment of morbid obesity: a randomized prospective study. Annals of surgery. 2004;239(4):433-7.
15. Nguyen NT, Goldman C, Rosenquist CJ, Arango A, Cole CJ, Lee SJ, et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Annals of surgery. 2001;234(3):279-89; discussion 89-91.
16. Westling A, Gustavsson S. Laparoscopic vs open Roux-en-Y gastric bypass: a prospective, randomized trial. Obesity surgery. 2001;11(3):284-92.
17. Leifsson BG, Gislason HG. Laparoscopic Roux-en-Y gastric bypass with 2-metre long biliopancreatic limb for morbid obesity: technique and experience with the first 150 patients. Obesity surgery. 2005;15(1):35-42.
18. Gadiot RP, Biter LU, Zengerink HJ, de Vos tot Nederveen Cappel RJ, Elte JW, Castro Cabezas M, et al. Laparoscopic sleeve gastrectomy with an extensive posterior mo-

bilization: technique and preliminary results. Obesity surgery. 2012;22(2):320-9.
19. Apers J, Wijkmans R, Totte E, Emous M. Implementation of mini gastric bypass in the Netherlands: early and midterm results from a high-volume unit. Surgical endoscopy. 2018;32(9):3949-55.
20. Lee WJ, Wang W, Lee YC, Huang MT, Ser KH, Chen JC. Laparoscopic mini-gastric bypass: experience with tailored bypass limb according to body weight. Obesity surgery. 2008;18(3):294-9.
21. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obesity surgery. 2014;24(1):42-55.
22. White GE, Courcoulas AP, King WC, Flum DR, Yanovski SZ, Pomp A, et al. Mortality after bariatric surgery: findings from a 7-year multicenter cohort study. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2019.
23. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British journal of anaesthesia. 1997;78(5):606-17.
24. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrun M, de Quelerij M, Verbrugge SJ, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.

PART I

Continuous evaluation and improvement of the ERABS protocol

2 ERABS 2.0: Results on patient outcome

Accepted: Surgical Endoscopy, 2020

ABSTRACT

Background

To optimize the postoperative phase following bariatric surgery, the Enhanced Recovery After Bariatric Surgery pathway (ERABS) has been developed. The aim of ERABS is to create a care path that is as safe, efficient and patient-friendly as possible. Continuous evaluation and optimization of ERABS are important to ensure a safe treatment path and may result in better outcomes. The objective of this study was to compare the clinical outcomes of patients undergoing bariatric surgery over 2014-2017, during which the ERABS protocol was continuously evaluated and optimized.

Methods

Retrospective cohort study. Data was collected from patients undergoing a primary Roux-en-Y gastric bypass or sleeve gastrectomy between January 2014 and December 2017. Outcomes were early complications, unplanned hospital revisits, readmissions, duration of surgery and length of hospital stay.

Results

2889 patients underwent a primary bariatric procedure in a single center. There was a significant decrease in minor complications over the years from 7.0% to 1.9% ($p<0.001$). Hospital revisit rates decreased after 2015 ($p<0.001$). Readmission rates decreased over time ($p<0.001$). The mean duration of surgery decreased from 52 (in 2014) to 41 (in 2017) minutes ($p<0.001$). Median length of hospital stay decreased from 1.8 to 1.5 days in 2015 ($p=0.002$) and remained stable since.

Conclusion

An improvement of the ERABS protocol was associated with a decrease in minor complication rates, number of unplanned hospital revisits and readmission rates after primary bariatric procedures.

INTRODUCTION

Obesity has become pandemic over the past decades(1). The obesity-related comorbidities, mortality and costs emphasize the need for both adequate prevention and treatment strategies. Bariatric surgery is the only long-term effective treatment for morbid obesity, with better results in terms of weight loss and resolution of obesity-associated comorbidities in comparison to non-surgical interventions(2).

At the end of the 20th century, the Enhanced Recovery After Surgery (ERAS) program was introduced for colorectal surgery(3) to standardize perioperative care and thereby provide more efficient, safe and cost-effective care. Subsequently, several study groups described an ERAS-like program for bariatric surgery implemented within their own clinics(4-7). These publications eventually lead to the composition of an official Enhanced Recovery After Bariatric Surgery (ERABS) program by the ERAS Society in 2016, setting the standard for and leading to the implementation of ERABS on a worldwide scale(8).

A meta-analysis of published studies on ERABS programs demonstrated the benefits of ERABS, such as a decreased length of hospital stay (LOS) without an increase of complications or readmissions(9). This could lead to more efficient and cost-effective bariatric care. After the implementation of the ERABS program in 2012 within our own clinic, the number of unplanned revisits to the outpatient clinic or emergency ward and the readmission rate was significantly increased from 12.5% to 16.8%, without an increase in the incidence of severe complications. Most patients who revisited the hospital shortly after discharge, had complaints of persisting pain or nausea, while serious complications were ruled out. The hypothesized reason for this was that patients were insufficiently informed on the postoperative course, when leaving the hospital(7). To complement our ERABS protocol with the most up-to date evidence-based and experience-based knowledge, the pathway is continuously under evaluation and improved where possible.

The aim of this study was to evaluate the outcomes of patients undergoing bariatric surgery between 2014 and 2017. In this period, the ERABS protocol was continuously being evaluated and optimized. Primary outcome measure was deviation from standard postoperative course, expressed as early complications, hospital readmissions and returns to emergency department or unscheduled visits to the outpatient clinic within 30 days postoperatively. Secondary outcome measures were duration of surgery and LOS.

MATERIALS AND METHODS

Design and setting

This was a retrospective cohort study with prospective data collection in the period between 2014 and 2017 in a single center setting. The Franciscus & Vlietland Hospital in Rotterdam,

the Netherlands has a bariatric clinic mainly performing laparoscopic Roux-en-Y gastric bypasses (LRYGB) and laparoscopic gastric sleeve gastrectomies (LSG). Since 2014 there has been an increase in patients undergoing a mini gastric bypass-one anastomosis gastric bypass (MGB-OAGB) or revisional surgery. All patients were treated according to the ERABS program(7). The patients were divided into groups based on the year of surgery.

Data collection

Data was collected from the electronic patient files of all consecutive patients undergoing a primary bariatric LRYGB or LSG in the period of January 2014 until December 2017. Patients undergoing a MGB-OAGB (n=145) or revisional surgery (n=228) were excluded, due to the relatively small numbers of procedures.

Outcomes

Outcome measures were 1) early complications, 2) readmissions and 3) returns to the emergency department or unscheduled visits to the surgical outpatient clinic within 30 days postoperative. Complications were defined as minor or major complications, based on the guidelines described by Brethauer et al.(10).

The revised ERABS protocol of the Franciscus Hospital

The ERABS protocol was implemented in the Franciscus Hospital in the course of 2012. The protocol was composed by a multidisciplinary team with delegates from all involved departments and was based on the guidelines published by Fried et al(11). Patients are referred to the bariatric center by their general practitioner and are evaluated for surgery according to the IFSO criteria(11). Following the IFSO guidelines, patients up to the age of 65 are candidates for surgery(8). All patients undergoing a bariatric procedure are treated according to the ERABS protocol and the protocol is the same for all bariatric procedure types. Next to several recommendations from the guidelines that were adopted in the protocol, additional alterations were made to the ERABS protocol itself. The latest ERABS protocol is described in the next paragraphs and summarized in Table 1. The protocol consists of a pre-operative phase, peri-operative phase and post-operative phase.

Pre-operative phase

On the intake day, patients are initially screened by the bariatric nurse on BMI and comorbidities. After confirmation of the patient meeting the (IFSO) criteria, the patient is screened by a dietician and a psychologist.

On the analysis day, on average about 8 weeks later, an endocrinologist screens the patient in combination with a physical examination, looking for genetic or pathologic causes of obesity. A dietician evaluates the patients compliance to their dietary advices to predict the chance of postoperative complications due to the patients eating behavior. In case of concerns about

Table 1: Key points of the ERABS protocol in the Franciscus Hospital

Pre-operatively	Information evening: extensive provision of information with films and interviews
	Intake day: Screening by bariatric nurse, dietician and psychologist
	Analysis day: Screening by physician, dietician and if indicated psychologist
	Planning day: Screening by surgeon and anesthesiologist
Peri-operatively	Mandatory weighing 1 week prior to surgery and at admission on the day of surgery
	Start LMWH (Dalteparin 5000 IE) on the evening before surgery
	Anti-thrombosis stockings in case of DVT or PE
	Intake of solid food up to 6h and clear fluids up to 2h prior to surgery
	No urinary catheters
	No sedative premedication
	Scheduling of high risk patients first on the OR
	Antibiotics, analgesia and anti-emetics 15 minutes before surgery
	Patient in French position with anti-Trendelenburg, head positioned on special HELP cushion
	Early ambulation by asking patient to slide into their bed from the operation table
Post-operatively	Direct encouraging to drink full liquid diet and ambulate
	Analgesia with 4 times daily 1000mg acetaminophen and 2 times daily 10 mg oxycodone when necessary
	Decrease anti-diabetic medication immediately for drug-dependent T2DM with close monitoring
	Low administration of intravenous fluids, decreased in accordance to oral intake
	Extra group session with dietician on the morning of discharge
	Mobilizing under guidance of physical therapist
	Discharge when patient meets discharge criteria

eligibility for bariatric surgery by the surgeon, physician, dietician or psychologist, patients are discussed in a weekly multidisciplinary meeting.
On the planning day, on average about 2 weeks later, the patient is screened by the surgeon and the type of surgery is chosen (RYGB, SG or MGB-OAGB). An anesthesiologist screens the patient at the pre-operative screening unit and trains the patient to self-administer subcutaneous low molecular weight heparin (LMWH) if indicated. The waiting list for bariatric procedures is about 8 weeks.

Peri-operative phase
Patients are admitted on the day of surgery and can eat solid food up to 6 hours before surgery and clear fluids up to two hours before surgery. Patients receive anti-embolism stockings only when indicated: in case of earlier thromboembolic events or other risk factors. Patients are instructed to urinate just before departure to the OR to avoid the need for urinary catheters.
Patients do not receive sedative premedication in the holding bay. Patients receive 3g of cefazolin or, in case of allergies, 600mg clindamycin. For analgesia, 1000mg acetaminophen intravenous is used and patients receive 4mg of dexamethasone and 4mg ondansetron as prophylactic anti-emetics. The patient is positioned while awake to avoid decubitus during

surgery. The anesthesia protocol has undergone some minimal changes. Induction is done with 100mcg remifentanil, combined with propofol titrated to effect (200-300mg) and rocuroniumbromide 30-40mg. Using a Head Elevated Laryngoscopy Position (HELP) cushion, intubation is done by the anesthesiologist. While the surgery is performed, the patient receives remifentanil 10-30ml/h, desflurane, 10-15mg morphine and 10-15mg ketamine. The operation is performed using intra-abdominal pressure up to 20mmHg, to warrant good surgical overview and working space in the obese patient. For termination, remifentanil and desflurane are discontinued and sugammadex 100mg is administered. As soon as the patient wakes, the patient slides by them self from the operating table onto a bed and is taken to the PACU. There, extra analgesia is only administered if indicated.

Patients are encouraged to mobilize as soon as they return from the OR. During admission the patient receives Dalteparin 5000 IE subcutaneously. Standardized pain protocol includes four times daily 1000 mg acetaminophen intravenous and – only if needed – up to six times daily 10–15 mg morphine intramuscular, for maximally 24 h. The usage of non-steroidal anti-inflammatory drugs (NSAIDs) was discouraged. The day after surgery, a standardized checklist is filled in by the ward doctor during morning rounds. A physical therapist helps the patient with mobilization and gives instructions and tips to take home. Intravenous fluid administration is quickly reduced to zero when liquid intake is sufficient. Patients are discharged in case of no suspicion of postoperative complications.

Protocol alterations

Based on the finding that patients were returning to the outpatient clinic or emergency ward more often, due to insufficient knowledge on the postoperative course and not due to major complications, the described protocol has undergone several alterations. Firstly, in 2014, a postoperative bariatric checklist was implemented to evaluate the safety of early discharge (12). Based on predetermined parameters and cut-off points a decision was made on the patient's discharge. Interestingly, the patient's willingness to leave the hospital was one of the significant predictors of presence or development of major complications. The checklist has become standard care within our ERABS program since 2014.

Secondly, as of 2016, the role of the dietician, psychologist and physical therapist grew importance. A psychologist already screened all patients on the intake day and can guide patients throughout the perioperative phase with additional consulting if needed. A physical therapist no longer screens patients preoperatively, but helps with early mobilization of patients on the first day postoperatively and provides information on what to expect in the postoperative period. In addition to the preoperative counseling by a dietician, an extra group lecture is held on the first postoperative day, in which patients are reminded of the content of the diet and importance of compliance to this diet. We believe that the best strategy to inform patients on the postoperative course, is spreading out the education over multiple visits. Therefore,

during each preoperative visit, all caregivers spend time informing the patient on their own area of expertise.
The hypothesis is that the patient gains confidence in recovering at home after practicing mobilization under the guidance of the physical therapist and having refreshed the information on dietary habits.

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Multivariable binary logistic regression was used to estimate the relationship between year of surgery and clinical outcome, correcting for age, gender, BMI at inclusion, hypertension, diabetes, dyslipidemia and type of surgery. Multivariate analysis was used to evaluate the differences in minor and major complication rates between the different types of procedures, corrected for surgeon, baseline characteristics and type of procedure. Multivariate analysis was also used for comparing the percentages of patients revisiting the hospital without having a complication over the years, correcting for the same covariates. Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

RESULTS

Between January 2014 and December 2017 2889 patients underwent a primary LRYGB or LSG within the Franciscus Hospital. Table 2 shows the patient characteristics and specifications of the procedures. No differences were found in baseline characteristics between the cohorts. The number of bariatric procedures that were performed by the different surgeons in 2014 varied from sixteen to 359 LRYGBs and fourteen to 417 LSGs, illustrating the wide range in surgical experience between the surgeons.

Table 2: Patient characteristics

Characteristics	**2014** *(n=669)*	**2015** *(n=598)*	**2016** *(n=847)*	**2017** *(n=775)*
Age at surgery (years) ***(median, IQR)***	44 (34.5-51.1)	43 (33.6-50.5)	43 (32.4-50.3)	43.2 (33.0-51.3)
Female gender ***(%)***	79.4	79.9	82.1	81.9
BMI at inclusion (kg/m^2) ***(mean, SD)***	43.7 (5.4)	43.7 (4.8)	43.3 (4.7)	42.6 (4.6)
Hypertension ***(%)***	22.3	32.9	23.6	28.0
Diabetes ***(%)***	15.4	19.7	16.6	11.9
Dyslipidemia ***(%)***	19.0	18.4	13.7	12.8
Roux-en-Y gastric bypass ***(%)***	55.8	65.1	61.3	46.7

Figure 1 shows the complication rates over the years since the introduction of the ERABS program. There was a significant decline in the rate of overall complications occurring within 30 days between 2014 and 2017 (p<0.001). Especially the minor complications decreased dramatically from 7.0% in 2014 to 1.9% in 2017 (p<0.001). The major complication rate was 4% on average over the years and did not change significantly (p=0.467). There were no significant differences in minor complication rates (p=0.144) or major complication rates (p=0.932) between LRYGB and LSG. Table 3 shows that the year of surgery significantly influenced minor complication rates (p=0.002), but not major complication rates (p=0.552), when using multivariable analysis, correcting for type of surgery, gender, age, BMI and comorbidities. Table 3 also shows that the surgeon did not influence minor complication rates (p=0.582) or major complication rates (p=0.885) significantly. Mortality within 30 days has remained stable with on average 0.05% each year.

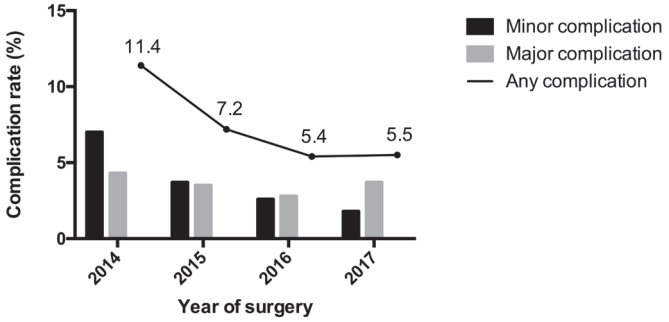


Figure 1: Crude overall complication rates between 2014-2016. There was a significant decrease in 2017 compared with 2014 (p<0.001), mainly due to the decrease in minor complications (p<0.001). The major complication rate did not change over the years (p=0.467).

Table 3: Multivariate analysis of year of surgery and surgeon on complication rates

	Minor complication rates		**Major complication rates**		**Any complication rates**	
	OR, 95% C.I.	*Sig.*	*OR, 95% C.I.*	*Sig.*	*OR, 95% C.I.*	*Sig.*
Year of surgery		0.002		0.552		0.005
2015 vs. 2014	0.588 (0.327-1.058)	0.076	0.787 (0.420-1.475)	0.455	0.654 (0.422-1.013)	0.057
2016 vs. 2014	0.439 (0.247-0.778)	0.005	0.641 (0.351-1.171)	0.148	0.507 (0.333-0.774)	0.002
2017 vs. 2014	0.314 (0.162-0.607)	0.001	0.818 (0.462-1.449)	0.491	0.524 (0.342-0.804)	0.003
Surgeon		0.582		0.885		0.888
Surgeon 1 vs. 5	0.592 (0.292-1.202)	0.147	1.380 (0.459-4.154)	0.567	0.766 (0.419-1.399)	0.386
Surgeon 2 vs. 5	0.648 (0.300-1.403)	0.271	1.664 (0.533-5.195)	0.381	0.885 (0.467-1.679)	0.709
Surgeon 3 vs. 5	0.514 (0.197-1.342)	0.174	1.586 (0.459-5.478)	0.465	0.776 (0.369-1.632)	0.504
Surgeon 4 vs. 5	0.526 (0.235-1.177)	0.118	1.623 (0.516-5.100)	0.407	0.785 (0.409-1.507)	0.467

*Data was corrected for type of surgery, gender, age, BMI and comorbidities

Figure 2 shows the rate of unplanned revisits to the outpatient clinic or emergency department within 30 days postoperatively. There was a significant increase in hospital revisits between 2014 and 2015 from 18% to 22%, without an increase in complications (Figure 1). Since then, the amount of hospital revisits has gradually decreased to 14% and was significantly lower in 2017 compared to 2015 ($p<0.001$). The percentage of patients revisiting the hospital without having a complication was increased to 18% in 2016, but later fell to 10% in 2017.

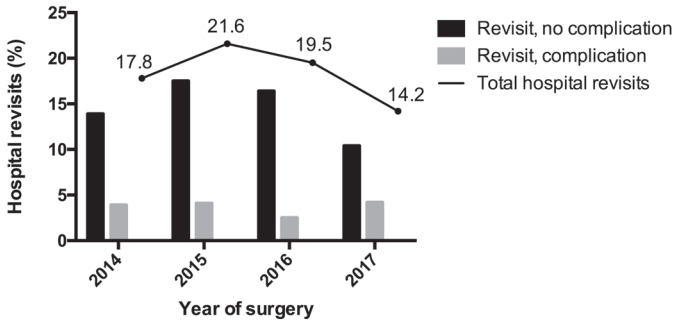


Figure 2: Percentage of hospital revisits within 30 days postoperative ($p<0.001$) and crude percentage of patients with and without major complications.

Figure 3 shows that the rate of hospital readmissions within 30 days postoperative significantly decreased over the years ($p<0.001$). Especially the percentage of patients being readmitted in the hospital without any (major) complications was minimal in 2017 (1%), making a bigger percentage of the readmissions justified. There were no significant differences in readmission rates between LRYGB and LSG ($p=0.278$). Also, there were no significant differences among the surgeons in minor complication rates ($p=0.774$), major complication rates ($p=0.901$) or readmission rates ($p=0.950$).

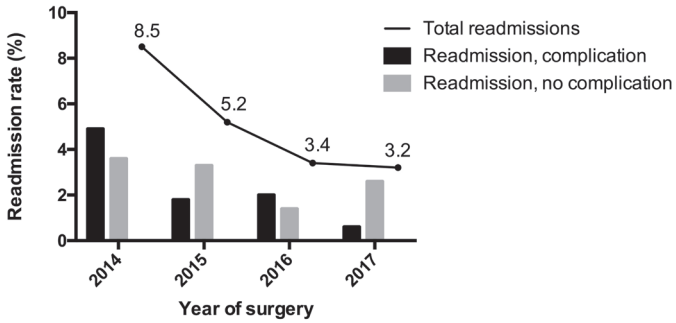


Figure 3: Crude hospital readmission rates within 30 days, decreasing over the years when comparing 2014 and 2017 ($p<0.001$).

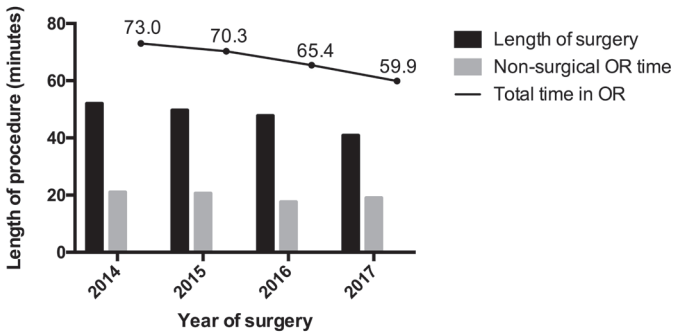


Figure 4: Crude mean length of procedure in minutes, divided in perioperative time and length of surgery ($p<0.001$).

Figure 4 shows the decrease in total duration of surgery, including anesthesiological care, from 73 (in 2014) to 60 (in 2017) minutes in the OR ($p<0.001$). A similar trend was seen regarding the decrease in duration of surgery from 52 (in 2014) to 41 (in 2017) minutes.
Figure 5 displays the decrease in LOS from median 1.8 to 1.5 days in 2015 ($p=0.002$) and remained stable ever since.

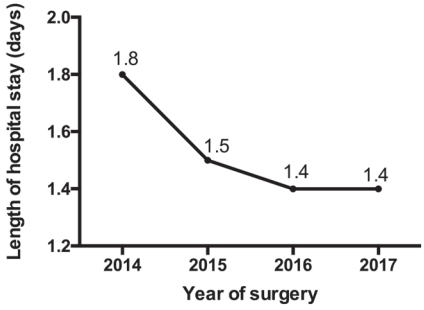


Figure 5: Crude mean length of hospital stay, stabilizing since 2015. There was a significant decrease in LOS from 2014 to 2015 ($p=0.048$).

DISCUSSION

The aim of this study was to compare the outcomes of patients undergoing bariatric surgery over the years since introduction of the ERABS program in 2012. Since then, the ERABS protocol has continuously been evaluated and optimized.
In our previous analysis of the ERABS protocol as described by Mannaerts et al, the implementation of the program was mainly associated with logistic benefits, such as shorter operation time and shorter LOS(7). Although the major complication rates remained stable, the number of hospital revisits had increased significantly. Under the hypothesis of this increase

being caused by a gap in knowledge on the expected postoperative course, the ERABS protocol was adjusted. In the revised protocol, additional information – provided *after* surgery – concerning the postoperative diet and early mobilization with the physical therapist plays a key role. In the following years, significant decreases were seen in minor complications, readmissions and unplanned hospital revisits. Also, the duration of surgery decreased and the major complications rates remained stable. An important question that arises is whether these changes are caused by the revisions in the ERABS protocol, or that they are mainly influenced by the experience of the surgeon and the anesthesiological team.

The decrease in duration of surgery and LOS may partially be explained by the learning curve of the surgeon and anesthesiological team(13), but also by the effect of the ERABS protocol on the logistics around bariatric surgery(7). Since 2016, the LOS remained stable. Patients are encouraged to leave the hospital on the first day postoperative, provided they meet the criteria for discharge according to the postoperative checklist. Nevertheless, hospital stay is prolonged on mild indications, to prevent premature discharge.

The decreasing minor complication rates and readmission rates are more likely to be caused by the improvements that were made to the ERABS protocol, as patients leave the hospital in optimal conditions: well informed and confident to go home for further recovery. Patients that did return to the hospital and/or were readmitted within 30 days postoperatively, more often actually had developed a complication, making the revisit or readmission justified. Mortality within 30 days has remained low with 0.05% annually over the years, which corresponds to the Dutch national average mortality rate of bariatric surgery of 0.05%(14).

With the finding of significantly less minor complications, hospital revisits and readmissions, this paper is the first ERABS paper to show an association with improvements in patient outcome rather than only logistic factors. While we aim for a further decrease in hospital revisits and readmissions, future research should focus on those patients who revisit the hospital without them having a complication. Also, future studies using questionnaires on Patient Reported Experience and Outcome Measures (PREMs/PROMs) may demonstrate an improvement in patient experience.

A limitation of this study is the variation in surgical experience between the surgeons. There are many factors that influence a surgeon's learning curve; the amount of performed bariatric procedures, the amount of other (laparoscopic) procedures performed and the number of bariatric procedures assisted, which can all have a substantial impact on their surgical skills. This study took place in a teaching hospital, meaning that the procedures were performed by bariatric surgeons or by residents under the supervision of a bariatric surgeon. Based on the number of performed procedures, we can stipulate that the five bariatric surgeons that performed the great majority of the procedures between 2014 and 2017 were in different stages of their learning curve. Even though their level of experience varied, the surgeon did not independently influence the complication rates in multivariate analysis. This result might be explained by the fact that we work with an experienced team of surgeons, scrub nurses and

anesthesiology staff. Further research is required to determine the precise effect of surgical experience on patient outcome.

Our study underlines that the ERABS program is a dynamic concept and that it is important to continuously monitor and improve the ERABS protocol. This paper suggests that even minor alterations on dietary education and guided ambulation may already have a substantial impact on readmission rates. Besides the logistic benefits, ERABS also seems to improve patient outcome in terms of minor complications and readmissions within 30 days postoperatively. Smart timing of effective patient information provision seems to play an important role. In our opinion, optimization of the ERABS protocol is currently the main factor driving better outcomes. Further research is required to determine the impact of this improved ERABS programs on the patient's experience on the hospital admission, surgery and postoperative care. Optimization of analgesia, anti-emetics and the preoperative diet can be interesting topics for future research.

REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet (London, England). 2011;377(9765):557-67.
2. Neovius M, Narbro K, Keating C, Peltonen M, Sjoholm K, Agren G, et al. Health care use during 20 years following bariatric surgery. Jama. 2012;308(11):1132-41.
3. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British journal of anaesthesia. 1997;78(5):606-17.
4. Dogan K, Kraaij L, Aarts EO, Koehestanie P, Hammink E, van Laarhoven CJ, et al. Fast-track bariatric surgery improves perioperative care and logistics compared to conventional care. Obesity surgery. 2015;25(1):28-35.
5. Elliott JA, Patel VM, Kirresh A, Ashrafian H, Le Roux CW, Olbers T, et al. Fast-track laparoscopic bariatric surgery: a systematic review. Updates in surgery. 2013;65(2):85-94.
6. Lemanu DP, Singh PP, Berridge K, Burr M, Birch C, Babor R, et al. Randomized clinical trial of enhanced recovery versus standard care after laparoscopic sleeve gastrectomy. The British journal of surgery. 2013;100(4):482-9.
7. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrun M, de Quelerij M, Verbrugge SJ, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
8. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
9. Malczak P, Pisarska M, Piotr M, Wysocki M, Budzynski A, Pedziwiatr M. Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis. Obesity surgery. 2017;27(1):226-35.
10. Brethauer SA, Kim J, el Chaar M, Papasavas P, Eisenberg D, Rogers A, et al. Standardized outcomes reporting in metabolic and bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(3):489-506.
11. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obesity surgery. 2014;24(1):42-55.
12. van Mil SR, Duinhouwer LE, Mannaerts GHH, Biter LU, Dunkelgrun M, Apers JA. The Standardized Postoperative Checklist for Bariatric Surgery; a Tool for Safe Early Discharge? Obesity surgery. 2017;27(12):3102-9.
13. Major P, Wysocki M, Dworak J, Pedziwiatr M, Pisarska M, Wierdak M, et al. Analysis of Laparoscopic Sleeve Gastrectomy Learning Curve and Its Influence on Procedure Safety and Perioperative Complications. Obesity surgery. 2018;28(6):1672-80.
14. Poelemeijer YQM, Liem RSL, Nienhuijs SW. A Dutch Nationwide Bariatric Quality Registry: DATO. Obesity surgery. 2018;28(6):1602-10.

3 Learning curve: Influence of surgeons in training on ERABS

Accepted: Obesity Surgery, 2020

ABSTRACT

Introduction

Short duration of surgery is an important aspect in fast-track protocols. Peroperative training of surgical residents could influence the duration of surgery, possibly affecting patient outcome. This study evaluates the influence of the operator's level of experience on patient outcome in fast-track bariatric surgery.

Methods

Data was analyzed of all patients who underwent a primary laparoscopic Roux-en-Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (LSG) between January 2004-July 2018. Residents were trained according to a stepwise training program. For each operator, learning curves of both procedures were created by dividing the procedures in time-subsequent groups (TSGs). Data was also analyzed by comparing 'beginners' with 'experienced operators', with a cut-off point at 100 procedures. Primary outcome measure was duration of surgery. Secondary outcome measures were length of hospital stay (LOS), complications and readmission rate within 30 days postoperatively.

Results

4901 primary procedures (53.1% LSG) were performed by seven surgeons or surgical residents. We found no difference between beginning versus experienced operators in complications or readmissions rates. The experience of the operator did not influence LOS (p=0.201). Comparing each new operator to previous operator(s), the starting point in terms of duration of surgery was shorter and the learning curve was steeper. The duration of surgery was significantly longer for supervised beginning operators as compared to experienced operators.

Conclusion

Within the stepwise training program for residents, there is a slight increase in duration of surgery in the beginning of the learning curve, without affecting the patient outcome.

INTRODUCTION

Enhanced Recovery After Bariatric Surgery (ERABS) protocols or fast-track protocols play a very important role in creating a clinical pathway that is both efficient and safe[1]. Short duration of surgery is an important aspect of the ERABS protocol, as earlier research showed that there is a direct, inverse relation between duration of surgery and complication rates[2-4]. Several factors can influence the duration of surgery, including the level of experience of the operator[5, 6]. Training of surgical residents requires time consuming education moments in the operating room and could influence duration of surgery, possibly affecting patient outcome and recovery after the procedure.

Over the years, many research groups have investigated the safety of resident involvement in high risk surgical procedures such as bariatric surgery. Overall, all studies on this topic concluded that resident involvement in bariatric surgery is safe[5-10]. Little is known on resident involvement in fast-track bariatric surgery, in which perioperative efficiency is a key point contributing to safe early discharge.

The aim of this study is to evaluate the learning curve for the laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) of different operators who were educated in different time frames. Furthermore, the aim is to evaluate the impact of the operator's position on the learning curve on postoperative recovery outcome, in patients being treated according to the ERABS protocol. The study hypothesis is that the postoperative recovery is equal for all patients following the ERABS protocol, regardless of the operator's position on the learning curve.

METHODS

Design and setting

Data was collected from all patients who underwent a primary LRYGB or LSG, performed by operators that started and completed their training in bariatric surgery between 2004 and 2018 in a teaching hospital in the Netherlands. In the hospital's bariatric clinic, mainly LRYGBs and LSGs are performed. Exclusion criteria were a bariatric procedure combined with other surgical procedures, such as adhesiolysis, cholecystectomy or diaphragmatic hernia repair, or in case of conversion to an open procedure. Because of missing data on complications before implementation of the Dutch national complication registration database in 2014, analyses on postoperative complications were only performed for patients operated between 2014 – 2018.

Outcomes

Primary outcome measure was duration of surgery, starting at placement of the Veress needle and ending after closing of all laparoscopic wounds. Secondary outcome measure was clini-

cal outcome, in terms of length of hospital stay (LOS), minor and major complication rates and readmission rates within 30 days postoperative. Type of complication was classified as described by Brethauer et al[11].

Training program

The operating techniques for LRYGB and LSG in our center have not changed significantly since 2004 and were described in previous publications[12, 13]. Residents are trained to perform bariatric procedures using a stepwise LRYGB and LSG training program (Figure 1), in which the surgeon in training starts with performing separated steps of the procedure instead of an entire procedure at once. During the training, an experienced surgeon was always present in the operating room or assisting in the procedure to be able to evaluate when a surgeon in training has become skilled enough to perform an entire procedure safely and in a timely manner. The results of the training program for the LRYGB are described by Walinga et al[14].

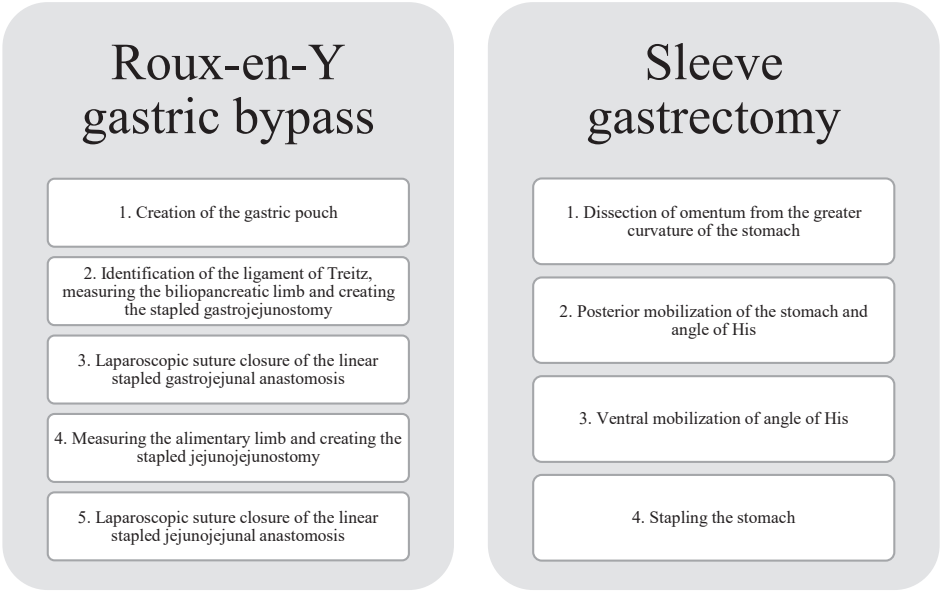


Figure 1: Steps of the training program for LRYGB and LSG

Statistical analysis

All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). For each operator, learning curves of both procedure types were created by dividing the procedures in time-subsequent groups (TSGs), with a maximum of 50 procedures per TSG. The learning curves were conducted based on the mean duration of surgery of the TSGs of each operator. The effect of the operator on the duration of surgery was evaluated using

linear regression analysis. The first 50 LRYGBs and the first 50 LSGs that were performed entirely by the beginning operator were identified and compared with procedures performed by other operators in the same time frame. The procedures were compared on duration of surgery and length of hospital stay using one-way ANOVA. Operators who had performed less than 50 procedures were excluded from this analysis.

Data from 2014-2018 was analyzed by comparing 'beginners' with 'experienced operators' as first operator using multivariate logistic regression analysis, correcting for year of surgery, patient characteristics and comorbidities (hypertension, type 2 diabetes (T2D) and dyslipidemia). After 100 procedures of one procedure type (either LRYGB or LSG), the operator was classified as 'experienced' for that particular procedure type. Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

RESULTS

In total, 5137 primary procedures were performed between 2004 and 2018, of which 236 cases were primary bariatric procedures combined with other surgical procedures and therefore excluded. Table 1 shows the baseline characteristics by type of procedure of the 2411 (46.9%) LRYGBs and 2726 (53.1%) LSGs that were analyzed.

Table 1: Baseline characteristics

Characteristics	**LRYGB *(n=2297)***	**LSG *(n=2604)***
Age at surgery (years), *median, IQR*	43 (34-50)	41 (32-49)
Female gender, n *(%)*	1951 (84.9%)	2005 (77.0%)
BMI at inclusion (kg/m^2), *mean ± SD*	43 ± 5	43 ± 5
Hypertension, n *(%)**	391 / 1341 (29.2%)	243 / 1289 (18.9%)
Diabetes, n *(%)**	245 / 1341 (18.2%)	177 / 1289 (13.7%)
Dyslipidemia, n *(%)**	203 / 1341 (15.1%)	168 / 1289 (13.0%)

*42% (LRYGB) and 50% (LSG) missing data

Learning curve per individual operator

Figures 2 show the mean duration of surgery in the first TSG (i.e. the first 50 procedures) of each operator for LRYGB (a) and LSG (b). The operators were put in chronological order by date of their first procedure. The mean duration of surgery decreased gradually with the start of each new operator for both procedure types, meaning that the starting point in terms of duration of surgery was shorter. Figure 3 illustrates the learning curve within the first 50 procedures of each operator. Duration of surgery was significantly shorter in the second half of the first TSG for LRYGB for all operators, and for LSG for only two operators.

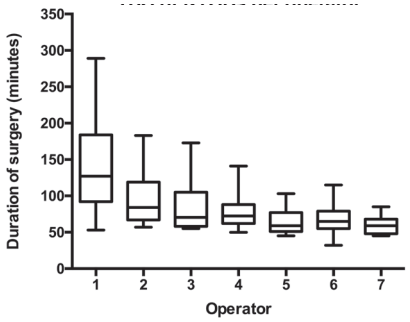


Figure 2a: Mean duration of surgery (minutes) of the first TSG of LRYGBs per operator

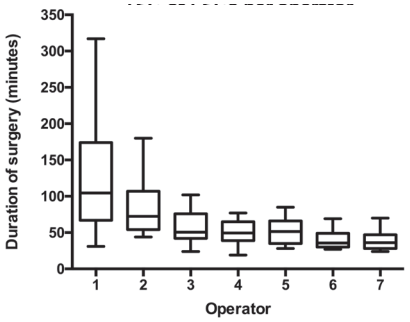


Figure 2b: Mean duration of surgery (minutes) of the first TSG of LSGs per operator

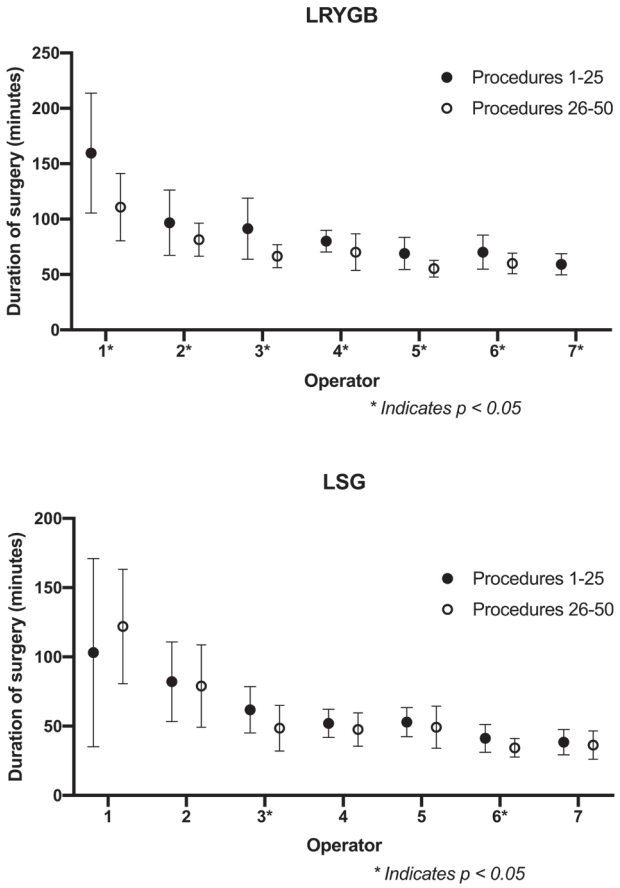


Figure 3: Mean duration of surgery (minutes) comparing the first 25 and second 25 procedures per operator

In multivariate analysis correcting for year of surgery, patient characteristics and comorbidities, there was no significant correlation between the operator and the duration of surgery (OR -0.210, 95%CI -0.915-0.496, p=0.557). The year of surgery (i.e. the experience of the operating team) was significantly correlated with the duration of surgery (OR -3.353, 95%CI -6.070-0.635, p=0.016).

Table 2 shows the duration of surgery (a) and LOS (mean ± sd) (b) for the first and second TSG of LRYGBs and LSGs of each individual operator. These means were compared to the duration of surgery and LOS performed by other operators in that same time frame (reference). No reference was available for the first operator, as this operator performed the first 50 procedures of both procedure types working as the only bariatric surgeon in this center and was therefore in the second TSG still the most experienced surgeon. After, for each operator and procedure type, the duration of the first 50 procedures was significantly longer compared to the reference. By the second TSG, one surgeon had equaled for duration of surgery with the reference operators for both LRYGB and LSG. Another surgeon had equaled the duration of surgery in the second TSG for only LSG. Most surgeons had shortened the duration of surgery, but not yet equaled with the reference operators. Nevertheless, already in the first TSG, no difference was found in LOS between the beginning operator and the reference operators. There was a wide range of the time frame of the first 50 procedures of LRYGB and LSG between operators, varying from four months to four years.

Table 2a: Duration of surgery (mean ± sd) of the first and second TSG of LRYGBs and LSGs of each operator (number 1 to 7), compared to the duration of surgery in that time frame.

a		Duration of LRYGB (minutes)			Duration of LSG (minutes)		
	TSG	Operator	Reference	Sig.	Operator	Reference	Sig.
1*	1	135.22 ± 49.96	-	-	112.52 ± 56.44	-	-
	2	70.98 ± 23.82	-	-	80.78 ± 28.21	-	-
2	1	89.10 ± 24.33	60.31 ± 18.56	<0.001	81.24 ± 29.11	65.89 ± 24.31	0.002
	2	73.21 ± 13.93	53.79 ± 17.65	<0.001	66.29 ± 19.20	50.78 ± 19.70	<0.001
3	1	81.65 ± 24.95	70.39 ± 28.72	0.022	55.37 ± 18.10	47.29 ± 18.37	0.006
	2	65.68 ± 17.07	67.17 ± 14.55	0.657	40.64 ±10.47	45.43 ± 13.23	0.060
4	1	75.45 ± 14.37	52.25 ± 16.78	<0.001	49.90 ± 11.06	38.90 ± 12.75	<0.001
	2	67.25 ± 18.34	52.45 ± 16.82	<0.001	48.10 ± 14.32	35.86 ± 8.44	<0.001
5**	1	61.94 ± 13.35	52.67 ± 16.47	<0.001	50.73 ± 13.14	38.17 ± 11.54	<0.001
	2	50.97 ± 8.16	46.04 ± 13.33	0.030	36.13 ± 9.20	33.05 ± 9.07	0.019
6***	1	66.24 ± 14.13	48.64 ± 13.68	<0.001	37.65 ± 9.09	36.33 ± 11.02	0.404
	2	-	-	-	-	-	-
7***	1	59.25 ± 9.57	44.80 ± 8.56	<0.001	37.25 ± 9.53	31.24 ± 7.31	<0.001
	2	-	-	-	-	-	-

Table 2b: Length of hospital stay (median ± IQR) of the first TSG of LRYGBs and LSGs of each operator (number 1 to 7), compared to the length of hospital stay in that time frame.

b	Length of hospital stay after LRYGB (days)			Length of hospital stay after LSG (days)		
	Operator	Reference	Sig.	Operator	Reference	Sig.
1*	3.18 ± 0.99	-	-	4.46 ± 2.04	-	-
2	2.00 ± 1.83	2.00 ± 1.00	0.903	3.09 ± 1.12	3.17 ± 1.02	0.775
3	2.52 ± 1.05	2.18 ± 0.94	0.966	3.05 ± 0.99	3.01 ± 1.00	0.064
4	1.20 ± 0.80	1.21 ± 0.22	0.399	1.29 ± 0.96	1.28 ± 0.34	0.433
5**	1.15 ± 0.12	1.16 ± 0.15	0.436	1.15 ± 0.20	1.21 ± 0.74	0.001
6***	1.15 ± 0.17	1.15 ± 0.15	0.344	1.13 ± 0.25	1.17 ± 0.28	0.323
7***	1.16 ± 0.11	1.15 ± 0.14	0.840	1.12 ± 0.18	1.18 ± 0.17	0.004

* No reference data available

** Operator performed less than 100 procedures in total

*** Operator performed less than 50 procedures in total

Beginning versus experienced operator

Table 3 shows the occurrence of complications and readmissions by level of experience for LRYGB and LSG. Chi square analysis showed that the occurrence of minor complications, major complications or readmissions was equal for both levels of experience of the surgeon. Multivariable analysis also showed that there was no significant difference between patients undergoing a LRYGB performed by a supervised beginner versus an experienced operator in minor complication rates (OR 0.712, 95%CI 0.323-1.568, p=0.399), major complication rates (OR 1.217, 95%CI 0.480-3.088, p=0.679) or readmission rates (OR 0.974, 95%CI 0.473-2.006, p=0.942). Similar results were found for LSG based on level of experience of the operator on minor complication rates (OR 0.835, 95%CI 0.335-2.079, p=0.699), major complication rates (OR 4.148, OR 95%CI 0.952-18.067, p=0.058) or readmission rates (OR 1.154, 95%CI 0.510-2.611, p=0.731). Considering the type of procedure and the year of surgery, the experience of the operator did not influence the LOS (p=0.201).

Table 3: Occurrence of complications and readmissions by level of experience for LRYGB (a) and LSG (b)

a: LRYGB	Beginning surgeon	Experienced surgeon	Sig.
Minor complications (n, %)	12/304 (3.9%)	34/1226 (2.8%)	0.283
Major complications (n, %)	10/304 (3.3%)	36/1226 (2.9%)	0.747
Readmissions (n, %)*	15/292 (5.1%)	47/1173 (4.0%)	0.391

b: LSG	Beginning surgeon	Experienced surgeon	Sig.
Minor complications (n, %)	4/284 (1.4%)	41/1158 (3.5%)	0.064
Major complications (n, %)	10/284 (3.5%)	27/1158 (2.3%)	0.256
Readmissions (n, %)*	12/259 (4.6%)	42/1111 (3.7%)	0.525

*Missing data on readmissions for LRYGB (4.2%) and for LSG (5.0%)

DISCUSSION

The aim of this study was to evaluate the impact of the level of experience of the operator on postoperative recovery, in patients being treated according to the ERABS protocol. We found that the experience of the operator is negatively correlated with the duration of surgery. In this report we show that although duration of surgery is longer in the learning curve period this does not affect postoperative recovery or complication rates. Therefore, we can conclude that it is safe to involve a resident training program in a fast track setting.

Duration of surgery

A gradual decrease was seen in the mean duration of surgery in the first TSG with the start of each new operator for both procedures. This can be explained by the fact that over the years, the mean duration of surgery shortened due to increasing experience of the dedicated bariatric team[15]. Therefore, each new operator started their education in an operating team that had already progressed in their own learning curves. Furthermore, education in the operating room became easier after introduction of the stepwise learning program for LRYGB and LSG in 2015[14].

Within the first TSG, duration of surgery was significantly shorter in the second half of the TSG for LRYGB for all operators, and for LSG for only two out of seven. This result demonstrates that the learning curve of the LRYGB is steeper than the learning curve of the LSG. Two theories can be formed on this matter. The first theory holds that steepness of the learning curve is a positive factor, meaning that the operator is quickly improving in the learning process. This would imply that the LRYGB is easier to learn than the LSG. The second theory, which we support, holds that a non-steep learning curve can imply that a procedure is easier to learn, as from the beginning, duration of surgery is relatively short.

There was a wide range in TSGs of four months - four years, which can be explained by the fact that some of the operators started performing bariatric procedures during their residency. During their residency, they followed different internships which were spread out into different hospitals. However, they have only performed bariatric procedures in this center, ensuring that their learning curve was not pursued during their absence.

The mean duration of surgery of the first 50 procedures was longer for each operator, in comparison to procedures performed by other operators in the same time frame. The extension of the procedure due to operating by a beginning operator was significant, yet small (15-30 minutes for LRYGB, 6-16 minutes for LSG). When working in a fast track setting, the time that the anesthesiological team needs for induction and emergence is short. Therefore, the extra time a beginning operator might need has a relatively large effect on the total duration of surgery and is therefore significantly different. However, the absolute amount of additional time is not excessive. Chan et al and Krell et al stated that duration of surgery was an independent predictor of postoperative venous thromboembolic events (VTE)[2, 16]. A

recently published article from our research group based on the same database revealed that the clinical VTE rates in this center have been very low since 2014 (<1%)[17], showing that training residents has not led to increased VTE rates.

Length of hospital stay

Earlier research has commented on the prolonged hospital stay of patients that were operated with resident involvement[18]. In this study, the level of experience of the operator did not influence the LOS (p=0.201). The mean difference of 0.71 days between beginning versus experienced operators seems substantial, but can easily be explained by the fact that the majority of the analyzed procedures that were performed by beginners, took place before introduction of ERABS. As earlier research has shown, the LOS has significantly reduced after the introduction of ERABS in our center[15].

Morbidity

A great concern with respect to resident involvement in bariatric surgery is the possible increase in morbidity due to insufficient experience of the operator. Several studies reported increased morbidity rates, but mainly in minor complications[7, 16, 19, 20]. In this study, there was no difference between patients undergoing a LRYGB or LSG performed by a beginner versus an experienced operator in minor complication rates, major complication rates or readmission rates. Similar results in the research area of upper gastrointestinal surgery were found by Philips et al., describing that patient outcomes are not compromised by supervised trainee involvement in transthoracic esophagectomy[21].

Limitations

A limitation of this study was that the baseline surgical experience of the operator was not taken into account. This was due to the lack of data on the number of bariatric procedures the surgeon or surgical resident had assisted and the years of additional experience as a resident and/or surgeon. Also, before performing a procedure entirely, the beginning surgeon has performed steps of the procedure while assisting the experienced surgeon. Herewith, the learning curve might have started before the first TSG. Unfortunately, it was impossible to determine which steps were performed by the beginner in each procedure from this retrospective data. Nevertheless, this data suggests that the learning curve for LRYGB or LSG and the patient outcome are mainly determined by level of experience of the surgical team that is teaching the procedure. Therefore, baseline surgical experience seems to have no additional value.

CONCLUSION

The level of experience of the surgeon did not influence patient complication rates or length of hospital stay. Within the stepwise training program for residents, there is a slight increase in duration of surgery in the beginning of the learning curve. Training residents is an essential task for all surgical units, including the bariatric unit. This study showed that resident involvement and peroperative training according to a stepwise learning program could be encouraged in bariatric surgery.

REFERENCES

1. Thorell A, MacCormick AD, Awad S, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
2. Chan MM, Hamza N, Ammori BJ. Duration of surgery independently influences risk of venous thromboembolism after laparoscopic bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(1):88-93.
3. Major P, Wysocki M, Pedziwiatr M, et al. Risk factors for complications of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. International journal of surgery (London, England). 2017;37:71-8.
4. Nandipati K, Lin E, Husain F, et al. Factors predicting the increased risk for return to the operating room in bariatric patients: a NSQIP database study. Surgical endoscopy. 2013;27(4):1172-7.
5. D'Souza N, Hashimoto DA, Gurusamy K, et al. Comparative Outcomes of Resident vs Attending Performed Surgery: A Systematic Review and Meta-Analysis. Journal of surgical education. 2016;73(3):391-9.
6. Major P, Wysocki M, Dworak J, et al. Are bariatric operations performed by residents safe and efficient? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2017;13(4):614-21.
7. Doyon L, Moreno-Koehler A, Ricciardi R, et al. Resident participation in laparoscopic Roux-en-Y gastric bypass: a comparison of outcomes from the ACS-NSQIP database. Surgical endoscopy. 2016;30(8):3216-24.
8. Iordens GI, Klaassen RA, van Lieshout EM, et al. How to train surgical residents to perform laparoscopic Roux-en-Y gastric bypass safely. World journal of surgery. 2012;36(9):2003-10.
9. Kuckelman J, Bingham J, Barron M, et al. Advanced laparoscopic bariatric surgery Is safe in general surgery training. American journal of surgery. 2017;213(5):963-6.
10. Rovito PF, Kreitz K, Harrison TD, et al. Laparoscopic Roux-en-Y gastric bypass and the role of the surgical resident. American journal of surgery. 2005;189(1):33-7.
11. Brethauer SA, Kim J, el Chaar M, et al. Standardized outcomes reporting in metabolic and bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(3):489-506.
12. Biter LU, Gadiot RP, Grotenhuis BA, et al. The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC obesity. 2015;2:30.
13. Gadiot RP, Biter LU, Zengerink HJ, et al. Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. Obesity surgery. 2012;22(2):320-9.
14. Walinga AB, van Mil SR, Biter LU, et al. A Stepwise Approach in Learning Surgical Residents a Roux-en-Y Gastric Bypass. Obesity surgery. 2018.
15. Mannaerts GH, van Mil SR, Stepaniak PS, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
16. Krell RW, Birkmeyer NJ, et al. Effects of resident involvement on complication rates after laparoscopic gastric bypass. Journal of the American College of Surgeons. 2014;218(2):253-60.
17. Leeman M, Biter LU, Apers JA, et al. A single-center comparison of extended and restricted thromboprophylaxis with LMWH after metabolic surgery. Obesity surgery. 2019;In press.

18. Carter J, Elliott S, Kaplan J, et al. Predictors of hospital stay following laparoscopic gastric bypass: analysis of 9,593 patients from the National Surgical Quality Improvement Program. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(2):288-94.
19. Major P, Wysocki M, Dworak J, et al. Analysis of Laparoscopic Sleeve Gastrectomy Learning Curve and Its Influence on Procedure Safety and Perioperative Complications. Obesity surgery. 2018;28(6):1672-80.
20. Zacharoulis D, Sioka E, Papamargaritis D, et al. Influence of the learning curve on safety and efficiency of laparoscopic sleeve gastrectomy. Obesity surgery. 2012;22(3):411-5.
21. Phillips AW, Dent B, Navidi M, et al. Trainee Involvement in Ivor Lewis Esophagectomy Does Not Negatively Impact Outcomes. Annals of surgery. 2018;267(1):94-8.

4 BAR-PRESS: A randomized pilot study

Accepted: Surgical Endoscopy, 2020

ABSTRACT

Background

For metabolic laparoscopic surgery, higher pressures up to 20 mmHg are often used to create a surgical field of sufficient quality. This randomized pilot study aimed to determine the feasibility, safety and tolerability of low intraabdominal pressure (IAP) and deep neuromuscular blockade (NMB) to reduce postoperative pain.

Methods

In a teaching hospital in the Netherlands, 62 patients eligible for a laparoscopic Roux-en-Y gastric bypass (LRYGB) were randomized into one of four groups in a 2x2 factorial design; deep/moderate NMB and standard (20 mmHg)/low IAP (12 mmHg). Patient and surgical team were blinded. Primary outcome measure was the surgical field quality, scored on the Leiden-Surgical Rating Scale (L-SRS). Secondary outcome measures were (serious) adverse events, duration of surgery and postoperative pain.

Results

62 patients were included. L-SRS was good or perfect in all patients that were operated under standard IAP with deep or moderate NMB. In 40% of patients with low IAP and deep NMB, an increase in IAP was needed to improve surgical overview. In patients with low IAP and moderate NMB, IAP was increased to improve surgical overview in 40%, and in 75% of these cases a deep NMB was requested to further improve the surgical overview. Median duration of surgery was 38min(IQR34-40min) in the group with standard IAP and moderate NMB and 52min(IQR46-55min) in the group with low IAP and deep NMB.

Conclusions

The combination of moderate NMB and low IAP can create insufficient surgical overview. Larger trials are needed to corroborate the findings of this study.

INTRODUCTION

Many published papers describe the advantages and side-effects of laparoscopy in the surgical obese patient[1-5]. Currently, laparoscopy is considered the golden standard in metabolic surgery[6]. Guidelines on laparoscopy recommend to operate under the minimum intra-abdominal pressure (IAP) needed for a good overview, ranging from seven to 19 mmHg[7]. In obese patients, higher pressures up to 20 mmHg are sometimes used to create a surgical field of sufficient quality[8]. However, a recent systematic review and meta-analysis has shown that higher IAPs might increase postoperative pain[9]. Therefore, patients undergoing metabolic surgery should preferably be operated with lower IAPs, while maintaining a good quality of the surgical field, and without increasing the number of adverse events.

Over the years, the technique of deep neuromuscular blockade (NMB) to create more surgical working space has gained popularity. This popularity has increased further due to the availability of Sugammadex, a selective relaxant-binding agent that can rapidly reverse neuromuscular blockade. It has been shown to be effective and to reduce the duration of surgery and the incidence of residual block during recovery[10]. Recent studies have shown that deep NMB can also be a promising technique for metabolic procedures[11-13]. However, the optimal combination of depth of NMB and amount of IAP in metabolic surgery has not yet been determined. As fast-track protocols are becoming more popular in metabolic surgery, it is important to determine the most optimal combination of IAP and NMB for this specific patient population.

Our research hypothesis is that patients undergoing metabolic surgery with deep NMB and low IAP compared to moderate NMB and standard IAP will have less postoperative pain, without causing deterioration of the surgical field or an increase in duration of surgery or complication rate. This could lead to an increase in patient satisfaction and potentially a decrease in costs due to shorter length of hospital stay, less usage of analgesia and less revisits to the emergency ward. The aim of this randomized pilot study is to evaluate the feasibility, safety and tolerability of standard- versus low-pressure pneumoperitoneum and deep versus moderate NMB.

METHODS

Study design and participants

This was a randomized single center pilot study comparing the effects of deep versus moderate NMB and standard versus low IAP in a 2x2 factorial design from September 2018 to March 2019 in a teaching hospital in the Netherlands. All patients found suitable for metabolic surgery according to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) guidelines and undergoing a primary laparoscopic Roux-en-Y gastric bypass

(LRYGB) were invited for study participation. Patients were excluded in case of allergies for used medication, neuromuscular comorbidities, a medical history of pain disorders such as abdominal cutaneous nerve entrapment syndrome (ACNES), fibromyalgia or complex regional pain syndrome (CRPS), or if they were unwilling or unable to give informed consent. All patients were treated according to the Enhanced Recovery After Bariatric Surgery (ERABS) protocol as earlier described by Mannaerts et al., which is the standard protocol for all patients undergoing metabolic surgery in this center[14]. This protocol describes usage of standard IAP and moderate NMB.

No formal sample size calculation was done for this pilot study. We included a convenience sample of 60 patients, fifteen patients per group. Later, eight more patients were included to make up for the patients that had to be excluded during the study period. The study protocol was approved by the institutional review board (IRB) and the regional Medical Research Ethics Committee MEC-U, Nieuwegein, the Netherlands. The study was registered in the Dutch Trial Register on 28 May 2018 (Trial NL7050).

Blinding and randomization

After obtaining informed consent at the outpatient clinic of the departments of surgery or anesthesiology, patients were randomized by the principal investigator into one of four groups using variable block randomization software (Castor EDC©) without stratification (randomization ratio 1:1:1:1). Figure 1 shows the treatment protocol. Patients received either deep or moderate NMB and either standard or low IAP. During the time-out procedure (TOP), the anesthesiology team verified the group of randomization and carried out the treatment accordingly. Patient and surgical team were blinded for the treatment, by covering the display of the pressure meter and the train-of-four (TOF) or post-tetanic count (PTC) measurements. Additionally, the surgeon left the operating room for ten minutes after the TOP to ensure blinding. The anesthesiologist, who cannot be blinded, coordinated the depth of NMB and adjusted parameters in case of emergency.

Perioperative management

The regular anesthesia policy was described earlier by Mannaerts et al. and includes preoperative administration of analgesia and anti-emetics[14]. For this study, patients in all four study groups received an induction dose of 30 mg rocuronium. In patients receiving moderate NMB, the depth of the NMB was sufficient with a TOF ratio of 1-2. It was kept in that range during surgery with incremental doses of rocuronium when necessary, with an anticipated dose of 30-130 mg. For patients receiving deep NMB, additional rocuroniumbromide was administered after induction, until the PTC was between one and two twitches. The PTC was kept in that range during surgery with incremental doses of rocuronium when necessary, with an expected average dose of 70 mg after induction, and a range of total rocuronium between 45-145 mg. Both types of neuromuscular blockades were reversed with Sugammadex, of

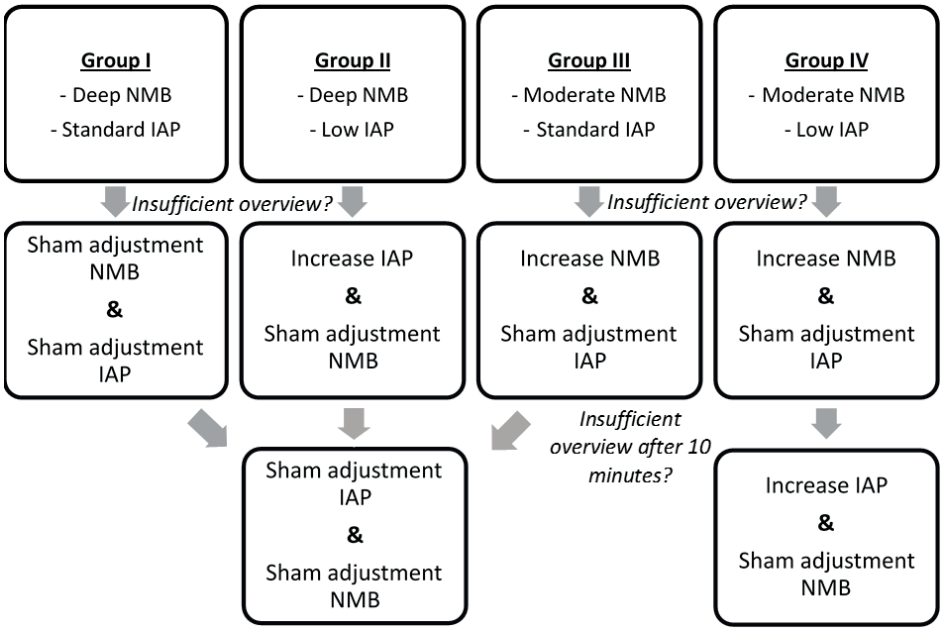


Figure 1: Treatment protocol and escape plan in case of insufficient surgical field quality

which the anticipated dose was 100-200 mg in moderate NMB and 180-370 mg in deep NMB. This protocol largely corresponds to the one published by Torensma et al[12].

All treatment groups underwent a LRYGB as described by Leiffson et al[15]. The standard IAP for metabolic surgery in our center is 20 mmHg, which is possibly higher compared to other centers performing metabolic procedures. However, because of the short duration of surgery within the ERABS protocol, we do not experience higher complication rates, specifically not those that are associated with a standard IAP. For low IAP, a pressure of 12 mmHg was used. In case of insufficient surgical overview, an 'emergency plan' was set up in which the surgeon could ask for a maximum of two adjustments (Figure 1). When requested by the surgeon, the anesthesiologist was able to either increase the NMB to 'deep' or increase IAP to 'standard'. In case the patient was already receiving deep NMB and standard IAP, a sham 'improvement' was performed by the anesthesiologist and the surgeon continued the procedure when assumed safe.

Outcome measures

The primary outcome measure was feasibility or the overview of the surgical field. Directly after the procedure, the surgeon evaluated the overall quality of the surgical field on the Leiden Surgical Rating Scale (L-SRS), ranging from 1 (extremely poor quality) to 5 (perfect quality). An extra evaluation of the surgical field was performed in case of peroperative alterations to either IAP or NMB due to insufficient surgical overview. Secondary outcome measures were

1) tolerability or postoperative pain until seven days postoperative, for which the patient kept a daily pain diary to score the pain of the wound, shoulder and intra-abdominal pain and register the used analgesia on a daily basis. A minimal clinically relevant difference in mean pain scores (at the group level) was defined as a difference of at least 3% of the score range, or 0.03*4=0.12. 2) safety, in terms of (serious) adverse events ((S)AEs) and 3) duration of surgery. To obtain as many responses as possible after discharge, patients were contacted on the fourth postoperative day to inform on their wellbeing and pain scores. Patients were contacted again after receiving back their pain dairy for confirmation of arrival of the study papers and to answer possible questions about their treatment.

Statistical analysis

Data management was performed in Castor EDC. Data were analyzed using SPSS (PASW) version 25 software (SPSS Inc., Chicago, Illinois, USA). Duration of surgery was reported in mean ± SD. Multiple linear regression analysis was used to estimate the impact of NMB and IAP on the L-SRS score and duration of surgery as dependent variables and NMB (deep/moderate) and IAP (standard/low) and the interaction effect of NMB and IAP as covariables. Repeated measurements analysis (linear mixed model) was used to estimate/quantify the impact of NMB and IAP on pain (covariance structure: unstructured). Dependent variable was the pain score, independent variables were time, NMB (deep/moderate), IAP (standard/low), and the baseline pain score, age, sex and preoperative body mass index (BMI) as covariables. In a secondary analysis, dependent variable was the pain score, independent variables were time, complication (present/absent), the four treatment groups (three dummy variables) and the baseline pain score, age, sex, and preoperative BMI as covariables.

Figure 2 shows the trial profile. In total, 68 patients were included in the study between September 2018 and March 2019. After this, the trial stopped because of reaching the required number of participants. Three patients withdrew consent and their data were removed. One patient was excluded because the surgery was postponed for personal reasons. Excluded were two patients with severe comorbidities; the anesthesiologist advised against surgery and trial participation. Table 1 shows the baseline characteristics of the 62 included patients. For four patients, the exact level of NMB was uncertain because of a malfunctioning TOF/PTC measuring device. For three patients, the decision was made peroperatively to perform a mini gastric bypass (MGB) instead of a LRYGB due to poor quality of the small intestines.

Table 2 shows the mean L-SRS scores by group. In patients that were operated with standard IAP, the L-SRS was always scored 4/5 (good) or 5/5 (perfect) and no adjustments were requested. In patients with low IAP and deep NMB (group II), 37.5% needed an increase in IAP to improve surgical overview. In patients with low IAP and moderate NMB (group IV), 53.8% needed a primary adjustment (deeper NMB) to improve surgical overview, after which a second adjustment (increase IAP) was requested in 57.1% of these cases. Overall, L-SRS scores increased on average +1.352 (95% CI 0.985 – 1.719) when using standard instead of

low IAP and L-SRS scores decreased on average -0.126 (95% CI -0.494 – 0.242) when using moderate instead of deep NMB.

Figure 3 shows the mean durations of surgery for the four groups. The duration of surgery increased on average with +4.3min (95% CI -0.3 ; 8.9min) when using moderate instead of deep NMB and the duration of surgery decreased on average with -8.9min (95% CI -13.6 ; -4.3min) when using standard instead of low IAP.

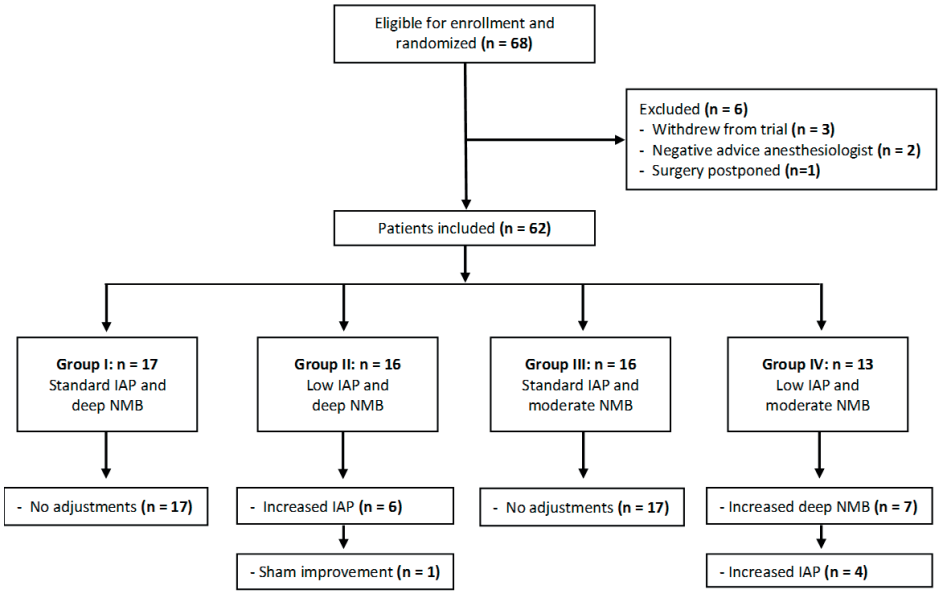


Figure 2: Trial profile

Table 1: Baseline characteristics

	Group I: Standard IAP + deep NMB *(n=17)*	Group II: Low IAP + deep NMB *(n=16)*	Group III: Standard IAP + mod NMB *(n=16)*	Group IV: Low IAP + mod NMB *(n=13)*
Female, n (%)	10 (58.8 %)	14 (87.5 %)	14 (87.5 %)	13 (100 %)
Age (years), mean ± sd	49 ± 12	48 ± 13	43 ± 11	49 ± 8
Baseline BMI (kg/m^2), mean ± sd	39.11 ± 3.91	40.54 ± 3.53	41.66 ± 5.44	44.4 ± 5.10
Waist circumference (cm), mean ± sd	126.4 ± 9.6	126.0 ± 8.6	126.2 ± 11.0	129.2 ± 8.5
Presence of T2D, n (%)	6 (35.3 %)	3 (18.8 %)	2 (12.5 %)	1 (7.7 %)
Presence of hypertension, n (%)	12 (70.6 %)	7 (43.8 %)	9 (56.3 %)	5 (38.5 %)
Presence of dyslipidemia, n (%)	5 (29.4 %)	7 (43.8 %)	5 (31.3 %)	6 (46.2 %)

Abbreviations: BMI = Body mass index. IAP = intraabdominal pressure. NMB = neuromuscular blockade. Sd = standard deviation. T2D = Type 2 diabetes.

Table 2: Surgical overview (L-SRS) without adjustments (mean ± sd)

	Group I: Standard IAP + deep NMB (n=17)	Group II: Low IAP + deep NMB (n=16)	Group III: Standard IAP + mod NMB (n=16)	Group IV: Low IAP + mod NMB (n=13)
L-SRS without adjustments, mean ± sd	4.94 ± 0.24	3.50 ± 1.03	4.75 ± 0.45	3.62 ± 1.04
First adjustment, n (%) ***L-SRS after adjustment***	0 (0.0%)	6 (37.5%) *3.71 ± 0.76*	0 (0.0%)	7 (53.8%) *3.14 ± 0.90*
Second adjustment, n (%) ***L-SRS after adjustment, mean ± sd***	0 (0.0%)	1 (6.3%) *3.00*	0 (0.0%)	4 (30.8%) *4.00 ± 0.82*

Abbreviations: L-SRS = Leiden surgical rating scale. IAP = intraabdominal pressure. NMB = neuromuscular blockade. Sd = standard deviation.

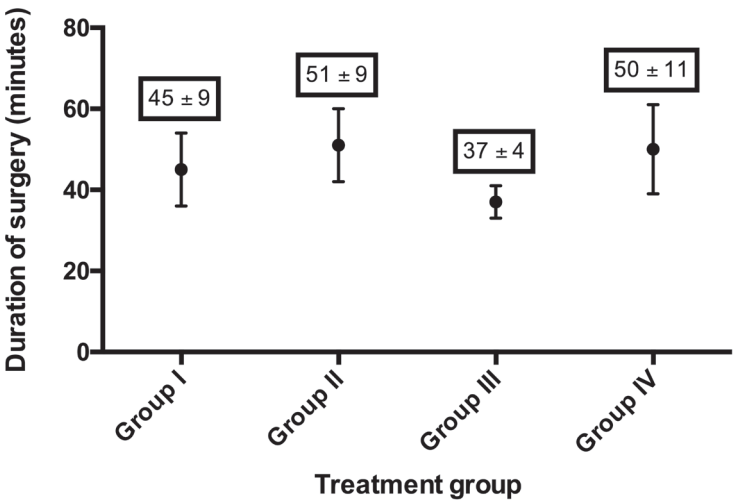
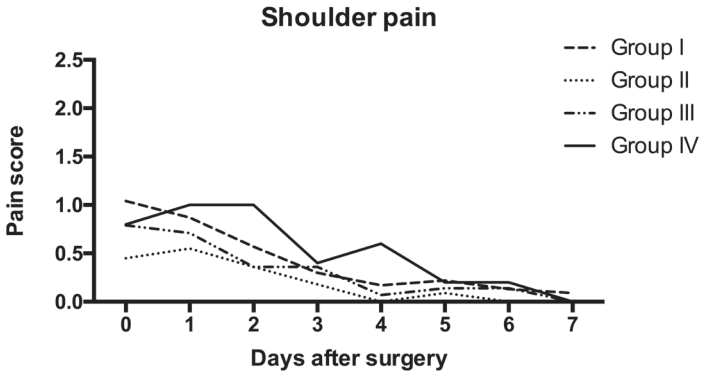
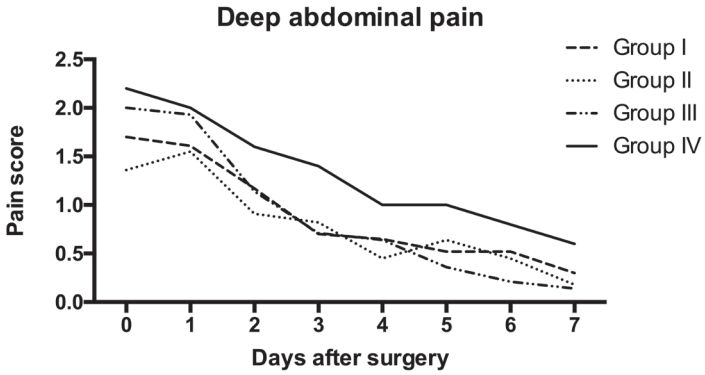


Figure 3: Duration of surgery in minutes per treatment group* (mean ± SD)
*Group I: Standard IAP + deep NMB; Group II: Low IAP + deep NMB; Group III: Standard IAP + mod. NMB; Group IV: Low IAP + mod. NMB
Abbreviations: IAP = intraabdominal pressure. NMB = neuromuscular blockade. SD = standard deviation.

Regarding safety, three SAEs occurred. In patient #1 in group I with standard IAP and deep NMB, surgical overview was perfect. This patient was readmitted one day after discharge and was reoperated to evacuate an intraabdominal hematoma. In patient #2 in group IV with low IAP and moderate NMB, because of malfunctioning of the TOF/PTC measure device, the IAP was increased to 20 mmHg, after which the L-SRS was scored 5. This patient underwent a reoperation due to a staple line leakage at the gastro-enterostomy. The patient was later excluded due to the malfunctioning device. Patient #3, operated with standard IAP and deep NMB (group I), had a L-SRS score of 5. This patient underwent a reoperation, in which three iatrogenic bowel defects were detected and sutured. All patients recovered well. The SAEs were reported to the MEC-U.





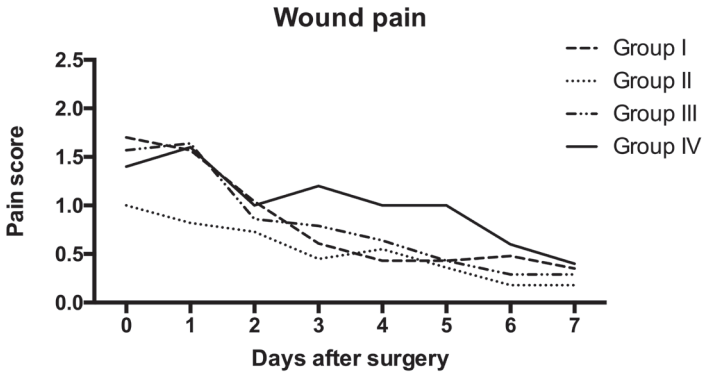


Figure 4a: Shoulder pain*
Figure 4b: (Superficial) wound pain*
Figure 4c: (Deep) abdominal pain*
*Group I: Standard IAP + deep NMB; Group II: Low IAP + deep NMB; Group III: Standard IAP + mod. NMB; Group IV: Low IAP + mod. NMB
Abbreviations: IAP = intraabdominal pressure. NMB = neuromuscular blockade.

Figures 4 show the pain scores over time for 53/62 (85.5%) patients. Three out of the 62 patients did not keep pain diaries after they developed early postoperative complications. There is no information on the reason for lost to follow-up for the other patients. Analgesia usage on day 4 postoperatively was 61% in group 1, 73% in group II, 50% in group III and 80% in group IV. The usage of analgesia was positively correlated with the reported pain scores.
Tables 3a and 3b shows the results of the repeated measurements analysis of shoulder pain, superficial pain or deep abdominal pain over time. After correcting for several covariables, pain scores on shoulder pain were slightly higher in group I (standard IAP + deep NMB) and in group II (low IAP + deep NMB) compared group IV (low IAP + moderate NMB).

DISCUSSION

In this randomized pilot study, we compared the effects of low (12 mmHg) or standard (20 mmHg) IAP and moderate or deep NMB on surgical overview, complications and postoperative pain in LRYGB surgery. The results display that in patients operated with low IAP, the surgeon evaluated the surgical overview insufficient in 40% of cases, suggesting low feasibility. Furthermore, patients operated with low IAP and moderate NMB scored slightly higher on postoperative pain compared to standard IAP.
Surgeons requested for an adjustment in nearly half of the patients that were randomized in the low IAP groups. In our center, an IAP of 20 mmHg is standard protocol for metabolic fast-track surgery. Surgeons might have accustomed to a spacious surgical overview, making the decrease in intraabdominal working space easily noticeable. Nevertheless, this decrease in working space might not necessarily lead to an increase in surgical difficulty or an increase in complication rates. The optimal intraabdominal pressure for metabolic (fast-track) surgery has not yet been determined. Other studies that address the optimal IAP in metabolic surgery describe a wide range of used IAP from 14 to 18 mmHg [8, 11, 12, 16, 17] which points to large practice variation.
The duration of surgery increased when using moderate NMB and decreased when using standard IAP. This result is in line with the results from previous studies, describing that deep NMB can shorten the duration of surgery due to an improved surgical overview and that the deep muscle relaxation can easily and quickly be reversed with the use of Sugammadex[10, 18]. Gaining nine minutes operating time is substantial for the RYGB procedures, as this could result in the possibility to perform one extra procedure per day.
The effects of moderate versus deep NMB were also investigated in this trial, which were based on the TOF or PTC measurements. During the 10 minutes in which the surgeon left the OR, the planned depth of NMB was reached and the procedure started. Unfortunately, the depth of NMB was sometimes difficult to manage, as each patient responded to the administered rocuronium at a different speed. The total costs of the procedure can vary between

the patients and the patient groups because of the differences in duration of surgery and the amount of NMB medication. However, these costs were not taken into account in this pilot study.

The L-SRSs were scored by four different surgeons and could therefore be vulnerable to inter-surgeon and intra-surgeon variability. As the L-SRS is a subjective score, it could also be biased by the position of trocars or the quality of the camera imaging. The score was an overall evaluation of the surgical field. Torensma et al. chose to score the L-SRS every ten minutes, with the aim to increase accuracy[12]. Nevertheless, the changes in L-SRS during a procedure were mainly related to the more complex part of the procedure. As the L-SRS scores of the Torensma study are similar to the results from our pilot study, repeated L-SRS scores present no advantage over one overall surgical overview score we used to judge feasibility.

Three SAEs occurred. All of these patients were operated under sufficient surgical overview. Therefore, these complications do not seem directly related to study participation or allocated treatment. We conclude that safety is not compromised by study participation. However, the occurrence of an SAE is likely to bias the pain scores of the patients. As no pain scores were available from the patients that had a SAE in this trial, no conclusions can be formed on the effect of an SAE on the pain scores.

A limitation of this pilot study is the fact that no formal sample size calculation was done. We aimed to do a pilot study, in order to use these results for the sample size calculation of the planned larger randomized-controlled trial. However, we felt that it was contributing to analyze the results of this pilot study and carefully draw conclusions, which we hope to further support in a future trial. Another limitation is the lack of data of patients who had a SAE. According to the intention-to-treat analysis, we would want to analyze the pain scores of these patients as well. The effect of an SAE on pain scores should be evaluated in a future trial. This future trial could also focus more on the cost-effectiveness of the different combinations of IAP and NMB.

Even though the patients were randomized, there were significant differences in gender and presence of T2D between the groups. These differences could potentially affect the pain scores. The abdominal wall thickness and visceral fat volume of men may differ from those of women, and might influence the ease of the operation and herewith the needed IAP. Also the presence of T2D could be correlated to fat deposition and the ease of the operation. In a future study, homogeneous groups should be stratified in order to rule out these potential biasing factors.

Across the four groups, we saw no great differences in pain scores and used analgesia, but patients operated with low IAP and moderate NMB scored slightly higher on postoperative pain compared to standard IAP. This difference was no longer present after correcting for patient characteristics and pain score on T0. Pain scores can be difficult to compare, as each individual experiences and scores pain in a different way. Even though the pain scores were

patient-reported, inter-individual differences in pain scores appeared modest. Moreover, in a larger randomized controlled trial, these individual-related factors influencing reporting behavior heterogeneity should be approximately equally divided across the groups and therefore cancel out in between group differences in pain scores.

CONCLUSIONS

The results from our pilot study suggest that a randomized controlled trial comparing the effects of low (12 mmHg) or standard (20 mmHg) IAP and moderate or deep NMB on surgical overview and postoperative pain in LRYGB surgery is feasible, safe and tolerable. The surgical overview was scored insufficient in a substantial percentage of patients operated under low IAP suggesting that 12 mmHg IAP is suboptimal. In a future trial, slightly higher pressures of 14-18 mmHg, e.g. 16 mmHg, may be a good alternative to compare the effects of IAP on postoperative pain score without risking a deterioration of the surgical overview. An IAP of 16 mmHg is used more frequently in metabolic surgery and therefore the results can be relevant. Factors that can influence the subjective L-SRS scores and pain scores, such as operator and individual-related factors, should be taken into account. Furthermore, a negative advice from the anesthesiologist to participate in a trial should be added to the exclusion criteria. Further larger trials are required to test the findings of this pilot study.

REFERENCES

1. Lujan JA, Frutos MD, Hernandez Q, Liron R, Cuenca JR, Valero G, Parrilla P (2004) Laparoscopic versus open gastric bypass in the treatment of morbid obesity: a randomized prospective study. Annals of surgery 239:433-437
2. Nguyen NT, Goldman C, Rosenquist CJ, Arango A, Cole CJ, Lee SJ, Wolfe BM (2001) Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Annals of surgery 234:279-289; discussion 289-291
3. Nguyen NT, Nguyen B, Shih A, Smith B, Hohmann S (2013) Use of laparoscopy in general surgical operations at academic centers. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 9:15-20
4. Sussenbach SP, Silva EN, Pufal MA, Casagrande DS, Padoin AV, Mottin CC (2014) Systematic review of economic evaluation of laparotomy versus laparoscopy for patients submitted to Roux-en-Y gastric bypass. PloS one 9:e99976
5. Westling A, Gustavsson S (2001) Laparoscopic vs open Roux-en-Y gastric bypass: a prospective, randomized trial. Obesity surgery 11:284-292
6. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, Yashkov Y, Fruhbeck G, International Federation for Surgery of O, Metabolic Disorders-European C, European Association for the Study of O, European Association for the Study of Obesity Obesity Management Task F (2014) Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 24:42-55
7. Neudecker J, Sauerland S, Neugebauer E, Bergamaschi R, Bonjer HJ, Cuschieri A, Fuchs KH, Jacobi C, Jansen FW, Koivusalo AM, Lacy A, McMahon MJ, Millat B, Schwenk W (2002) The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surgical endoscopy 16:1121-1143
8. Mulier JP, Dillemans B, Van Cauwenberge S (2010) Impact of the patient's body position on the intraabdominal workspace during laparoscopic surgery. Surgical endoscopy 24:1398-1402
9. Donatsky AM, Bjerrum F, Gogenur I (2013) Surgical techniques to minimize shoulder pain after laparoscopic cholecystectomy. A systematic review. Surgical endoscopy 27:2275-2282
10. Hristovska AM, Duch P, Allingstrup M, Afshari A (2017) Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. The Cochrane database of systematic reviews 8:Cd012763
11. Baete S, Vercruysse G, Vander Laenen M, De Vooght P, Van Melkebeek J, Dylst D, Beran M, Van Zundert J, Heylen R, Boer W, Van Boxstael S, Fret T, Verhelst H, De Deyne C, Jans F, Vanelderen P (2017) The Effect of Deep Versus Moderate Neuromuscular Block on Surgical Conditions and Postoperative Respiratory Function in Bariatric Laparoscopic Surgery: A Randomized, Double Blind Clinical Trial. Anesthesia and analgesia 124:1469-1475
12. Torensma B, Martini CH, Boon M, Olofsen E, In 't Veld B, Liem RS, Knook MT, Swank DJ, Dahan A (2016) Deep Neuromuscular Block Improves Surgical Conditions during Bariatric Surgery and Reduces Postoperative Pain: A Randomized Double Blind Controlled Trial. PloS one 11:e0167907
13. Bruintjes MH, van Helden EV, Braat AE, Dahan A, Scheffer GJ, van Laarhoven CJ, Warle MC (2017) Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: a systematic review and meta-analysis. British journal of anaesthesia 118:834-842

14. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrun M, de Quelerij M, Verbrugge SJ, Zengerink HF, Biter LU (2016) Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery 26**:**303-312
15. Leifsson BG, Gislason HG (2005) Laparoscopic Roux-en-Y gastric bypass with 2-metre long biliopancreatic limb for morbid obesity: technique and experience with the first 150 patients. Obesity surgery 15**:**35-42
16. Aceto P, Modesti C, Sacco T, De Cicco R, Perilli V, Raffaelli M, Lai C, Sollazzi L (2018) Patient-Related Factors Predicting Workspace Conditions during Laparoscopic Bariatric Surgery. Obesity surgery 28**:**3172-3176
17. Scotland H, Widmer JD, Wildi S, Bueter M, Weber M, Muller MK (2016) How to cope with insufficient pneumoperitoneum and exposure when performing laparoscopic gastric bypass surgery. Langenbeck's archives of surgery 401**:**299-305
18. Badaoui R, Cabaret A, Alami Y, Zogheib E, Popov I, Lorne E, Dupont H (2016) Reversal of neuromuscular blockade by sugammadex in laparoscopic bariatric surgery: In support of dose reduction. Anaesthesia, critical care & pain medicine 35**:**25-29

5 Thromboprophylaxis: Only in low risk patients?

Accepted: Obesity Surgery, 2019

ABSTRACT

Introduction

Morbid obesity is an important risk factor for developing a venous thromboembolic events (VTE) after surgery. Fast-track protocols in metabolic surgery can lower the risk of VTE in the postoperative period by reducing the immobilization period. Administration of thromboprophylaxis can be a burden for patients. This study aims to compare extended to restricted thromboprophylaxis with low molecular weight heparin (LMWH) for patients undergoing metabolic surgery.

Methods

In this single center retrospective cohort study, data was collected from patients undergoing a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2014-2018. Patients operated in 2014-2017 received thromboprophylaxis for two weeks. In 2018, patients only received thromboprophylaxis during hospital admission. Patients already using anticoagulants were analyzed as a separate subgroup. The primary outcome measure was the rate of clinically significant VTEs within three months. Secondary outcome measures were postoperative hemorrhage and reoperations for hemorrhage.

Results

3666 Patients underwent a primary RYGB or SG following the fast-track protocol. In total, two patients in the 2014-2017 cohort were diagnosed with VTE versus zero patients in the 2018 cohort. In the historic group, 34/2599 (1.3%) hemorrhages occurred and in the recent cohort 8/720 (1.1%). Postoperative hemorrhage rates did not differ between the two cohorts (multivariable analysis, $p=0.475$). In the subgroup of patients using anticoagulants, 21/347(6.1%) patients developed a postoperative hemorrhage. Anticoagulant use was a significant predictor of postoperative hemorrhage ($p<0.001$).

Conclusion

Despite the restricted use of thromboprophylaxis administration since 2018, the rate of VTEs did not increase. This may be explained by quick mobilization and hospital discharge, as encouraged by the fast-track protocol. There was no significant difference in postoperative hemorrhage rates by thromboprophylaxis protocol. Short term use of thromboprophylaxis in metabolic surgery is safe in patients at low risk of VTE.

INTRODUCTION

Severe obesity (body mass index (BMI) ≥ 40 kg/m^2) is associated with increased mortality rates, with most deaths attributed to heart disease, cancer and diabetes [1]. These increased risks can largely be reversed by significant weight loss, which is most permanently achieved by metabolic surgical procedures [2]. Whilst these procedures are safe, morbidly obese patients are at increased risk of developing short-term postoperative complications [3, 4]. Reduction of BMI-related health risks are thought to outweigh the risks of metabolic surgery such as venous thromboembolic events (VTE) with high mortality rates [5].

Rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) after metabolic surgery are moderate: 0.3-2.2% within one month after surgery for DVT and 1% for PE [4]. Nevertheless, PE plays an important role in the mortality of this patient category and guidelines advice to administer prophylactic low molecular weight heparin (LMWH) perioperatively and after discharge to all patients undergoing metabolic surgery [6, 7]. There is no consensus on type, dosage or duration of prophylaxis, but a recent publication from the American Society for Metabolic and Bariatric Surgery (ASMBS) Clinical Issues Committee suggested that extended pharmacological thromboprophylaxis can be restricted to only those patients who are deemed high risk of developing venous thromboembolic events (VTEs) [6]. Guidelines for perioperative care in metabolic surgery with respect to the Enhanced Recovery After Bariatric Surgery (ERABS) protocols recommend early mobilization and mechanical prophylaxis, such as intermittent pneumatic compression or graduated compression stockings. However, there are also guidelines that additionally encourage extended use of thromboprophylaxis for three to four weeks [7]. The effect of exclusive preoperative and/or extended pharmacological thromboprophylaxis on the incidence of postoperative bleeding is currently unknown.

Over the years, multiple studies have been published on the advantages of following an ERABS protocol. One of the most important items in these fast-track protocols is to stimulate early mobilization after surgery, thereby allowing for early hospital discharge and reducing the number of VTEs. At the same time, the fast-track program aims to prevent overtreatment with potentially unnecessary pharmacological thromboprophylaxis. Studies suggest that the rate of VTE after laparoscopic metabolic surgery nowadays is relatively low [8, 9], while the incidence of major bleeding seems to increase [10, 11]. Thus, not only preventive measures for VTE should be undertaken, but also for postoperative hemorrhage.

This study aims to investigate if the VTE risk of restricted LMWH prophylaxis is sufficiently low in patients undergoing metabolic surgery with no or little risk factors besides their obesity. In addition, we assessed whether the risk of postoperative hemorrhage decreased when the duration of thromboprophylaxis was shortened.

METHODS

Design and data collection

We performed a retrospective cohort study using two cohorts (details mentioned below). Data was collected prospectively from all patients undergoing a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between January 2014 and December 2018 in a single center teaching hospital. The mean (± SD) duration of surgery was 53 ± 19 minutes for RYGB and 36 ± 13 minutes for SG. The median (IQR) length of hospital stay for the complete cohort was 1.17 (0.18) days. The primary outcome measure was the clinically significant VTE within three months postoperatively. Secondary outcome measures were postoperative hemorrhage within one month and reoperation for postoperative hemorrhage within one month.

Cohorts

All patients were treated in accordance with the ERABS protocol in use in that period [12]. Two cohorts were formed according to the two regimens of thromboprophylaxis; I) 2014-2017: Extended thromboprophylaxis: Dalteparin 5000 IE from 12 hours pre-operatively until two weeks postoperatively for all patients; II) 2018: Restricted thromboprophylaxis: Dalteparin 5000 IE only during hospital admission, starting postoperatively. High risk patients were identified according to the Caprini score (Table 1) [13] and received pharmacological thromboprophylaxis according to the 2014-2017 protocol: Dalteparin 5000 IE starting the day before surgery and continuing until two weeks postoperatively. Patients who had had previous VTEs were advised to wear their own stockings. Patients using vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) would bridge the perioperative period using a prophylactic dosage of Dalteparin instead of therapeutic, because of the non-negligible risk of postoperative hemorrhage.

The protocol alteration to restricted thromboprophylaxis in 2018 was implemented because the risk of hemorrhage was thought to exceed the risk of VTE and based on gained experience with pharmacological thromboprophylaxis, and supported by the work of Blanchet et al., showing that extended pharmacological prophylaxis can increase the incidence of postoperative bleeding [11].

Types of surgery

The surgical techniques did not change over the years for any of the procedures [14-16]. For SG, clips are applied on the staple line in case of visible bleeding in normotensive patients. In some cases of peroperative bleeding, a drain is placed, which is removed the next day in case of no or little production. The RYGB is checked at the entero-enterostomy and gastro-enterostomy for bleeding spots. During the operation and certainly towards the end, the aim is to keep the patient normotensive and to control the possible bleeding spots properly.

Table 1: Caprini score and treatment per patient group

Patient group	Treatment
Therapeutic anticoagulants	Pre- and postoperative bridging with Dalteparin 1 dd 5000 IE, continue until INR is adequate
• Vitamin K antagonists	
• Direct Oral Anticoagulant (DOAC)	
• Low Molecular Weight Heparin (LMWH)	
One or more risk factors:	Dalteparin 5000 IE from 1 day pre-operatively until 14 days postoperatively In case of medical history of VTE: Patient wears own stockings
• Age ≥ 75 years	
• Medical history of VTE	
• Known hereditary thrombophilia*	
• Recent cerebrovascular accident (≤ 1 month)	
• Malignancy	
No risk factors	Dalteparin 1 dd 5000 IE during hospital admission

* For example protein C-, protein S-, or antithrombin-deficiencies, factor V Leiden, prothrombin 20210A mutation

Postoperative complications

VTE was defined as clinically apparent VTE, as no routine venous duplex ultrasound of the calf veins was performed. On the first postoperative day, patients were asked about complaints of calf pain as part of the ERABS protocol postoperative checklist [17]. In case of a positive answer, physical examination would be performed, followed by diagnostic imaging of the calf veins, if indicated, by venous duplex ultrasound. This treatment pathway also applies to patients presenting themselves at the emergency ward or outpatient clinic with complaints of calf pain.

Postoperative hemorrhage was confirmed when clinically apparent (e.g., hematemesis or melena) or when visualized on diagnostic imaging or during reoperation. In several cases, hemorrhage was suspected based on clinical and chemical parameters such as tachycardia, hypotension, severe abdominal pain in combination with a decrease in hemoglobin. In these patients, no diagnostic imaging was performed and tranexamic acid was administered pragmatically, 1000 mg per dose, and repeated after a minimum of six hours if considered necessary by the surgeon. If a hemorrhage was not confirmed by diagnostic imaging and the patient was hemodynamically stable, cases were classified as ‘no hemorrhage’.

Statistical analysis

All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). The risk of VTE in the two cohorts with different thromboprophylaxis regimens was compared using the binomial test, testing the hypothesis that not more than three VTE cases occur when restricted thromboprophylaxis regimen II is implemented. For patients without anticoagulants use, risks of hemorrhage in the two regimens were compared using Fisher’s

Exact test. Moreover, the adjusted risk of hemorrhage was analyzed with multivariable binary logistic regression analysis, with presence of hemorrhage as the dependent variable and the two thromboprophylaxis regimens (one dummy variable) as independent variables, adjusting for patient characteristics, type of surgery and presence of comorbidities. All characteristics listed in Table 2a were also included to avoid that differences between regimens I and II could be attributed to differences in casemix between regimens. A similar multivariable logistic regression analysis was performed to assess the difference in risk of postoperative hemorrhage between patients with and without anticoagulant use. Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

Table 2a: Baseline characteristics based on thromboprophylaxis regimen

	No anticoagulants use; 2 weeks thromboprophylaxis (regimen I, n=2599)	**No anticoagulants use; thromboprophylaxis during hospitalization (regimen II, n=720)**	**p-value**
Female, n (%)	2145 (82.5%)	592 (82.2%)	0.847
Age (years), mean ± sd	40.5 ± 11.0	40.1 ± 11.4	0.759
Baseline BMI (kg/m^2), mean ± sd	43.4 ± 4.8	42.8 ± 4.9	0.001
RYGB, n (%)	1460 (56.2%)	309 (42.9%)	<0.001
Presence of hypertension, n (%)	655 (25.2%)	166 (24.1%)	0.552
Presence of T2D, n (%)	404 (15.6%)	74 (10.8%)	0.001
Presence of dyslipidemia, n (%)	300 (11.6%)	41 (6.0%)	<0.001

Table 2b: Baseline characteristics based on anticoagulants use

	Anticoagulants use (n=347)	**Non-anticoagulants use (n=3319)**	**p-value**
Female, n (%)	231 (66.6%)	2737 (82.5%)	<0.001
Age (years), mean ± sd	50.6 ± 8.9	40.5 ± 11.0	<0.001
Baseline BMI (kg/m^2), mean ± sd	42.2 ± 5.2	43.3 ± 4.8	<0.001
RYGB, n (%)	214 (61.7%)	1769 (53.3%)	<0.001
Presence of hypertension, n (%)	196 (57.3%)	821 (24.7%)	<0.001
Presence of T2D, n (%)	110 (32.2%)	478 (14.4%)	<0.001
Presence of dyslipidemia, n (%)	143 (41.8%)	341 (10.3%)	<0.001

RESULTS

Between 2014 and 2018, 3666 patients underwent a primary RYGB (n=1983) or SG (n=1683). Over the years, popularity of the sleeve gastrectomy as opposed to the RYGB gradually increased from 296/669 (44.2%) in 2014 to 437/777 (56.2%) in 2018. Table 2a shows the baseline characteristics and comorbidities for the two thromboprophylaxis regimens. Significant differences were found between the two regimens for baseline BMI, type of surgery,

type 2 diabetes (T2D) and hypercholesterolemia. Table 2b shows the baseline characteristics divided by anticoagulant usage. Patients who used anticoagulants were more often males of older age, and had higher rates of hypertension, diabetes and dyslipidemia compared to patients without anticoagulant use.

Two patients were diagnosed with postoperative VTE in regimen I (2014-17): 2/2599 (0.01%, exact 95%CI: 0.0-0.3%). In regimen II (2018) the postoperative VTE rate was 0/720 (0%, exact 95%CI: 0.0%-0.51%), hereby not exceeding the pre-set threshold of three VTE cases (exact binomial test, p>0.99). Both patients diagnosed with VTE had developed early postoperative complications prior to the VTE occurrence, and did therefore not follow the fast-track protocol.

The absolute hemorrhage rates for patients without anticoagulants use were 34/2599 (1.3%, exact 95%CI 0.9-1.8%) for regimen I (2014-17) and 8/720 (1.1%, exact 95%CI 0.5-2.2%) for regimen II (cohort 2018) (p=0.675). The thromboprophylaxis regimen in the group not on anticoagulant therapy was not significantly associated with higher postoperative hemorrhage rates, adjusted for patient characteristics, type of surgery and comorbidities: OR 1.370, 95%CI 0.577-3.254, p=0.475.

The absolute hemorrhage rate for the group with preexisting anticoagulant use was 6.1% (95%CI: 3.9-8.9%) versus 1.3% (95%CI: 0.9-1.7%) without anticoagulant use (Figure 1). Anticoagulant use was significantly associated with postoperative hemorrhage: OR 3.143, 95%CI 1.642-6.019, p=0.001, adjusted for patient characteristics, type of surgery and comorbidities.

In the period of 2014-2016, before the introduction of tranexamic acid, 33/2114 patients (1.6%, exact 95%CI 1.1-2.2%) had a postoperative hemorrhage requiring a reintervention. Of the 1552 patients that underwent a metabolic procedure in 2017-2018 (after implementa-

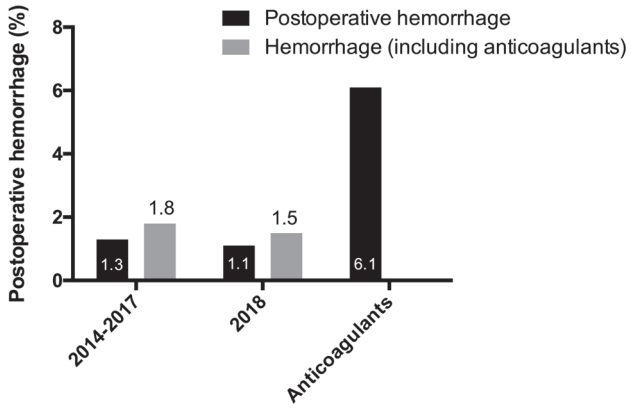


Figure 1: Crude postoperative hemorrhage rates per thromboprophylaxis regimen. There were no significant differences in hemorrhage rates by thromboprophylaxis regimen either including (p=0.674, grey bars) or excluding (p=0.675, black bars) patients with anticoagulant use.

tion of tranexamic acid), 24 (1.5%) patients received tranexamic acid and still underwent a reintervention due to hemorrhage. Six additional (0.4%) patients underwent a reintervention, but did not receive tranexamic prior to this. Another 35 (2.3%) patients received tranexamic acid and did not undergo a reintervention.

DISCUSSION

This study aimed to determine the safety of a restricted policy of pharmacological prophylaxis for VTE in patients undergoing metabolic surgery with no or few risk factors besides their obesity, and to determine the risk of postoperative bleeding under different pharmacological thromboprophylaxis protocols. This study showed that a VTE was observed in none of the patients managed according to the restricted thromboprophylaxis protocol. A total of two of the patients with an intention-to-treat according to the fast-track protocol developed a VTE, both with extended use of thromboprophylaxis. Adequate thromboprophylaxis is considered to be of great importance because of the high mortality rate associated with VTE [8]. Therefore, the ERABS guidelines recommend both pharmacological prophylaxis and compression devices of the lower extremities [7]. Quick mobilization after surgery might be an even more important aspect in preventing VTE. In the fast-track setting, mobilization starts directly after surgery. On the first postoperative day, physical therapists practice mobilization and advise patients on how to mobilize after discharge.

Before the introduction of fast-track programs, VTE was a feared complication of metabolic surgery and a significant contributor of the mortality associated with these procedures [18]. In 2007, Raftopoulos et al. concluded that extended thromboprophylaxis was safe and effective in reducing the incidence of VTE as compared to in-hospital thromboprophylaxis only [19]. The authors mention a mean duration of surgery of 220 minutes. The current study showed a mean duration of surgery of 53 minutes for RYGB and 36 minutes for SG in our cohort, supporting the earlier findings that duration of surgery independently influences the risk of VTE [20].

Nowadays, the incidence of VTE after laparoscopic metabolic surgery is relatively low [8] which is also confirmed in our study: only two patient developed VTEs. Interestingly, these patients did not follow the fast-track protocol because of short-term postoperative complications. In one case, the patient was readmitted within one week postoperatively and underwent a reoperation because of staple line leakage. During a two month hospital admission because of persistent staple line leakage and the patient being bedridden and in a poor clinical condition, the patient eventually developed a DVT while on thromboprophylaxis. In the second case, the pharmacological thromboprophylaxis was paused directly after surgery, because of suspicion of postoperative hemorrhage that was later confirmed on diagnostic imaging. After several days of bedrest due to poor clinical condition and no safe possibility to administer

thromboprophylaxis, pulmonary embolisms occurred. These two cases emphasize the importance of close monitoring for the presence of VTE in patients that do not follow the fast-track protocol.

The importance of close monitoring of patients with an extended length of hospital stay was also shown by Froehling et al. The authors state that the incidence of VTE rose from 0.3% to 1.9% between thromboprophylaxis for seven and 30 days postoperatively [21]. However, the patients that developed VTEs had a mean length of hospital stay of six days. In the current study, the median length of hospital stay was 1.16 days.

Our results, supported by the available literature, demonstrate that a short length of hospital stay (during which mobilization is encouraged) can be beneficial for patients. However, the window to detect complications during admission is small. It is suggested that the incidence of major bleeding is increasing [10]. More specifically, postoperative hemorrhage occurs in 2.0% of patients undergoing SG and in 1.5-3.1% of patients undergoing a RYGB [22, 23]. While our results are in line with these rates (2.2% for SG and 1.3% for RYGB), our study does not corroborate the increasing trend.

As expected, the rates of postoperative hemorrhage were higher in patients using anticoagulants. Also, this patient group had higher rates of hypertension, diabetes and dyslipidemia, suggesting that these patients' clinical condition was already worse preoperatively. The study by Coblijn et al. found that the use of anticoagulants is associated with postoperative complications (OR 1.5, 95%CI 0.884-2.394, p=0.142)[24]. Our results correspond to these findings. Postoperative hemorrhage can have a very serious course and prevention of hemorrhage should therefore receive at least equal attention as prevention of VTE. In 2017-2018, patients that were suspected of postoperative hemorrhage were given tranexamic acid, a plasminogen inhibitor that can reduce blood loss by inhibiting fibrinolysis [25]. This decision was mainly influenced by the patient's clinical condition, the direct availability of an operating room and the surgeon-on-call's experience with tranexamic acid. Klaassen et al. performed a retrospective analysis on postoperative administration of tranexamic acid in case of suspected hemorrhage and suggested that tranexamic acid can reduce the reoperation rate for bleeding after metabolic surgery [26]. Our retrospective study has insufficient power to draw a conclusion on the possible prevention of reoperations due to administration of tranexamic acid. Because of the increasing experience with tranexamic acid over the years and the negligible disadvantages, the threshold to prescribe tranexamic acid in case of suspicion of hemorrhage is currently low. A randomized controlled trial should further investigate the effects of tranexamic acid administration on the reoperations rates for hemorrhage.

Many studies report on either the risk of VTE or the risk of postoperative hemorrhage. No articles were found on the optimal balance between VTE risk and hemorrhage risk in patients undergoing metabolic surgery and following a fast-track program. Altieri et al. do report on both the risk of VTE and the risk of hemorrhage and conclude that postoperative VTE chemoprophylaxis is associated with decreased VTE events compared to no prophylaxis,

while minimizing hemorrhage compared to pre-operative prophylaxis [27]. However, their patients did not follow a fast-track protocol, which is known to accelerate mobilization and shorten hospital stay. To our knowledge, this article is the first to demonstrate that a restricted thromboprophylaxis strategy for certain low-risk patients while following the fast-track protocol does not increase the risk of VTE.

This study has several limitations. It was a single-center, retrospective study and cohorts were consecutive instead of parallel in time. However, these factors did not contribute to heterogeneity of the cohorts, except for the type of surgery. The sample size of regimen II was limited, VTE is a rare event and observed VTE incidence rates were low. A formal comparison of regimens I and II in a randomized controlled trial would require at least 98,000 patients per treatment arm to demonstrate the superiority of regimen II, and a non-inferiority study probably would require even more patients. Such an unrealistically large study would clearly be unfeasible. As such, our study does not demonstrate in absolute terms that regimen II is superior (or non-inferior) to regimen I. However, what our study actually does show is that it is highly likely that the observed VTE rate of regimen II is below a reasonably chosen threshold of three VTE cases. Also, routine venous duplex ultrasound was not performed. Therefore, only clinically significant VTEs could be registered, and there may have been some underreporting. However, it is unclear whether the not-clinically apparent VTEs are relevant to diagnose and should receive aggressive therapy when diagnosed. Unfortunately, due to the retrospective aspect of this study, it was not possible to perform a valid comparative analysis on the effects of tranexamic acid on postoperative hemorrhage. Therefore, the results were stated purely in descriptive terms and we refrained from any conclusions regarding tranexamic acid use. We aim to address this matter in future research projects.

CONCLUSION

This study demonstrates that a restricted thromboprophylaxis strategy did not adversely affect the rates of VTE and postoperative hemorrhage for patients following the fast-track protocol with no preexisting risk factors for VTE. Furthermore, our study underlines that patients using anticoagulants have an increased risk of postoperative hemorrhage as compared to patients not on anticoagulant therapy. From our data, we cannot conclude if administration of tranexamic acid for clinical suspicion of hemorrhage could prevent reintervention after metabolic surgery. Large national databases could play an important role in further research on the topic of short term thromboprophylaxis. Also, future studies should focus on prevention of postoperative hemorrhage in patients with a restricted thromboprophylaxis strategy following the fast-track protocol.

REFERENCES

1. Kitahara CM, Flint AJ, Berrington de Gonzalez A, Bernstein L, Brotzman M, MacInnis RJ, et al. Association between class III obesity (BMI of 40-59 kg/m2) and mortality: a pooled analysis of 20 prospective studies. PLoS medicine. 2014;11(7):e1001673.
2. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. The Cochrane database of systematic reviews. 2014(8):Cd003641.
3. Nimeri AA, Bautista J, Ibrahim M, Philip R, Al Shaban T, Maasher A, et al. Mandatory Risk Assessment Reduces Venous Thromboembolism in Bariatric Surgery Patients. Obesity surgery. 2018;28(2):541-7.
4. Stein PD, Matta F. Pulmonary embolism and deep venous thrombosis following bariatric surgery. Obesity surgery. 2013;23(5):663-8.
5. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obesity surgery. 2014;24(1):42-55.
6. ASMBS updated position statement on prophylactic measures to reduce the risk of venous thromboembolism in bariatric surgery patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(4):493-7.
7. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
8. Bhattacharya S, Kumar SS, Swamy PDK, Palanivelu C, Raj PP. Deep vein thrombosis prophylaxis: Are we overdoing? An Asian survey on trends in bariatric surgery with a systematic review of literature. Journal of minimal access surgery. 2018;14(4):285-90.
9. Thereaux J, Lesuffleur T, Czernichow S, Basdevant A, Msika S, Nocca D, et al. To What Extent Does Posthospital Discharge Chemoprophylaxis Prevent Venous Thromboembolism After Bariatric Surgery?: Results From a Nationwide Cohort of More Than 110,000 Patients. Annals of surgery. 2018;267(4):727-33.
10. Becattini C, Agnelli G, Manina G, Noya G, Rondelli F. Venous thromboembolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012;8(1):108-15.
11. Blanchet MC, Gignoux B, Matussiere Y, Vulliez A, Lanz T, Monier F, et al. Experience with an Enhanced Recovery After Surgery (ERAS) Program for Bariatric Surgery: Comparison of MGB and LSG in 374 Patients. Obesity surgery. 2017;27(7):1896-900.
12. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrun M, de Quelerij M, Verbrugge SJ, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
13. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Disease-a-month : DM. 2005;51(2-3):70-8.
14. Apers J, Wijkmans R, Totte E, Emous M. Implementation of mini gastric bypass in the Netherlands: early and midterm results from a high-volume unit. Surgical endoscopy. 2018;32(9):3949-55.
15. Biter LU, Gadiot RP, Grotenhuis BA, Dunkelgrun M, van Mil SR, Zengerink HJ, et al. The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC obesity. 2015;2:30.
16. Gadiot RP, Biter LU, Zengerink HJ, de Vos tot Nederveen Cappel RJ, Elte JW, Castro Cabezas M, et al. Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. Obesity surgery. 2012;22(2):320-9.

17. van Mil SR, Duinhouwer LE, Mannaerts GHH, Biter LU, Dunkelgrun M, Apers JA. The Standardized Postoperative Checklist for Bariatric Surgery; a Tool for Safe Early Discharge? Obesity surgery. 2017;27(12):3102-9.
18. Raftopoulos I, Ercole J, Udekwu AO, Luketich JD, Courcoulas AP. Outcomes of Roux-en-Y gastric bypass stratified by a body mass index of 70 kg/m2: a comparative analysis of 825 procedures. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2005;9(1):44-52; discussion -3.
19. Raftopoulos I, Martindale C, Cronin A, Steinberg J. The effect of extended postdischarge chemical thromboprophylaxis on venous thromboembolism rates after bariatric surgery: a prospective comparison trial. Surgical endoscopy. 2008;22(11):2384-91.
20. Chan MM, Hamza N, Ammori BJ. Duration of surgery independently influences risk of venous thromboembolism after laparoscopic bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(1):88-93.
21. Froehling DA, Daniels PR, Mauck KF, Collazo-Clavell ML, Ashrani AA, Sarr MG, et al. Incidence of venous thromboembolism after bariatric surgery: a population-based cohort study. Obesity surgery. 2013;23(11):1874-9.
22. Zafar SN, Miller K, Felton J, Wise ES, Kligman M. Postoperative bleeding after laparoscopic Roux en Y gastric bypass: predictors and consequences. Surgical endoscopy. 2018.
23. Zellmer JD, Mathiason MA, Kallies KJ, Kothari SN. Is laparoscopic sleeve gastrectomy a lower risk bariatric procedure compared with laparoscopic Roux-en-Y gastric bypass? A meta-analysis. American journal of surgery. 2014;208(6):903-10; discussion 9-10.
24. Coblijn UK, Karres J, de Raaff CAL, de Castro SMM, Lagarde SM, van Tets WF, et al. Predicting postoperative complications after bariatric surgery: the Bariatric Surgery Index for Complications, BASIC. Surgical endoscopy. 2017;31(11):4438-45.
25. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2019;30(1):1-10.
26. Klaassen RA, Selles CA, van den Berg JW, Poelman MM, van der Harst E. Tranexamic acid therapy for postoperative bleeding after bariatric surgery. BMC obesity. 2018;5:36.
27. Altieri MS, Yang J, Hajagos J, Spaniolas K, Park J, Gasparis AP, et al. Evaluation of VTE prophylaxis and the impact of alternate regimens on post-operative bleeding and thrombotic complications following bariatric procedures. Surgical endoscopy. 2018.

6 PATAS: Peroperative tranexamic acid in sleeve gastrectomy

Accepted: BMJ Open, 2020

ABSTRACT

Introduction

Fast-track protocols often include short-term thromboprophylaxis and short length of hospital stay. These treatment strategies may negatively affect the occurrence and diagnosis of postoperative hemorrhage. Over the years, the rates of venous thromboembolic events (VTE) have decreased, while there seems to be an increase in the occurrence of postoperative hemorrhage. Tranexamic acid (TXA) can potentially lower the incidence of postoperative hemorrhage. This trial aims to investigate whether peroperative administration of TXA reduces the peroperative and postoperative hemorrhage rates in laparoscopic sleeve gastrectomy (LSG).

Methods and analysis

This is a single center double-blind randomized placebo-controlled trial. Patients undergoing a LSG are included after obtaining informed consent. Patients are randomized between two groups: 1) Administration of placebo infusion, and 2) Administration of 1500mg TXA. In both groups, the infusions will be administered during the induction phase of the procedure. Primary outcome measures are peroperative use of hemostatic clips, postoperative hemoglobin decrease and postoperative hemorrhage. Secondary outcome measure is rates of VTE.

Ethics and dissemination

The protocol version 3 was approved by the medical ethical committee Medical Research Ethics Committees United (MEC-U), Nieuwegein, on 29 July 2019. The trial results will be submitted for publication in a peer-reviewed journal and at conference presentations.

BACKGROUND

Because of the increasing rates of morbid obesity and herewith increasing incidence of bariatric surgery, the popularity of fast-track protocols is growing. These Enhanced Recovery After Bariatric Surgery (ERABS) protocols often include short-term thromboprophylaxis and short length of hospital stay (LOS), with the aim to discharge patients on the first postoperative day.[1, 2] Even though ERABS has many positive outcomes, it may also negatively affect the diagnosis of postoperative hemorrhage due to the short time window for diagnosing postoperative complications.

Current literature states that postoperative hemorrhage occurs in 2.0% of patients undergoing laparoscopic sleeve gastrectomy (LSG) and in 1.5-3.1% of patients undergoing a laparoscopic Roux-en-Y gastric bypass (LRYGB).[3, 4] It is described that over the years, there seems to be an increase in the occurrence of postoperative hemorrhage, while the risk of venous thromboembolic events (VTE) is decreasing.[5] In our center, overall postoperative hemorrhage rates of LRYGB and LSG have been stable since 2014, with more hemorrhage occurring after a LSG (2.2%) than after a LRYGB (1.3%). The rates of peroperative hemorrhage requiring hemostatic clips was 63.3% between January 2017 and March 2019. The rate of diagnosed VTE within 3 months postoperative is 0.05% since 2014 in our center.

Tranexamic acid (TXA) is a plasminogen inhibitor that can be used to inhibit fibrinolysis during or after surgery and thus minimize the risk of developing perioperative hemorrhage. Little is known about the use of TXA in bariatric surgery. Nevertheless, in several other surgical areas such as for coronary-artery surgery and arthroplasty, perioperative administration of TXA has proven its value in preventing postoperative hemorrhage.[6-8] Until now, the use of TXA to prevent postoperative hemorrhage in bariatric surgery has been described once by Hussain et al.[9] The authors performed a meta-analysis of administration of TXA during laparoscopic sleeve gastrectomies and concluded that administration of TXA is a simple yet effective way to lower the rates of staple line hemorrhage, while shortening the length of surgery. In the end of 2018, Klaassen et al described that reoperations may be prevented due to postoperative administration of TXA in case of a suspicion of an already present hemorrhage.[10]

Because of the serious risks of postoperative hemorrhage, the need for preventive measures in bariatric fast-track surgery is increasing. This manuscript reports the protocol of a randomized controlled trial (RCT) investigating the outcome of peroperative administration of TXA in patients undergoing a LSG. The hypothesis is that the administration of TXA can lead to less use of peroperative hemostatic staples, a smaller hemoglobin decrease postoperatively and a lower reoperation rate, without increasing the VTE rates. By publishing this protocol, we hope to create more awareness of the hemorrhage risks of bariatric surgery and to further stimulate research in this area.

METHODS/DESIGN

Study design and participants

This is a double-blind, single center, parallel-group RCT that takes place in a high-volume bariatric center in the Netherlands. We aim to include 100 patients. Patients are randomized with an allocation ratio of 1:1 between two groups: 1) Administration of a placebo infusion (sodium chloride), and 2) Administration of 1500mg TXA. In both groups, the infusions will be administered during the induction phase of the procedure by the anesthesiologist.
All patients found suitable for bariatric surgery according to the international guidelines and undergoing a LSG will be asked to participate in the study. In order to be eligible to participate in this study, a subject must meet all of the following criteria: Primary bariatric procedure; good knowledge of the Dutch or English language. A potential subject who meets any of the following criteria will be excluded from participation in this study: Patients unwilling to give informed consent, patients with a medical history of bleeding or VTE and patients who use therapeutic anticoagulants. Patients will also be excluded in case of peroperative arterial bleeding or (iatrogenic) bleeding coming from surrounding organs or vascular structures such as the liver or the spleen.

Patient involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and will not be consulted to develop patient relevant outcomes or interpret the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

Outcome measures

Primary outcome measures are peroperative use of hemostatic staples, the decrease in hemoglobin after the procedure at day one postoperative and rates of postoperative hemorrhage (i.e. hemorrhage needing administration of packed cells or a surgical or radiological re-intervention) within 30 days postoperative. Secondary outcome measure is rates of VTE within three months postoperative. Comorbidities such as hypertension, diabetes en dyslipidemia will be taken into account. Also, the peroperative blood pressure will be registered.

Interventions

This study will compare an intervention group with a control group. In the intervention group, patients will be administered TXA (Cyklokapron©) 1500 mg intravenously during the induction of the procedure. A set dose of 1500 mg will be used, based on the study population with morbid obesity.[11] The TXA will be intravenously administered, dissolved in 100 ml sodium chloride 0.9% in a time frame of 15-30 minutes, with a maximum of 100 mg/min. In the control group, patients will receive a placebo infusion containing 100 ml sodium

chloride 0.9%, to be administered in a time frame of 15-30 minutes. The hospital's pharmacy will prepare and label the investigational medicinal products according to the relevant Good Manufacturing Practice (GMP) guidelines.

For all patients participating in the trial, three topics are addressed in more detail in this protocol. Firstly, we want to determine the hemoglobin decrease. A blood sample (one EDTA tube) will be obtained in the week preoperative by venipuncture. From this blood sample, a hemoglobin test is performed in the hospital's laboratory. The postoperative hemoglobin value will be obtained from the blood sample that is obtained in all bariatric patients on the first postoperative day. Secondly, we aim for an unambiguous policy on fluid balance. Patients can eat up to eight hours preoperatively and drink clear fluids up to four hours preoperatively. To compensate for this preoperative "nothing per os (NPO)" policy, all patients receive one liter of Ringer's lactate solution preoperatively. After the procedure, all patients receive intravenous administration of sodium chloride 0.9% (two liters per 24 hours). Furthermore, the fluid intake of each individual patient is registered starting after surgery. Thirdly, the peroperative conditions need to be standardized for all trial patients. The peroperative mean arterial pressure (MAP) is to be kept above 60 mmHg. Information on peroperative use of hemostatic staples, administration of packed cells, postoperative TXA, rates of postoperative hemorrhage and VTE are obtained from the electronical patient report. Adverse events will be reported to the medical ethical committee and the national trial committee. All patients undergo a LSG as described by Gadiot et al.[12] Hemostatic clips will be placed according to the step-by-step plan as shown in Table 1.

Table 1: Steps to be followed by the surgeon before placement of hemostatic clips

Steps before placing hemostatic clips
• Staple gastric sleeve
• Remove nasogastric tube
• Remove sleeve from the abdomen
• Aim for normotension
• Decrease intraabdominal pressure to 12 mmHg
• Inspection of staple line
• Place clips in case of ≥1 bleeding spot

Education of study personnel

All involved personnel is educated on the study design by the coordinating researcher before the start of the study by walking through a digital presentation. In this presentation, all tasks will be discussed in detail, specified by function type. Surgeons are informed of how to include patients in the study at the outpatient clinic. The personnel of the hospital pharmacy is educated on how to prepare the individually labelled study medication. The anesthesiology team is informed on the study design and to be aware of administering the medication as delivered by the hospital pharmacy. Bariatric nurses are educated on how to send out study information to all patients eligible for a bariatric procedure. Another important task of the bariatric nurse is the follow-up after surgery, which is done by a phone call one week after surgery. In this phone call, patients are asked about respiratory complaints of calve pain. In this same phone call, patients are once again reminded of the importance to contact

the bariatric clinic in case of calve pain or respiratory complaints. No active follow-up (for example duplex imaging of the calve veins) is performed to diagnose asymptomatic VTE, as it is unclear whether the not-clinically apparent VTEs are relevant to diagnose and should receive aggressive therapy when diagnosed.

Sample size

The performed power analysis (power=80%, alfa=5% two-sided) calculated a required sample size of 2x36=72 patients. The analysis was based on an expected 50% decrease of the percentage of patients for whom peroperative placement of hemostatic staples was required. To be able to compensate for potential exclusions, we decided to include 100 patients in total.

Recruitment

In the Franciscus Gasthuis & Vlietland, approximately 1000 patients undergo a bariatric procedure each year. Approximately 40% of these patients undergo a primary laparoscopic sleeve gastrectomy and is herewith eligible for inclusion in this trial. Therefore, we expect to have included 100 patients within three to six months. All patients found suitable for bariatric surgery according to the international guidelines and undergoing a LSG will have received written information attached with the invitation letter for the appointment at the outpatient clinic. The surgeon and/or the anesthesiologist will inform the patient once more about the study protocol at the outpatient clinic. If willing to participate, patients will be asked to fill in the informed consent form. Patients will have one week to reconsider their decision.

Blinding and randomization

After obtaining informed consent at the outpatient clinic of the surgical or anesthesiological department, patients will be randomized into one of the two groups using Variable Block Randomization software by Ciwit B.V. (Castor EDC©). Patients will either receive TXA or placebo (sodium chloride) during induction. Patient, surgical team and anesthesiological team will be blinded for the treatment, as the hospital pharmacy will prepare the infusion bags for each individual patient. Availability of the patient's individualized infusion bag will be checked at the Time Out Procedure (TOP). The coordinating researcher and the pharmacologist are unblinded in order to prepare the infusions properly. In case of suspicion of complications due to administration of the trial infusion bag, the anesthesiologist and the OR team can be unblinded by contacting the pharmacy or the coordinating researcher by phone.

Data management

Identification of participants will be protected by using study numbers non-traceable to patient's identity. Only members of the research-team will have access to the databases with study data. Data will be kept for 20 years. The data will be monitored by a committee that is appointed by the hospital's research department.

Statistical analysis

Statistical analyses will be performed using IBM-SPSS version 24 (IBM Corporation, Armonk, New York, USA). Efforts will be made to prevent missing data by checking completeness of collected data. Missing data may be expected because of failed hemoglobin tests, or (less likely) due to unregistered administration of TXA or packed cells. Differences in use of hemostatic staples between the 2 groups will be calculated using Chi-Square tests. The difference in hemoglobin decrease will be tested using multivariate logistic regression analysis, correcting for comorbidities (hypertension, diabetes, dyslipidemia) and use of hemostatic staples. These same analyses will be performed to assess the differences in number of patients needing to undergo a re-intervention, but adding postoperative administration of TA as a covariate. Differences in rates of VTE and postoperative administration of TXA between the two groups will be calculated using Chi-Square (Fisher's Exact) tests. Results will be evaluated at a significance threshold of $p<0.05$ (two-sided).

DISCUSSION

The complication rates in fast-track bariatric surgery are modest: 2-4% of all patients undergoing a bariatric procedure develops a major complication such as staple line leakage or hemorrhage.[13, 14] Hemorrhage is not a frequently seen complication, but does have a substantial impact on the patient's recovery. This study tests the effects of peroperative administration of TXA on per- and postoperative hemorrhage rates in patients undergoing a LSG.

TXA has already been proven to be beneficial in prevention of hemorrhage in several studies. The range of the dosage of TXA amongst these studies is wide, varying from 100 mg/kg bodyweight[8] to 20mg/kg[15], or multiple doses of ten mg/kg before and after surgery.[16] The dosage of TXA can be determined based on patient's bodyweight or renal function, or a standard dose can be given to each patient.[17] In this study, a fixed dosage of 1500 mg TXA was used. For general (non-topical) fibrinolysis in adults, TXA is administered intravenously in a dosage of 15 mg/kg bodyweight in a solution with sodium chloride. Administration can be repeated every six to eight hours.[18] In our study population, body weight varies between 100 and 200 kg. TXA has a small volume of distribution (9-12 liters) and will mostly be present in a watery environment and will not spread to fatty tissue.[11] Therefore, it is expected that a dosage above 1500 mg will not be of additional value.

Very little is known on the risks of TXA in patients with an increased risk of VTE. In this study, patients who used therapeutic anticoagulants were therefore excluded from participation. Earlier research showed that patients who use anticoagulants, are at the highest risk of developing postoperative hemorrhage.[19]

As administration of TXA can hypothetically increase the risk of VTE, patients will be followed-up for three months postoperatively to diagnose symptomatic VTEs. This follow-up is observational, meaning that no routine diagnostic imaging of the calve veins will be performed. The VTE rates in metabolic fast-track surgery are very low: <1%. Therefore, we do not expect to be able to find a significant difference in VTE rates between the groups.

The procedures in this trial will be performed by one of the four metabolic surgeons, assisted by a surgical resident or a physician assistant. This might create a risk of inter-operator variance on placing hemostatic clips. We have therefore created a step-by-step plan to create uniformity in the placement of hemostatic clips. Also, the operator will be included as a covariate in the multivariate regression analysis.

In this trial, we investigate the effect of peroperative TXA in patients undergoing a LSG on the usage of hemostatic clips, hemoglobin decrease, re-interventions due to hemorrhage and rates of VTE. Our results will be relevant for clinics performing fast-track metabolic surgery, as administration of TXA may decrease per- and postoperative hemorrhage rates. We aim to present the outcome of this trial in future publications.

REFERENCES

1. Malczak P, Pisarska M, Piotr M, et al. Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis. Obesity surgery. 2017;27(1):226-35.
2. Mannaerts GH, van Mil SR, Stepaniak PS, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
3. Zafar SN, Miller K, Felton J, et al. Postoperative bleeding after laparoscopic Roux en Y gastric bypass: predictors and consequences. Surgical endoscopy. 2018.
4. Zellmer JD, Mathiason MA, Kallies KJ, et al. Is laparoscopic sleeve gastrectomy a lower risk bariatric procedure compared with laparoscopic Roux-en-Y gastric bypass? A meta-analysis. American journal of surgery. 2014;208(6):903-10; discussion 9-10.
5. Becattini C, Agnelli G, Manina G, et al. Venous thromboembolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012;8(1):108-15.
6. Kirsch JM, Bedi A, Horner N, et al. Tranexamic Acid in Shoulder Arthroplasty: A Systematic Review and Meta-Analysis. JBJS reviews. 2017;5(9):e3.
7. Meftah M, White PB, Siddiqi A, et al. Tranexamic Acid Reduces Transfusion Rates in Obese Patients Undergoing Total Joint Arthroplasty. Surgical technology international. 2019;34.
8. Myles PS, Smith JA, Forbes A, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. The New England journal of medicine. 2017;376(2):136-48.
9. Hussain A, Al-Shoek I, El-Hasani S. The Use of Tranexamic Acid in Sleeve Gastrectomy. Obesity surgery. 2017;27(1):198-9.
10. Klaassen RA, Selles CA, van den Berg JW, et al. Tranexamic acid therapy for postoperative bleeding after bariatric surgery. BMC obesity. 2018;5:36.
11. National Center for Biotechnology Information. PubChem Database. Tranexamic acid, CID=5526, https://pubchem.ncbi.nlm.nih.gov/compound/Tranexamic-acid (accessed on July 29, 2019).
12. Gadiot RP, Biter LU, Zengerink HJ, et al. Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. Obesity surgery. 2012;22(2):320-9.
13. Blanchet MC, Gignoux B, Matussiere Y, et al. Experience with an Enhanced Recovery After Surgery (ERAS) Program for Bariatric Surgery: Comparison of MGB and LSG in 374 Patients. Obesity surgery. 2017;27(7):1896-900.
14. Dogan K, Kraaij L, Aarts EO, et al. Fast-track bariatric surgery improves perioperative care and logistics compared to conventional care. Obesity surgery. 2015;25(1):28-35.
15. Friedman RJ, Gordon E, Butler RB, et al. Tranexamic acid decreases blood loss after total shoulder arthroplasty. Journal of shoulder and elbow surgery. 2016;25(4):614-8.
16. Pauzenberger L, Domej MA, Heuberer PR, et al. The effect of intravenous tranexamic acid on blood loss and early post-operative pain in total shoulder arthroplasty. The bone & joint journal. 2017;99-b(8):1073-9.
17. Melvin JS, Stryker LS, Sierra RJ. Tranexamic Acid in Hip and Knee Arthroplasty. The Journal of the American Academy of Orthopaedic Surgeons. 2015;23(12):732-40.
18. CBG. Samenvatting van de productkenmerken: Tranexaminezuur Mylan 100 mg/ml, oplossing voor injectie. Geneesmiddeleninformatiebank. 2017.
19. Coblijn UK, Karres J, de Raaff CAL, et al. Predicting postoperative complications after bariatric surgery: the Bariatric Surgery Index for Complications, BASIC. Surgical endoscopy. 2017;31(11):4438-45.

7 Neutrophils-to-lymphocyte ratio: Marker for early postoperative complications?

Submitted: Surgical Endoscopy, 2020

ABSTRACT

Background

In metabolic fast-track surgery, patients are scheduled for discharge on day-one postoperatively. The neutrophil-to-lymphocyte ratio(NLR) could be an inexpensive and rapid way to identify patients at risk of early complications. This study aimed to determine the predictive value of the NLR on early postoperative major complications.

Methods

Prospective data of all patients undergoing a primary metabolic procedure in a single center was collected between April 2018 and April 2019. Serum CRP, total leukocyte count and NLR preoperatively and at day-one postoperatively, were measured and the associations with major complications and readmissions within 30 days postoperatively were investigated.

Results

In total, 834 patients underwent a primary metabolic procedure: 339(40.6%) Roux-en-Y gastric bypass, 411(49.3%) sleeve gastrectomy and 84(10.1%) one anastomosis gastric bypass-minigastric bypass. Major complications occurred in 19(2.3%) patients, who had significantly higher levels of postoperative NLR(OR 1.105, 95%CI 1.006-1.215, p=0.038), delta-NLR(OR 1.290, 95%CI 1.141-1.460, p<0.001) and higher postoperative leukocyte count(OR 1.196, 95%CI 1.042-1.372, p=0.011) than patients without major complications. The ideal cutoff points to predict complications after metabolic surgery were 6.5 for postoperative NLR(sensitivity 67% and specificity 66%) and 3.74(sensitivity 72% and specificity 62%) for delta-NLR. The AUC for postoperative leukocyte count(0.582, p=0.221) and postoperative CRP(0.619, p=0.075) were not significant for postoperative major complications.

Conclusion

Postoperative- and delta-NLR may be useful predictive markers for early postoperative major complications after metabolic surgery. Integration of postoperative- and delta-NLR into a standardized checklist of clinical and laboratory parameters can aid in the clinical decision-making on day-one postoperatively.

INTRODUCTION

Due to the increasing rates of morbid obesity worldwide, metabolic surgery has become a frequently performed procedure. With the introduction of Enhanced Recovery After Bariatric Surgery (ERABS) protocols, patients are scheduled for discharge on day-one postoperatively to ensure efficient and patient-friendly care[1]. Nonetheless, metabolic surgery remains major abdominal surgery in a high-risk patient group due to obesity-related comorbidities. Therefore, alertness for early postoperative complications is warranted.

Surgical interventions in general are associated with a systemic inflammatory response, and the level of systemic inflammation has been shown to predict surgical complications. A commonly used inflammatory marker for complications after abdominal surgery is C-reactive protein (CRP)[2]. However, CRP shows insufficient sensitivity at day-one postoperatively to detect major adverse events, due to high inter-patient variability[3, 4]. Therefore, a more sensitive early marker to aid in the detection of postoperative complications in metabolic surgery is needed.

Inflammation after surgery is characterized by a relative increase in circulating neutrophil levels as compared to circulating lymphocytes[5, 6]. The neutrophil-to-lymphocyte ratio (NLR) has been shown to correlate with organ dysfunction scores and the clinical course in critically ill patients[7]. The NLR could therefore turn out to be an inexpensive and rapid way to identify patients at risk of complications on the first day postoperatively. Preoperative NLR as a marker for individual systemic inflammation levels is an independent predictor for complications following cardiac surgery, cardiac percutaneous interventions, elective abdominal surgery and oncological resections[8-11]. With regard to metabolic surgery, one study found that an NLR of $\geq$ 10 at day-one postoperatively was associated with 30-day complications following metabolic surgery[12]. However, this was a retrospective database review, and a study with a prospective methodology and statistical techniques to identify an optimal threshold for the bariatric surgical population was suggested.

The aim of this study was to determine the predictive value on 30-day postoperative complications of 1) NLR prior to metabolic surgery, 2) NLR at day-one postoperatively, and 3) delta-NLR between pre- and postoperatively. We hypothesized that an increased NLR preoperatively could identify patients that are at higher risk of developing postoperative complications better than CRP. We also hypothesized that an increased delta-NLR indicates an increased risk of overall complications better than the day-one postoperative NLR. Furthermore, we aimed to determine the ideal cut-off points for use of NLR and delta-NLR in metabolic surgery practice.

METHODS

Design and data collection

Data was collected prospectively from all patients undergoing a primary metabolic surgical procedure between April 2018 and April 2019 in a single-center teaching hospital, and analyzed after all data was collected. Patients with a metabolic procedure in their medical history were not included in this study, due to the increased risk of complications in revisional surgery[13, 14]. The primary outcome measure was major complications within 30 days postoperatively, based on the guidelines described by Brethauer et al.: any complication that result in a prolonged hospital stay (beyond 7 days), administration of an anticoagulant, re-intervention, or re-operation (for example anastomotic leak, postoperative hemorrhage, thromboembolic events, etcetera)[15]. The secondary outcome measure was readmission within 30 days postoperatively. Readmissions in other hospitals were not taken into account, but are expected to be very low, as patients are instructed very carefully to report to this hospital in case of emergency. Patient characteristics, obesity-related comorbidities, preoperative- and one-day postoperative laboratory results, major complication rates, length of hospital stay and readmission rates were recorded. The study protocol was approved by the institutional review board (IRB) and the regional Medical Research Ethics Committee TWOR, Rotterdam, the Netherlands (protocol number 2018-10).

Cohort

All included patients were found eligible for metabolic surgery according to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) guidelines and underwent a laparoscopic Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (SG) or a laparoscopic one-anastomosis gastric bypass – mini gastric bypass (OAGB-MGB), depending on comorbidities or preference of the patient or the surgeon[16]. The methods of the procedures were described in earlier publications[17-19]. All patients were treated according to the ERABS protocol with the intention to be discharged on day-one postoperative[1]. Patients were excluded from the study in case of conversion from laparoscopy to laparotomy. No power calculation was performed in this observational study.

Laboratory tests

Neutrophil and lymphocyte counts were measured twice: first preoperatively on the intake day at the outpatient clinic of the department of Internal Medicine, and second on the ward on day-one after surgery. The delta-NLR was calculated by extracting the preoperative NLR from the postoperative NLR, leading to a positive result in case of an increase in NLR. Laboratory parameters were determined at the hospital's Department of Clinical Chemistry according to the standard procedures. Blood cell counts and hemoglobin were measured on DxH800 analyzers (Beckman Coulter) and CRP was measured on the Architect c8000 (Abbott).

Statistical analysis

All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). Multivariable logistic regression analysis was used to estimate the relationship between the occurrence of major complications and the NLR (preoperative, postoperative and delta), correcting for sex, age, baseline body mass index [BMI], comorbidities (hypertension, type two diabetes [T2D] and hypercholesterolemia), type of surgery and duration of surgery. Independent T-tests were used for analyzing the relationship between specific types of complications and NLR, CRP and leukocyte count. Receiver operating characteristics (ROC) curves were constructed for NLR (preoperative, postoperative and delta), postoperative CRP and Leukocyte count on major complications. For all values with an area under the curve (AUC) greater than 0.70, the optimal cutoff value for predicting postoperative complications was determined. Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

RESULTS

Between April 2018 and April 2019, 834 patients underwent primary metabolic surgery, of whom 339 (40.6%) RYGB, 411 (49.3%) SG and 84 (10.1%) OAGB-MGB. The mean (± sd) duration of surgery was 47.4 ± 13.2 minutes for RYGB, 33.9 ± 9.3 minutes for SG and 43.0 ± 13.5 minutes for OAGB-MGB. The median (± SE) length of hospital stay for the complete cohort was 1.17 ± 0.03 days. Table 1 shows the baseline characteristics by type of procedure and for the complete cohort.

In total, nineteen (2.3%) major complications occurred within 30 days postoperatively: thirteen postoperative hemorrhages (1.6%, range of hours between procedure and event 14-105), three stenotic problems requiring a reintervention (0.4%, range of days between procedure and event 2-21), and three other complications (0.3%) (internal herniation, perforation of the small intestine and admission on intensive care unit because of diabetic ketoacidosis). No anastomotic leaks or staple line leaks were diagnosed in this cohort.

Table 1: Baseline characteristics

	RYGB (N=339)	*SG (N=411)*	*OAGB-MGB (N=84)*	*Total (N = 834)*
Female, n (%)	288 (85.5%)	318 (77.4%)	51 (60.7%)	657 (78.8%)
Age (years), mean ± sd	44.1 ± 10.6	39.5 ± 12.2	55.15 ± 6.9	43.0 ± 12.1
Baseline BMI (kg/m^2), mean ± sd	41.5 ± 4.2	43.5 ± 5.4	43.5 ± 6.0	42.7 ± 5.1
History of hypertension, n (%)	109 (32.2%)	97 (23.6%)	49 (58.3%)	255 (30.6%)
History of T2D, n (%)	54 (15.9%)	35 (8.5%)	40 (47.6%)	129 (15.5%)
History of dyslipidemia, n (%)	48 (14.2%)	38 (9.2%)	28 (33.3%)	114 (13.7%)

Abbreviations: SD: standard deviation. BMI: body mass index. T2D: type 2 diabetes. RYGB: Roux-en-Y gastric bypass. LSG: sleeve gastrectomy. OAGB-MGB: one-anastomosis gastric bypass – mini gastric bypass.

Day-one postoperative NLR was higher in patients with major complications compared to patients without (respectively 8.85 ± 4.15 vs. 5.90 ± 3.13, p=0.008). A similar trend was observed for delta-NLR (respectively 6.57 ± 3.81 vs. 3.50 ± 2.56, p=0.003) (Figure 1). No significant differences were found for patients with- or without complications on day-one postoperative in leukocyte count (respectively 13.37 ± 4.44 vs. 11.87 ± 2.98, p=0.159) or CRP (respectively 31.05 ± 20.01 vs. 23.66 ± 19.79, p=0.108), or in preoperative NLR (respectively 2.24 ± 0.83 vs. 2.43 ± 1.55, p=0.606). Although total complication rates were low, the predictive values were also studied with regard to specific complications. For postoperative hemorrhage significant differences were found in postoperative NLR (p=0.015) and delta-NLR (p=0.015), but no difference was found in postoperative CRP (p=0.924) or leukocyte count (0.217). No significant differences were found for stenotic problems in postoperative NLR (p=0.725), delta-NLR (p=0.533), postoperative CRP (p=0.358) or leukocyte count (p=0.400). For the other complications, significant differences were found in postoperative CRP (p=0.001) and leukocyte count (p<0.001), but not in postoperative NLR (p=0.296) or delta-NLR (p=0.064). Additional analysis showed no significant differences in mean laboratory values for readmissions within 30 days (data not shown).

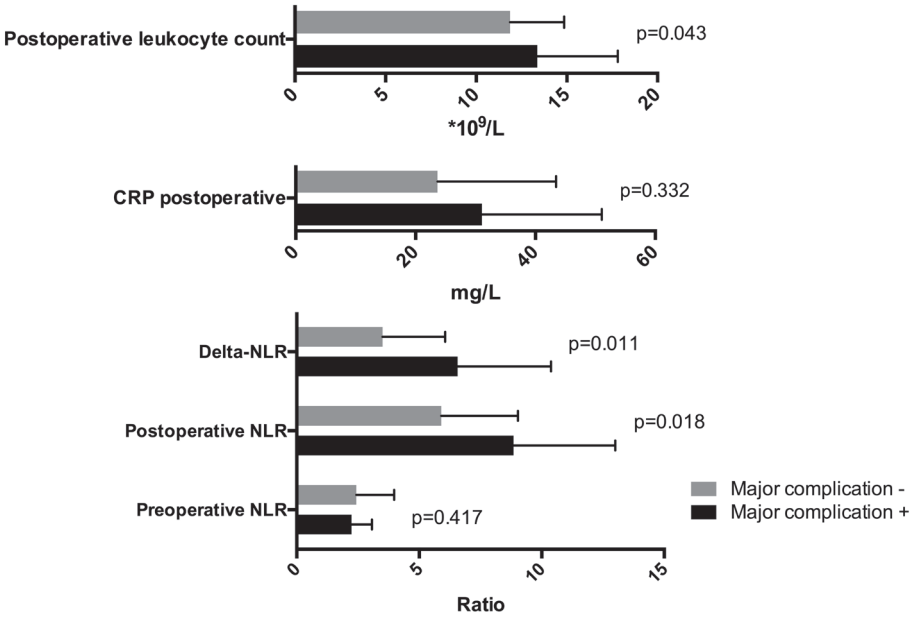


Figure 1: Mean ± sd laboratory values divided by occurrence of major complication

Patients who developed a major complication, had significantly higher levels of postoperative NLR (OR 1.105, 95%CI 1.006-1.215, p=0.038), delta-NLR (OR 1.290, 95%CI 1.141-1.460, p<0.001) and postoperative leukocyte count (OR 1.196, 95%CI 1.042-1.372, p=0.011) (Figure 2). CRP levels at day-one postoperative were not significantly different (OR 1.014, 95%CI 0.995-1.033, p=0.140). Baseline characteristics and the presence of T2D, hypertension or dyslipidemia showed no significant correlations with the occurrence of major complications. The AUC according to the ROC analysis for postoperative NLR and delta-NLR was 0.731 (p=0.001) and 0.765 (p<0.001), respectively. The ideal cutoff point for postoperative NLR was determined as 6.5, with a sensitivity of 67% and a specificity of 66%. The ideal cutoff point for delta-NLR was determined as 3.7, with a sensitivity of 72% and a specificity of 62%. ROC curves of postoperative NLR and delta-NLR are shown in Figures 3. The AUC for postoperative leukocyte count and postoperative CRP were not significant for postoperative major complications; respectively 0.582 (p=0.221) and 0.619 (p=0.075) (Table 2.)

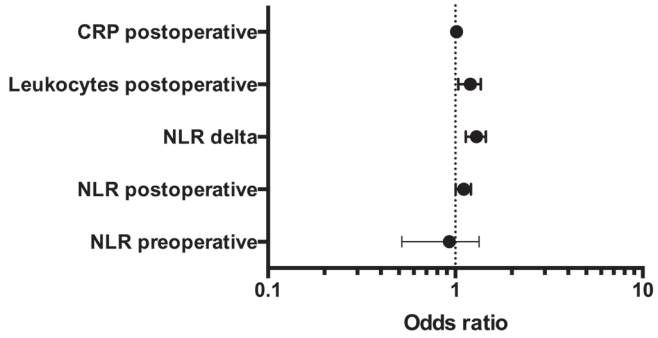


Figure 2: Multivariate regression analysis on laboratory results on major complications, corrected for sex, age, baseline BMI, comorbidities (hypertension, T2D and hypercholesterolemia), type of surgery and duration of surgery

Table 2: Characteristics of ROC curves for postoperative major complications of laboratory results

	AUC	*95% CI*	*Sig.*
Preoperative NLR	0.489	0.365-0.613	0.871
Postoperative NLR	0.731	0.612-0.850	**0.001**
Delta-NLR	0.765	0.655-0.874	**<0.001**
Postoperative leukocyte count	0.582	0.450-0.714	0.221
Postoperative CRP	0.619	0.475-0.764	0.075

Abbreviations: ROC: receiver operating characteristics. AUC: area under the curve. CI: confidence interval. Sig.: significance. NLR: neutrophil-to-lymphocyte ratio. CRP: C-reactive protein.

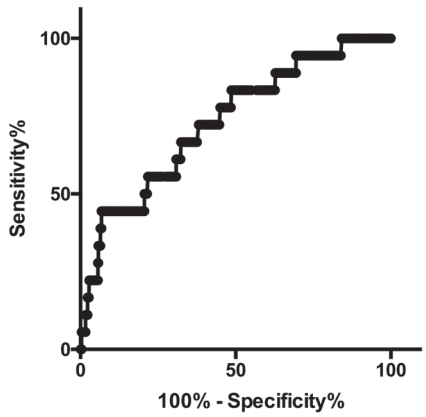


Figure 3a: ROC curve of postoperative NLR of postoperative major complications

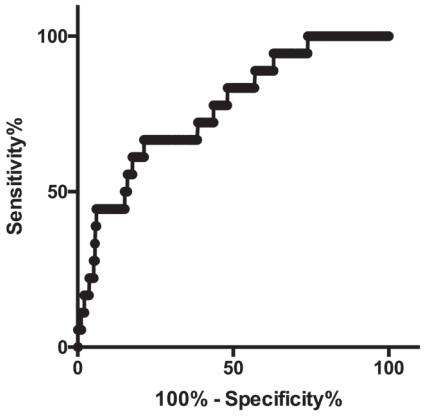


Figure 3b: ROC curve of delta-NLR of postoperative major complications

Abbreviations: SD: standard deviation. BMI: body mass index. T2D: type 2 diabetes. ROC: receiver operating characteristics. NLR: neutrophil-to-lymphocyte ratio. CRP: C-reactive protein.

DISCUSSION

ERABS protocols have proven their value in standardizing post-operative care, allowing for an early hospital discharge[1]. Our group previously demonstrated that a standardized postoperative checklist of clinical parameters and laboratory findings proved useful in predicting post-operative complications. A hemoglobin decrease of more than one point and the unwillingness of a patient to go home were significant predictive factors of postoperative complications[3]. However, there is need for a more sensitive biomarker of postoperative complications.

We found that the postoperative NLR and the delta-NLR showed a stronger correlation to postoperative complications than CRP or leukocyte count. Our data suggest that cutoff points of 6.5 for postoperative NLR and 3.74 for delta-NLR can be used in the decision-making for day-one postoperative discharge.

Preoperative NLR levels have been shown to predict high risk patients in other surgical areas[7-10]. In the current study, the preoperative NLR was mostly obtained weeks to months preoperatively, and was used as the patients NLR in a non-stressful situation, as a baseline value. We found that the preoperative NLR did not correlate to postoperative complications. In line with this outcome, the baseline characteristics and presence of comorbidities were neither correlated to the occurrence of major complications. Preoperative CRP levels have also been the subject of analysis in the search for predictive markers of postoperative complications. A recently published article showed that a high preoperative CRP level predicts a worse survival prognosis in patients who have undergone curative resection for esophageal

squamous cell cancer[20]. However, this correlation has not been described yet in metabolic surgery. Unfortunately, preoperative CRP levels were not available in our study and remain of interest for future research.

None of the patients were known to have systemic inflammatory diseases. As systemic inflammatory diseases influence the inflammatory markers such as CRP and NLR, these patients would deserve a separate analysis to determine the value of the NLR for detecting postoperative complications.

In 2017, Da Silva et al. found that an NLR ≥ 10 postoperatively was independently associated with the 30-day outcomes following metabolic surgery[12]. This study included 737 patients undergoing a RYGB (88.6%) or SG (11.4%). The major complication rate was 6.4%, of which the percentage of postoperative hemorrhage was not reported. Our study reports a lower rate for major complications (2.4%), but shows a similar association. Da Silva et al. did not determine an optimal cutoff point for the NLR, but based the cutoff value on previously published articles on the postoperative NLR to predict postoperative complications[21]. For our study population, the cutoff values of 6.5 for postoperative NLR and 3.7 for delta-NLR provided the best ratios of sensitivity and specificity. Delta-NLR was not determined in the above-mentioned study[21]. Therefore, our data provide more insight and extend those observations. We found that the delta-NLR correlated better with postoperative complications than day-one postoperative NLR. The calculated specificity of 60-70% may be acceptable, as the NLR is not intended to be used as a diagnostic test, but as part of an integrated set of clinical and laboratory parameters to aid in the clinical decision-making for discharge in a standardized way(2). An elevated postoperative NLR or delta-NLR in an otherwise asymptomatic patient should not always warrant a prolonged hospital stay. The physician in charge should take the elevated laboratory values in consideration, but in the end rely on clinical experience.

CRP as a predictive marker for complications at day-one postoperative has been evaluated more thoroughly. Several studies have pointed out the insufficient sensitivity of day-one postoperative CRP levels[3, 4]. Other studies did find CRP to be a useful marker. Kröll et al found that a CRP of < 70 mg/L on day-one postoperative can exclude early intraabdominal infections with high accuracy in patients undergoing metabolic surgery[22]. A meta-analysis by Bona et al. concluded that a CRP value lower than 6.1 mg/dl on postoperative day-one, combined with reassuring clinical signs, could be useful to rule out early postoperative leak and complications after SG and RYGB[23]. A study by Albanopoulos et al. found that the CRP at only 6 hours after the operation was already significantly higher in patients with a leak or an abscess. Interestingly, no significant increase in CRP, WBC or neutrophils was recorded for the patients with bleeding[24]. A very recent systematic review and meta-analysis stated that CRP can be a useful and cost-effective test to detect postoperative infectious complications following bariatric surgery[25]. In the current study, no correlation was found between elevated levels of day-one postoperative CRP and major complication rates. A possible explanation for this, might be the relatively high amount of postoperative hemorrhage and the lack of leaks in our cohort in order to find CRP a sensitive marker.

The data was also analyzed with regard to specific complications. The postoperative NLR and delta-NLR showed significant differences for the occurrence of postoperative hemorrhage, but not for the other types of complications. Due to the low complication rate in this cohort, these results should be interpreted with caution. Further research should further investigate this matter.

In the current study, we included three procedure types. As this was not a randomized study and there was no stratification, the patient characteristics were not equal between the three procedure types. However, we do not believe that this affected the results. As mentioned earlier, the baseline characteristics and presence of comorbidities were not shown to correlate to the occurrence of major complications. In the future, it could be interesting to investigate the effects of different baseline characteristics on the NLR. Another interesting parameter could be the difficulty or ease of the procedure, as technical difficulties during the procedure could potentially influence the postoperative laboratory results without indicating the presence of a postoperative complication. Unfortunately, we do not have sufficiently detailed information of the course of each procedure. Further research would be necessary to address these matters.

Procalcitonin and preseptin are other biomarkers that have demonstrated prognostic value in sepsis[26, 27]. In metabolic surgery, procalcitonin has been found to be helpful in predicting postoperative complications[28, 29]. Future research should evaluate if procalcitonin and NLR have complementary value in predicting complications when combined. A recently published systematic review and meta-analysis on the complications of metabolic surgery in patients with T2D showed that most complications are not necessarily higher in the diabetic population, but dependent on the type of surgery[30]. In our study, T2D had no influence on developing postoperative complications. The NLR ratio is a cheap, easily implemented marker in which rapid neutrophil responses as a result of complications are measured against a patient's own lymphocyte count. This study shows that the NLR is a more reliable marker than CRP for postoperative complications. Combined with other standardized parameters, the NLR can aid the clinician in the decision-making for early discharge. Limitations of this study include a single center design and a relatively low rate for major complications. However, patient numbers are large enough to demonstrate the predictive value of the NLR for postoperative complications.

CONCLUSION

The postoperative NLR and the delta-NLR show predictive value for early postoperative complications after metabolic surgery in our study. Combined with other clinical and laboratory parameters in a standardized checklist, the NLR can aid in the clinical decision-making for safe day-one postoperative discharge.

REFERENCES

1. Mannaerts GH, van Mil SR, Stepaniak PS, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
2. Adamina M, Steffen T, Tarantino I, et al. Meta-analysis of the predictive value of C-reactive protein for infectious complications in abdominal surgery. The British journal of surgery. 2015;102(6):590-8.
3. van Mil SR, Duinhouwer LE, Mannaerts GHH, et al. The Standardized Postoperative Checklist for Bariatric Surgery; a Tool for Safe Early Discharge? Obesity surgery. 2017;27(12):3102-9.
4. Villard MA, Helm MC, Kindel TL, et al. C-Reactive protein as a predictor of post-operative complications in bariatric surgery patients. Surgical endoscopy. 2019;33(8):2479-84.
5. Dionigi R, Dominioni L, Benevento A, et al. Effects of surgical trauma of laparoscopic vs. open cholecystectomy. Hepato-gastroenterology. 1994;41(5):471-6.
6. O'Mahony JB, Palder SB, Wood JJ, et al. Depression of cellular immunity after multiple trauma in the absence of sepsis. The Journal of trauma. 1984;24(10):869-75.
7. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratislavske lekarske listy. 2001;102(1):5-14.
8. Cho KI, Ann SH, Singh GB, et al. Combined Usefulness of the Platelet-to-Lymphocyte Ratio and the Neutrophil-to-Lymphocyte Ratio in Predicting the Long-Term Adverse Events in Patients Who Have Undergone Percutaneous Coronary Intervention with a Drug-Eluting Stent. PloS one. 2015;10(7):e0133934.
9. Gibson PH, Croal BL, Cuthbertson BH, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. American heart journal. 2007;154(5):995-1002.
10. Malietzis G, Giacometti M, Askari A, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Annals of surgery. 2014;260(2):287-92.
11. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surgical oncology. 2014;23(1):31-9.
12. Da Silva M, Cleghorn MC, Elnahas A, et al. Postoperative day one neutrophil-to-lymphocyte ratio as a predictor of 30-day outcomes in bariatric surgery patients. Surgical endoscopy. 2017;31(6):2645-50.
13. Radtka JF, 3rd, Puleo FJ, Wang L, et al. Revisional bariatric surgery: who, what, where, and when? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2010;6(6):635-42.
14. Zhang L, Tan WH, Chang R, et al. Perioperative risk and complications of revisional bariatric surgery compared to primary Roux-en-Y gastric bypass. Surgical endoscopy. 2015;29(6):1316-20.
15. Brethauer SA, Kim J, el Chaar M, et al. Standardized outcomes reporting in metabolic and bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(3):489-506.
16. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obesity surgery. 2014;24(1):42-55.
17. Apers J, Wijkmans R, Totte E, et al. Implementation of mini gastric bypass in the Netherlands: early and midterm results from a high-volume unit. Surgical endoscopy. 2018;32(9):3949-55.

18. Biter LU, Gadiot RP, Grotenhuis BA, et al. The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC obesity. 2015;2:30.
19. Gadiot RP, Biter LU, Zengerink HJ, et al. Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. Obesity surgery. 2012;22(2):320-9.
20. Huang W, Wu L, Liu X, et al. Preoperative serum C-reactive protein levels and postoperative survival in patients with esophageal squamous cell carcinoma: a propensity score matching analysis. Journal of cardiothoracic surgery. 2019;14(1):167.
21. Cook EJ, Walsh SR, Farooq N, et al. Postoperative neutrophil-lymphocyte ratio predicts complications following colorectal surgery. International journal of surgery (London, England). 2007;5(1):27-30.
22. Kroll D, Nakhostin D, Stirnimann G, et al. C-Reactive Protein on Postoperative Day 1: a Predictor of Early Intra-abdominal Infections After Bariatric Surgery. Obesity surgery. 2018;28(9):2760-6.
23. Bona D, Micheletto G, Bonitta G, et al. Does C-reactive Protein Have a Predictive Role in the Early Diagnosis of Postoperative Complications After Bariatric Surgery? Systematic Review and Bayesian Meta-analysis. Obesity surgery. 2019.
24. Albanopoulos K, Alevizos L, Natoudi M, et al. C-reactive protein, white blood cells, and neutrophils as early predictors of postoperative complications in patients undergoing laparoscopic sleeve gastrectomy. Surgical endoscopy. 2013;27(3):864-71.
25. Lee Y, McKechnie T, Doumouras AG, et al. Diagnostic Value of C-Reactive Protein Levels in Postoperative Infectious Complications After Bariatric Surgery: a Systematic Review and Meta-Analysis. Obesity surgery. 2019;29(7):2022-9.
26. Kondo Y, Umemura Y, Hayashida K, et al. Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis. Journal of intensive care. 2019;7:22.
27. van Oers JAH, de Jong E, Kemperman H, et al. Diagnostic Accuracy of Procalcitonin and C-reactive Protein Is Insufficient to Predict Proven Infection: A Retrospective Cohort Study in Critically Ill Patients Fulfilling the Sepsis-3 Criteria. The journal of applied laboratory medicine. 2019.
28. Munoz JL, Ruiz-Tovar J, Miranda E, et al. C-Reactive Protein and Procalcitonin as Early Markers of Septic Complications after Laparoscopic Sleeve Gastrectomy in Morbidly Obese Patients Within an Enhanced Recovery After Surgery Program. Journal of the American College of Surgeons. 2016;222(5):831-7.
29. Ruiz-Tovar J, Munoz JL, Gonzalez J, et al. C-reactive protein, fibrinogen, and procalcitonin levels as early markers of staple line leak after laparoscopic sleeve gastrectomy in morbidly obese patients within an Enhanced Recovery After Surgery (ERAS) program. Surgical endoscopy. 2017;31(12):5283-8.
30. Kabir A, Mousavi S, Pazouki A. The Complications of Bariatric Surgery Patients with Type 2 Diabetes in the World: A Systematic Review and Meta-Analysis. Current diabetes reviews. 2019;15(1):49-61.

PART II

Outcomes after bariatric surgery

8 ASSISI: IMT and PWV measurements after bariatric surgery

Accepted: Surgery for Obesity And Related Diseases, 2019

ABSTRACT

Background

Obesity is a major risk factor for cardiovascular disease (CVD). Data on structural and functional arterial changes after bariatric surgery are scarce. The aim of this study was to determine the effects of bariatric surgery on the carotid intima media thickness (cIMT) and pulse wave velocity (PWV).

Methods

We collected data prospectively in 200 patients scheduled for bariatric surgery between 2015-2017. Based on an increase or decrease of one standard deviation of the mean difference in cIMT and PWV, 1 year post-operatively patients were divided into 'progressors', 'regressors' and 'unchanged'. We analyzed data on medical history, baseline body mass index (BMI), surgery type and difference in BMI after 1 year.

Results

Data on cIMT were available for 134 patients. 34 patients (25.4%) had a cIMT regression with a mean decrease of 0.1 mm [-0.24 to -0.06]; 10 patients (7.5%) were progressors with a mean increase of 0.1 mm [0.07 to 0.30] and 90 patients (67.2%) remained unchanged. Progressors more often had T2D (p=0.035) and hypertension (p=0.020). Data on PWV were available for 120 patients, of whom 91 (75.8%) were regressors, 26 (21.6%) remained unchanged and 3 (2.5%) were progressors. Predictors of PWV changes were total plasma cholesterol and hypertension at baseline.

Conclusions

A significant improvement of the vascular quality already after 1 year of follow up was established in 25-76% of all patients after bariatric surgery and the vast majority showed stabilization.

INTRODUCTION

Atherosclerosis is a low-grade chronic inflammatory disease and the most common cause of cardiovascular disease (CVD) worldwide [1]. The first-line intervention in the treatment and prevention of CVD is lifestyle adaptation followed by medical interventions. The incidence of CVD in patients with obesity is significantly increased compared to lean patients [2].
Recent literature has shown that the carotid intima-media thickness (cIMT) is a good predictor of the severity of cardiovascular disease in patients with obesity and that cIMT can improve significantly after bariatric surgery [2, 3]. The cIMT measurement describes the combined thickness of the intimal and medial layer of the arterial wall and measures indirectly the severity of the fatty streak. Ageing is the most important determinant of cIMT changes resulting in a physiological increase in cIMT of 0.013-0.015 millimeters per year [4].
Another way to investigate the arterial health is by measuring the pulse wave velocity (PWV), which is the golden standard for measuring the arterial stiffness. It is known that obesity is associated with an increased PWV [5]. Several research groups have studied the effects of exercise training on the arterial stiffness, but the reversibility of the arterial stiffness after bariatric surgery has not been determined yet [6, 7].
Earlier work from our group already described that besides age, the blood pressure and lipid profile contribute significantly to the levels of cIMT in morbid obesity. PWV was mainly determined by differences in gender, age, waist circumference and blood pressure [8]. The present study aims to assess the short-term effects of bariatric surgery on the structure and function of the vascular wall by assessing cIMT and PWV. Also, we aimed to evaluate the effects of the type of surgery on these variables and to identify factors that are related to the changes in cIMT and PWV after bariatric surgery.

METHODS

As part of the ASSISI (Adipose tissue mediated inflammation in morbid obesity) study that was performed in a single center, we collected data prospectively of 200 patients undergoing bariatric surgery between 2015-2017. The interventions were a primary Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) or mini gastric bypass-one anastomosis gastric bypass (MGB-OAGB). The cIMT and PWV were measured in these patients pre-operatively and 1 year post-operatively, as described previously [8]. Patients were excluded from the analysis in case of missing data on cIMT or PWV. The study was approved by the local ethical committee “Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (TWOR)”. Consent was obtained from each participant after full explanation of the purpose and nature of all procedures used.

Carotid intima media thickness (cIMT)

Carotid ultrasound scans were carried out using the ART-LAB (Esaote, Italy) by trained and experienced sonographers as described earlier [9]. Each common carotid artery was imaged in three different projections. The carotid intima media thickness (cIMT) consists of the mean of the six different measurements. Mean cIMT was only calculated when a minimum of 2 measurements per carotid artery were available.

Pulse wave velocity (PWV)

The PWV was analyzed with a Mobil-O-Graph (IEM, Germany). The PWV was measured with an ambulatory oscillometric device at the left arm and the mean PWV was calculated from three measurements. PWV is considered the gold standard to measure arterial stiffness as a marker for endothelial function. The velocity of the pulse wave increases when the aortic stiffness increases.

Laboratory measurements

A standardized set of measurements was performed in each subject. Laboratory parameters were determined at the hospital's Department of Clinical Chemistry according to standard procedures. Renal and liver function as well as glucose, total cholesterol, HDL-C, triglycerides and C-reactive protein (CRP) were determined using Architect c8000 (Abbott, Chicago Ill, USA) or Synchron DxH analyzers (Beckman Coulter, Anaheim CA, USA). LDL-C was calculated using the Friedewald formula. Apolipoprotein (apo) B was determined by rate nephelometry using an IMMAGE analyzer (Beckman Coulter, Brea CA, USA). Hemoglobin A1c (A1c) was measured using an G8 analyzer (Tosoh, San Franciscus CA, USA).

Statistical methods

For each patient, the absolute difference in cIMT and PWV between preoperative and 1 year after surgery was determined. Based on an increase or decrease of one standard deviation of the mean difference in cIMT and PWV of the total cohort, patients were divided into progressors (worsened values), regressors (improved values) and 'unchanged', for both cIMT and PWV. Data was analyzed on differences between these groups on gender, ethnicity, age at time of surgery, type of surgery, difference in BMI after 1 year and medical history of T2D, hypertension, hypercholesterolemia or smoking, using one-way ANOVA, Chi^2, Mann-Whitney and Spearman tests. Differences in comorbidities and laboratory results at baseline and 1 year postoperative were analyzed between progressors, regressors and unchanged IMTs and PWVs in order to detect potential predictive factors using ANOVA tests. Differences in laboratory results at baseline and 1 year postoperative within groups were tested using Paired samples T-tests for parametric variables and Wilcoxon Signed Rank tests for variables in which normal distribution was not assumed. Data are presented as mean ± SD. Analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, IL, USA). Statistical significance was achieved with a significance threshold of $p<0.05$ (two-sided).

RESULTS

A complete data set was available for 134 patients with respect to cIMT measurements and for 120 (out of these 134) patients for PWV measurements. Missing data were caused by loss to follow up, administrative faults or transient software problems (especially with the PWV measurements). Baseline characteristics and outcomes at 1 year postoperative are shown in Table 1.

Table 1: Baseline characteristics based on either cIMT or PWV changes after 1 year

Characteristics	Cohort based on cIMT changes (n=134)		Cohort based on PWV changes (n=120)	
	Baseline	1 year postoperative	Baseline	1 year postoperative
Female (n, %)	102 (76.1%)		92 (23.3%)	
Caucasian ethnicity (n, %)	109 (81.3%)		92 (80.0%)	
Age in years (mean, range)	42 (18-61)		42 (18-61	
BMI (mean, range)	42.7 (35.0 – 74.7)	28.2 (17.8 - 54.4)	42.7 (35.0 – 74.7)	28.2 (17.8 - 54.4)
Systolic blood pressure (mean ± SD)	141 ± 18	128 ± 15	141 ± 20	128 ± 16
Diastolic blood pressure (mean ± SD)	83 ± 10	78 ± 11	83 ± 10	78 ± 12
Type of surgery				
• Gastric bypass (n, %)	75 (56%)		65 (54.2%)	
• Gastric sleeve (n, %)	50 (37.3%)		47 (39.2%)	
• Gastric minibypass (n, %)	9 (6.7%)		8 (6.7%)	
Comorbidities				
• T2D (n, %)	24 (17.9%)	10 (7.5%)	21 (17.5%)	9 (7.5%)
• Hypertension (n, %)	51 (38.1%)	20 (14.9%)	43 (35.8%)	18 (15.0%)
• Hypercholesterolemia (n, %)	43 (32.1%)	5 (3.7%)	38 (31.7%)	5 (4.2%)
• Smoking (n, %)	32 (23.9%)		28 (23.3%)	

Abbreviations: IMT = Intima media thickness. PWV = Pulse wave velocity. BMI = Body mass index (kg/m2). T2D = Type 2 diabetes

34 (25.4%) Patients had a significant regression of cIMT with a mean decrease of 0.1 mm [-0.24 to -0.06]; 10 patients (7.5%) were progressors with a mean increase in cIMT of 0.1 mm [0.07 to 0.30] and 90 patients (67.2%) had no significant difference in cIMT (Figure 1). Comparing progressors to regressors, there were significant differences in terms of T2D and hypertension at baseline. Three out of 10 progressors had T2D in contrast to 2 out of 32 regressors (p=0.035). Furthermore, progressors more often had hypertension (7/10) than regressors (10/24) (p=0.020). Figure 2 shows the data for cIMT and PWV in terms of response after 1 year of surgery for the different types of surgery. No significant difference was found between the types of surgery on cIMT (p=0.310) nor PWV (p=0.867) when comparing progressors, unchanged and regressors, neither in absolute differences in cIMT (p=0.669) or

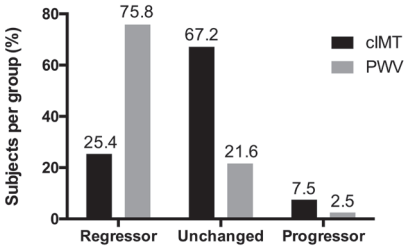


Figure 1: IMT and PWV in different groups. The data show the percentage of subjects in each group based on IMT after 1 year (black) and PWV (grey).

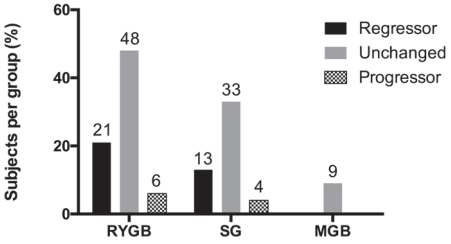


Figure 2a: Response of cIMT after 1 year postoperative divided by type of surgery

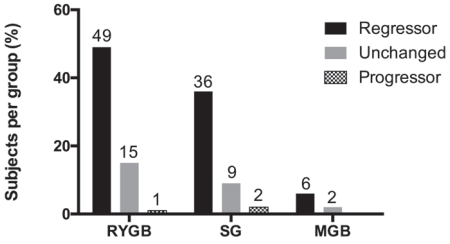


Figure 2b: Response of PWV after 1 year postoperative divided by type of surgery

PWV (p=0.459). Other variables like BMI at baseline, age at time of surgery, gender, smoking behavior and BMI loss after surgery were not associated with the cIMT changes at 1 year postoperatively. We found no significant differences between cIMT-progressors, regressors and unchanged patients for classical cardiovascular risk factors, such as hypertension, T2D or hypercholesterolemia. Differences between the three groups at baseline were found for total leukocyte counts (p=0.018), neutrophils (p=0.022) and eosinophils concentration (p=0.045). At 1 year follow up, only diastolic blood pressure differed between the groups (Table 2). Age was significantly correlated to baseline cIMT, as shown in Figure 3a.

Data on PWV was available for 120 patients, of whom 91 (75.8%) were regressors, 26 (21.6%) remained unchanged and 3 (2.5%) were progressors (Figure 1). All 3 progressors had hypertension, whereas 46% of the unchanged patients and 31% of the regressors had hypertension (p=0.022). There were no differences in smoking behavior, T2D, hypercholesterolemia, type of surgery or BMI loss after surgery.

As shown in Table 3, there were significant differences between the PWV-groups in baseline total and LDL cholesterol and apoB. At 1 year, differences were found in blood pressure, total and LDL cholesterol. Comparing baseline and 1 year postoperative values, significant differences were found on BMI, diastolic blood pressure, cholesterol, triglycerides, HDL-C, LDL-C, apoB, A1c and leukocytes for regressors and unchanged patients. Figure 3b shows the correlation of baseline PWV and age.

For cIMT, at baseline 4/34 regressors, 12/90 unchanged and 2/10 progressors used statins (p=0.800). At 1 year, 4/34 regressors, 12/90 unchanged and 3/10 progressors of cIMT used

Table 2: Data based on cIMT changes after 1 year postoperative

IMT (n=134)	Regressors (n=34)		Unchanged (n=90)		Progressors (n=10)		p-value
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Age at time of surgery (years)	39.76	11.27	43.4	11.26	45.2	8.74	0.20
BMI at baseline (kg/m^2)	42.00	4.44	42.93	5.94	42.44	4.66	0.70
BMI at 1 year FU (kg/m^2)	27.81***	3.79	28.43***	4.74	27.63***	3.93	0.72
BMI loss at 1 year FU (kg/m^2)	14.19	3.54	14.5	3.87	14.82	4.99	0.88
Systolic BP at baseline (mmHg)	137	19	143	19	143	18	0.23
Systolic BP at 1 year FU (mmHg)	124	17	129	15	130	15	0.21
Diastolic BP at baseline (mmHg)	81	10	83	9	86	11	0.26
Diastolic BP at 1 year FU (mmHg)	73	13	80*	11	75	8	0.02
Cholesterol at baseline (mM)	5.42	1.23	5.29	1.04	4.85	0.82	0.34
Cholesterol at 1 year FU (mM)	4.56***	0.86	4.46***	0.89	4.15*	0.77	0.45
Triglycerides at baseline (mM)	2.1	1.27	1.99	1.02	2.23	1.12	0.74
Triglycerides at 1 year FU (mM)	1.16***	0.47	1.15***	0.51	1.21*	0.73	0.95
HDL-C at baseline (mM)	1.19	0.25	1.27	0.3	1.21	0.24	0.35
HDL-C at 1 year FU (mM)	1.3*	0.3	1.37***	0.34	1.32	0.21	0.61
LDL-C at baseline (mM)	3.39	1.09	3.14	0.94	2.71	0.77	0.16
LDL-C at 1 year FU (mM)	2.74**	0.68	2.57***	0.73	2.3	0.66	0.23
ApoB at baseline (g/L)	1.23	0.33	1.16	0.3	1.02	0.26	0.15
ApoB at 1 year FU (g/L)	0.82***	0.17	0.82***	0.23	0.73**	0.21	0.45
CRP at baseline (mg/L)	7.59	8.16	8.3	6.55	6.00	5.72	0.58
CRP at 1 year FU (mg/L)	1.17*	0.41	87.29	162.00	1.00		0.43
A1c at baseline (mmol/mol)	40.44	9.9	42.41	9.93	44.8	9.81	0.41
A1c at 1 year FU (mmol/mol)	35.65**	3.5	35.9***	5.13	36.8**	4.69	0.80
Leukocytes at baseline (G/L)	8.56	2.61	8.82	2.09	10.92	3.3	0.02
Leukocytes at 1 year FU (G/L)	6.88**	1.59	7.02***	2.2	7.64*	1.99	0.68
Neutrophils conc at baseline (G/L)$^{\$}$	5.44	2.09	5.41	1.65	7.13	2.6	0.02
Eosinophils conc at baseline (G/l)$^{\$}$	0.2	0.13	0.18	0.11	0.29	0.23	0.05

Abbreviations: IMT = intima media thickness. SD = standard deviation. BMI = body mass index. BP = blood pressure. HDL-C = high density lipoprotein cholesterol. LDL-C = low density lipoprotein cholesterol. ApoB = Apolipoprotein B. CRP = C-reactive protein

*p<0.05 versus baseline. **p<0.01 versus baseline. ***p<0.001 versus baseline. $^{\$}$leukocyte differentiation was not available at 1 year follow up

statins (p=0.321). Concerning antihypertensive medication: at baseline 8/34 cIMT regressors, 32/90 unchanged and 7/10 progressors used antihypertensive medication (p=0.025). At 1 year postoperative, 4/34 cIMT regressors, 18/90 constant and 5/10 progressors used antihypertensive medication (p=0.030).

For PWV, at baseline 10/91 regressors, 6/26 unchanged and 0/3 progressors used statins (p=0.220). At 1 year, 13/91 PWV-regressors, 2/26 unchanged and 1/3 progressors used statins (p=0.401). Concerning antihypertensive medication, at baseline 26/91 regressors,

12/26 unchanged and 3/3 progressors used antihypertensive medication (p=0.013). At 1 year, 17/91 PWV-regressors, 7/26 constant and 1/3 progressors used antihypertensive medication (p=0.570).

Table 3: Data based on PWV changes after 1 year postoperative

PWV (n=120)	Regressors (n=91)		Unchanged (n=26)		Progressors (n=3)		p-value
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Age at time of surgery (years)	41.19	11.27	45.08	10.14	48.33	6.03	0.18
BMI at baseline (kg/m^2)	43.11	6.12	41.49	3.48	39.00	2.85	0.23
BMI at 1 year FU (kg/m^2)	28.36***	4.82	28.03***	3.74	26.49*	1.93	0.76
BMI loss at 1 year FU (kg/m^2)	14.75	3.93	13.46	4.07	12.50	4.71	0.24
Systolic BP at baseline (mmHg)	141	21	141	15	147	8	0.87
Systolic BP at 1 year FU (mmHg)	124	15	138*	13	153	8	<0.001
Diastolic BP at baseline (mmHg)	82	10	65	10	86	8	0.16
Diastolic BP at 1 year FU (mmHg)	75***	10	84	10	98	17	<0.001
Cholesterol at baseline (mM)	5.41	1.03	4.72	1.00	6.10	1.05	<0.01
Cholesterol at 1 year FU (mM)	4.54***	0.78	4.16**	0.97	5.57	1.38	0.02
Triglycerides at baseline (mM)	1.97	1.01	2.13	1.13	1.99	0.90	0.78
Triglycerides at 1 year FU (mM)	1.18***	0.51	1.20***	0.62	0.93	0.17	0.71
HDL-C at baseline (mM)	1.27	0.28	1.16	0.31	1.23	0.12	0.20
HDL-C at 1 year FU (mM)	1.37**	0.30	1.25*	0.33	1.57	0.42	0.11
LDL-C at baseline (mM)	3.27	0.95	2.74	0.97	3.97	1.12	0.02
LDL-C at 1 year FU (mM)	2.65***	0.69	2.39*	0.70	3.53*	0.99	0.02
ApoB at baseline (g/L)	1.17	0.31	1.04	0.26	1.43	0.29	0.03
ApoB at 1 year FU (g/L)	0.83***	0.22	0.76***	0.20	1.05*	0.26	0.07
CRP at baseline (mg/L)	8.23	6.61	6.15	7.47	14.33	14.47	0.12
CRP at 1 year FU (mg/L)	55.91	132.82	1.00***		2.00		0.87
A1c at baseline (mmol/mol)	41.35	9.53	42.77	11.14	42.33	3.79	0.81
A1c at 1 year FU (mmol/mol)	35.84***	5.05	35.65***	4.45	37.00	1.00	0.90
Leukocytes at baseline (G/L)	8.98	2.28	8.65	2.53	8.60	1.51	0.80
Leukocytes at 1 year FU (G/L)	7.15***	2.09	6.50***	1.62	6.50	2.42	0.42
Neutrophils conc at baseline (G/L)$^{\$}$	5.66	1.86	5.30	2.12	4.73	0.75	0.53
Eosinophils conc at baseline (G/l)$^{\$}$	0.21	0.13	0.19	0.11	0.21	0.10	0.80

Abbreviations: PWV = pulse wave velocity. SD = standard deviation. BMI = body mass index (kg/m2). BP = blood pressure. HDL-C = high density lipoprotein cholesterol. LDL-C = low density lipoprotein cholesterol. Apob = Apolipoprotein B. CRP = C-reactive protein

*p<0.05 versus baseline. **p<0.01 versus baseline. ***p<0.001 versus baseline. $^{\$}$leukocyte differentiation was not available at 1 year follow up

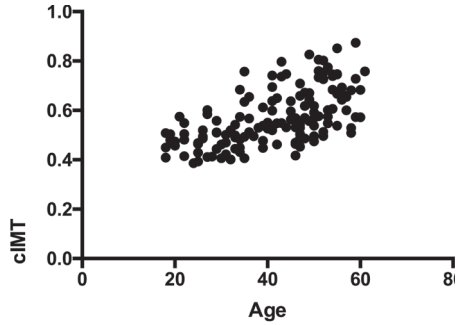


Figure 3a: Association between age and cIMT at baseline (p<0.001).

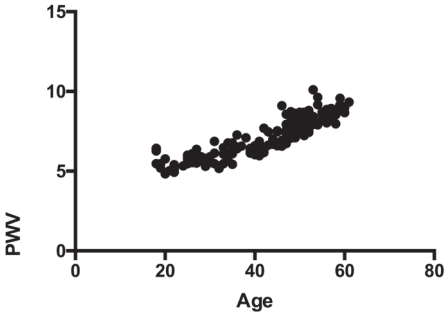


Figure 3b: Association between age and PWV at baseline (p<0.001).

DISCUSSION

This study shows a significant improvement of functional and structural vascular changes for 25-76% of patients undergoing bariatric surgery, already after 1 year. This is of importance because the data underline the effectiveness of this intervention in this group of patients at high risk for cardiovascular disease [5]. Moreover, our data are in line with the well-known beneficial effects shown in the long-term Swedish Obese Subjects (SOS) study, including over 4000 participants and showing 31% lower overall mortality in the operated subjects after adjustment for gender, age and risk factors [10]. Interestingly, these results were observed after 13 years of follow up. Reduction of cardiovascular events became obvious after 8-10 years [10]. Our data suggest that significant cardiovascular improvements already occur after 1 year postoperatively. Therefore, bariatric surgery has an unexpected rapid effect on vascular changes.

The question remains whether cardiovascular mortality in morbid obesity is primarily driven by atherosclerotic disease or non-atherosclerotic cardiovascular disease, such as myocardial dysfunction and heart failure. Our study does not provide any information on that aspect.

When compared to other effective interventions in cardiovascular medicine, like for example statin treatment, bariatric surgery in morbid obesity seems extremely efficient. A review published in 2009 stated that statins demonstrated a regression of cIMT in the general population, but that this was a consequence of intensive drug dosage and an adequate long term treatment period [11]. A more recent review found that particular types of statins can significantly reduce the cIMT, but only in the setting of statin's use in secondary prevention during a longer period of time [12]. In our study, we found no major differences between groups of regressors, unchanged or progressors for either cIMT or PWV in statin use at baseline or at 1 year post-operatively. Moreover, the use of these drugs did not decline in time. However, differences in the use of antihypertensive medication were found between the groups and the use of these

drugs was lower after 1 year, suggesting that body weight reduction had especially an impact on blood pressure regulation.

In this study, age seemed to be the major determinant of cIMT and PWV in morbid obesity, which also accounts to lean populations [9, 13]. Recently, it was described that bariatric surgery resulted in a significant cIMT decrease in patients with morbid obesity after 12 months of follow up, independent of age [3], which is also supported in other publications [14, 15]. The current paper is in line with those data and extends those observations showing improvements in vascular function by PWV measurements in the majority of these patients.

In the present study, we also evaluated possible predictors of vascular improvement after bariatric surgery. We did not find any effects of the classical risk factors such as T2D and hypertension. Others already reported a lack of between baseline PWV and gender, smoking or cardiometabolic markers (including blood pressure) [16].

Granulocyte counts were associated to the postoperative course of the cIMT and PWV in our study. Such an association was already described earlier by Phillips et al., who found that white blood cell count and granulocyte number were positively related to cIMT and PWV in a Chinese elderly population [17]. This may be related to the systemic inflammation as present in patients with morbid obesity or by increasing age. The general assumption is that bariatric surgery decreases systemic inflammation by reducing total fat mass, although direct evidence for this concept has not been provided yet. Whether body weight reduction by other interventions like lifestyle will lead to reduced systemic inflammation is not known.

Due to the relatively small groups of patients, especially the group of progressors in cIMT as well as PWV, we have to be cautious when interpreting our results. Long term follow up is necessary to establish whether progressors as defined in our study, will eventually show more cardiovascular complications than regressors. In other words, whether IMT or PWV changes after bariatric surgery will help to identify those subjects at higher cardiovascular risk who will need a more intensive risk-factor approach. Finally, targets for cardiovascular intervention in subjects with obesity have not been proposed yet in contrast to other risk groups like diabetics or patients with cardiovascular events. Long term studies are necessary to establish such targets.

In conclusion, this study found that positive changes of the vascular wall can already be seen 1 year after bariatric surgery. There was an improvement in cIMT in 25.4% of all patients, and PWV improved in 75.8%, after 1 year post-surgery. Further research should focus on identification of predictive cardiovascular markers associated with clinical outcome in subjects with morbid obesity.

REFERENCES

1. Aday AW, Ridker PM. Antiinflammatory Therapy in Clinical Care: The CANTOS Trial and Beyond. Frontiers in cardiovascular medicine. 2018;5:62.
2. Lundby-Christensen L, Tarnow L, Hansen DL, et al. Carotid intima-media thickness is reduced 12 months after gastric bypass surgery in obese patients with type 2 diabetes or impaired glucose tolerance. Journal of diabetes and its complications. 2014;28(4):517-22.
3. Jonker FHW, van Houten VAA, Wijngaarden LH, et al. Age-Related Effects of Bariatric Surgery on Early Atherosclerosis and Cardiovascular Risk Reduction. Obesity surgery. 2018;28(4):1040-6.
4. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet (London, England). 2012;379(9831):2053-62.
5. Strasser B, Arvandi M, Pasha EP, Haley AP, Stanforth P, Tanaka H. Abdominal obesity is associated with arterial stiffness in middle-aged adults. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2015;25(5):495-502.
6. DeVallance E, Fournier S, Lemaster K, et al. The effects of resistance exercise training on arterial stiffness in metabolic syndrome. European journal of applied physiology. 2016;116(5):899-910.
7. Montero D, Roberts CK, Vinet A. Effect of aerobic exercise training on arterial stiffness in obese populations : a systematic review and meta-analysis. Sports medicine (Auckland, NZ). 2014;44(6):833-43.
8. van Mil SR, Biter LU, van de Geijn GM, et al. Contribution of Type 2 Diabetes Mellitus to Subclinical Atherosclerosis in Subjects with Morbid Obesity. Obesity surgery. 2018.
9. van Breukelen-van der Stoep DF, van Zeben D, Klop B, et al. Association of Cardiovascular Risk Factors with Carotid Intima Media Thickness in Patients with Rheumatoid Arthritis with Low Disease Activity Compared to Controls: A Cross-Sectional Study. PloS one. 2015;10(10):e0140844.
10. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. Journal of internal medicine. 2013;273(3):219-34.
11. Riccioni G. Statins and carotid intima-media thickness reduction: an up-to-date review. Current medicinal chemistry. 2009;16(14):1799-805.
12. Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. Journal of atherosclerosis and thrombosis. 2013;20(1):108-21.
13. Alipour A, Valdivielso P, Elte JW, et al. Exploring the value of apoB48 as a marker for atherosclerosis in clinical practice. European journal of clinical investigation. 2012;42(7):702-8.
14. Sturm W, Tschoner A, Engl J, et al. Effect of bariatric surgery on both functional and structural measures of premature atherosclerosis. European heart journal. 2009;30(16):2038-43.
15. Tschoner A, Sturm W, Gelsinger C, Ress C, Laimer M, Engl J, et al. Long-term effects of weight loss after bariatric surgery on functional and structural markers of atherosclerosis. Obesity (Silver Spring, Md). 2013;21(10):1960-5.
16. Hudson L, Kinra S, Wong I, Cole TJ, Deanfield J, Viner R. Is arterial stiffening associated with adiposity, severity of obesity and other contemporary cardiometabolic markers in a community sample of adolescents with obesity in the UK? BMJ paediatrics open. 2017;1(1):e000061.

17. Phillips AC, Jiang CQ, Thomas GN, et al. White blood cell subsets are associated with carotid intima-media thickness and pulse wave velocity in an older Chinese population: the Guangzhou Biobank Cohort Study. Journal of human hypertension. 2012;26(8):485-92.

9 DUCATI: Vitamin deficiencies after distal RYGB

Accepted: British Journal of Nutrition, 2020

ABSTRACT

Laparoscopic Roux-en-Y Gastric Bypass (RYGB) is considered the gold standard for surgical treatment of morbid obesity. It is hypothesized that reducing the length of the common limb positively affects the magnitude and preservation of weight loss, but may also impose a risk of malnutrition. The aim of this study was to compare patients' nutrient and vitamin deficiencies in standard RYGB with a Very Long Roux Limb RYGB (VLRL-RYGB). This study was part of the multicenter randomized controlled trial (DUCATI), including 444 patients undergoing a RYGB or a VLRL-RYGB. Laboratory results, use of multivitamin supplements and reoperations were collected at baseline and one year postoperative. Primary outcome measure was nutrient deficiency after one year postoperative. Secondary outcome measure was the reoperation rate due to malabsorption. In total, 227 patients underwent RYGB and 196 patients underwent VLRL-RYGB. Most common deficiencies at one year postoperative were Ferritin(17.2-18.2%), Iron(23.4-35.6%), Potassium(7.4-15.2%), Vitamin B12(9.0-9.9%) and Vitamin D(22.7-34.5%). Patients undergoing VLRL-RYGB had slightly but significantly lower levels of calcium, iron and vitamin D compared to patients undergoing RYGB at 1 year postoperative, but significantly higher levels of folic acid and sodium. Reoperation rates due to malabsorption were not significantly different between RYGB(2/227, 0.9%) and VLRL-RYGB(7/196, 3.6%)(p=0.088). We concluded that patients undergoing VLRL-RYGB had significantly lower levels of calcium, iron and vitamin D compared to patients undergoing RYGB at one year postoperative, but higher levels of folic acid and sodium. Reoperation rates did not differ. Close monitoring on nutrient deficiencies should be performed in patients undergoing VLRL-RYGB.

INTRODUCTION

Metabolic or bariatric surgery supplemented with dietary, behavioral and lifestyle changes, is the only effective method in facilitating permanent or long term weight loss and improving medical comorbidities in morbid obese patients[1]. Laparoscopic Roux-en-Y Gastric Bypass (RYGB) is considered the gold standard for effective treatment of morbid obesity[2].

The common channel of the RYGB is the part where most of the nutrients are absorbed and where enterohepatic circulation of bile salts and fat is preserved[3]. It is hypothesized that the length of the common limb affects the amount of weight loss and preservation of weight loss on the long term, but a longer roux limb may also influence the risk of malnutrition[4, 5]. Until now, there is no consensus on the optimal length of the limbs of a RYGB.

Most common nutrient and vitamin deficiencies described after RYGB are iron, vitamin B12, folic acid, vitamin D and calcium[6, 7]. The Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery advises to prescribe to all bariatric patients lifelong daily vitamins (A, D, E and K, in water-soluble form) and micronutrient supplementation, a recommended minimally protein intake of approximately 90g/day and extra supplements according to laboratory findings[1, 7]. Additionally, the National Institute for Health and Care Excellence (NICE) advises a minimum follow-up period of two years in the bariatric surgical service and lifelong follow-up at the physician to monitor the patient's nutrient and vitamin status[8]. However, the efficacy of bariatric multivitamins in terms of prevention of nutrient deficiencies in RYGB with different lengths of the common limb is unclear.

The aim of this study was to compare standard RYGB with a Very Long Roux Limb RYGB (VLRL-RYGB) in terms of vitamin and nutrient deficiencies in patients undergoing a primary bariatric procedure.

METHODS

Design and data collection

The current study was performed as a part of the Dutch Common Channel Trial (DUCATI), a multicenter randomized controlled trial comparing RYGB with VLRL-RYGB[3]. In the DUCATI, 444 patients were included between 2014-2017 in two hospitals in the Netherlands. These patients were randomized with a 1:1 ratio between two procedure types: RYGB versus VLRL-RYGB. All patients found suitable for bariatric surgery according to the international IFSO guidelines and undergoing a primary laparoscopic RYGB were invited to participate in the DUCATI. DUCATI exclusion criteria were no informed consent, prior major abdominal surgery (such as colonic resection, septic abdomen, aorta surgery, or other procedures with a high risk of intra-abdominal adhesions, which might jeopardize the possibility of performing a VLRL-RYGB), ASA (American Society for Anesthesiologists) score ≥ IV and the inability

or unwillingness to fill out follow up questionnaires. For this separate analysis, patients were also excluded in case of conversion of the procedure type to a sleeve gastrectomy or a mini-gastric bypass.

Outcomes

Primary outcome measure of the current investigation was nutrient deficiency at one year postoperative. Secondary outcome measures were reoperations due to malabsorption. Data was collected on patient characteristics, vitamin usage, laboratory results at baseline and one year postoperative and reoperations due to malabsorption. Laboratory results of blood samples measuring Albumin, Calcium, Ferritin, Folic acid, Iron, Potassium, Magnesium, Sodium, Transferrin, Vitamin B12 and Vitamin D were collected preoperatively and one year postoperative. Nutrients were scored as deficient in case of a value below the lower bound of the reference value of the hospital's laboratory (Table 2).

Operation techniques

For both procedure types, a standard size of the pouch of 15-20 ml was used. For the RYGB, the biliopancreatic limb length was 60 cm and the alimentary limb length was 150 cm, resulting in a variable length of the common channel. For the VLRL-RYGB, the biliopancreatic limb length was also 60 cm, but the common limb was measured at 100 cm, resulting in a variable length of the alimentary limb. Total small bowel length was measured in all patients. The surgical techniques were described in more detail in the study protocol[3].

Diet and vitamin supplement usage

In the pre-operative phase, patients receive dietary advice for a healthy diet; low in refined sugars, rich in nutrients, a minimum intake of half a liter of dairy, and a distribution over six meals per day. Furthermore, a group lecture is held on the first postoperative day, in which patients are reminded of the content of the diet and importance of compliance to this diet. The dietary advice is the same for both procedure types. Patients are also counseled in the pre-operative phase on the importance of using multivitamins that are specifically tailored for the bariatric patient. Commonly used multivitamin brands in the Netherlands are FitForMe© and Elan©. These multivitamins contain increased levels of multiple vitamins and minerals, in particular iron, folic acid and vitamin B12[6]. As patients have to purchase these multivitamins themselves, they were free to choose the supplement of their preference. Patients were asked about the usage of (bariatric) multivitamins during the annual check-up at the outpatient clinic. Usage of vitamins was scored as 'none', 'standard multivitamin' or 'bariatric multivitamin'.

Statistical analysis

Patients that were scheduled for VLRL-RYGB but underwent a regular RYGB because of technical difficulties or perceived unsafety were analyzed as cross-overs to the RYGB group.

We chose to not exclude these patients, as their data remains valuable for the study aim: it is thought that the length of the common limb affects the malabsorption and possibly nutrient and vitamin deficiencies. Mann-Whitney U tests were used to compare differences in the absolute values of each nutrient between the groups at baseline and at one year postoperative. X^2 test was applied to compare multivitamin usage between groups. Multiple linear regression analyses were used to compare changes in nutrient levels between the two types of surgery, adjusting for baseline patient characteristics (sex, age, BMI, presence of type two diabetes (T2D), hypertension and/or hypercholesterolemia) and multivitamin usage. Unadjusted differences in deficiencies (yes/no) of each nutrient between groups were analyzed using X^2 tests. Unadjusted reoperation rates because of malabsorption were compared between the groups using X^2 tests. No adjustment for multiple testing was made. All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

RESULTS

Figure 1 illustrates the study profile. In total, 444 patients were included in the DUCATI study. 21 patients were excluded because of conversion of the procedure type to a sleeve gastrectomy or a minigastric bypass. Sixteen patients crossed over from the VLRL-RYGB group to the standard RYGB group because of technical difficulties during the procedure. Table 1 shows the baseline characteristics of the 423 included patients by procedure type. Table 2 shows the absolute baseline laboratory results on nutrients divided by type of procedure. Between the groups, median levels of nutrients were comparable for all but potassium (4.0 mmol/L for standard RYGB vs. 3.9 mmol/L for VLRL-RYGB, p=0.009).

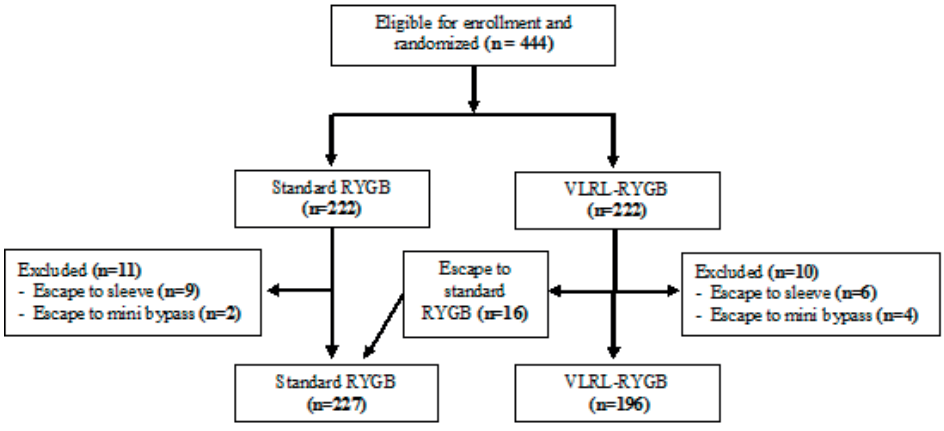


Figure 1: Study profile: patient selection and randomization

Table 1: Baseline characteristics (n=423)

	Standard RYGB (n=227)	VLRL-RYGB (n=196)
Female, n (%)	191 (84.1%)	169 (86.2%)
Age (years), mean ± sd	42.4 ± 10.6	42.1 ± 10.3
Baseline BMI (kg/m^2), mean ± sd	42.2 ± 4.2	42.5 ± 4.6
Procedures performed in hospital 1 (%)	89 (39.2%)	75 (38.3%)
Presence of hypertension, n (%)	86 (37.9%)	69 (35.2%)
Presence of T2D, n (%)	52 (22.9%)	32 (16.3%)
Presence of dyslipidemia, n (%)	93 (41.0%)	82 (41.8%)

Abbreviations: RYGB, roux-en-Y gastric bypass. VLRL-RYGB, very long roux limb roux-en-Y gastric bypass. sd, standard deviation. BMI, body mass index. T2D, type 2 diabetes.

Table 2: Baseline laboratory results on nutrients and vitamins (median ± IQR) with lower and upper bound of normal values

Nutrient parameter **(normal values)***	Standard RYGB		VLRL-RYGB		p
	Median	IQR	Median	IQR	
Albumin **(35-52 g/L)**	39	37-41	39	37-41	0.528
Calcium **(2.10-2.65 mmol/L)**	2.32	2.27-2.38	2.32	2.26-2.38	0.842
Ferritin **(22-275 ug/L)**	61	36-105	54	29-92	0.121
Folic acid **(> 5 nmol/L)**	12	9-17	12	9-16	0.668
Iron **(11.6-31.3 umol/L)**	13.0	10.0-16.9	12.9	9.3-17.0	0.485
Potassium **(3.5-5.1 mmol/L)**	4.0	3.8-4.2	3.9	3.7-4.1	0.009
Magnesium **(0.66-1.07 mmol/L)**	0.82	0.77-0.88	0.81	0.78-0.85	0.422
Sodium **(135-145 mmol/L)**	139	137-140	138	137-140	0.713
Transferrin **(50-90 g/L)**	61	3-71	63	3-75	0.240
Vitamin B12 **(130-700 pmol/L)**	205	157-275	210	154-268	0.997
Vitamin D **(50-250 nmol/L)**	39	27-55	42	29-55	0.616

*Between brackets the upper and lower bounds of the normal values
Abbreviations: RYGB, roux-en-Y gastric bypass. VLRL-RYGB, very long roux limb roux-en-Y gastric bypass. IQR, interquartile range.

Information on multivitamin usage at one year postoperative was missing for 27/227 (11.8%) patients in the standard RYGB group and 28/168 (16.7%) patients in the VLRL-RYGB group. At one year postoperative, 137/200 (68.5%) patients in the standard RYGB group versus 120/168 (71.4%) in the VLRL-RYGB group were documented to be using bariatric multivitamins. 61/200 (30.5%) in the standard RYGB group versus 47/168 (28.0%) in the VLRL-RYGB group used standard multivitamins. 2/200 (1.0%) in the standard RYGB group versus 1/168 (0.6%) in the VLRL-RYGB group used no vitamin supplements. There was no significant difference between the standard RYGB group and the VLRL-RYGB group at one year postoperative on usage of standard multivitamin (p=0.718) or bariatric multivitamin (p=0.657).

Figure 2 shows the laboratory results on nutrients and vitamins at one year postoperative by type of surgery. Patients undergoing VLRL-RYGB had significantly lower levels of albumin, potassium, transferrin and vitamin D compared to patients undergoing RYGB at one year postoperative.

Figure 3 shows the unadjusted percentages of patients with deficiencies of nutrients at one year postoperative by type of surgery. The differences in percentage of patients with nutrient deficiencies between the groups were significantly different for Iron (23.4 versus 35.6%, p=0.009), Potassium (7.4 versus 15.2%, p=0.030) and Vitamin D (22.7 versus 34.5%, p=0.011). Deficiencies that were equally present in both groups were in Ferritin (17.2 versus 18.2%, p=0.811) and Vitamin B12 (9.0 versus 9.9%, p=0.777).

Table 3 shows the results of the linear regression analysis of 227 patients undergoing RYGB and 196 patients undergoing VLRL-RYGB for nutrients pre- and one year postoperative, corrected for baseline patient characteristics (age, sex, BMI), presence of comorbidities (hypertension, T2D and dyslipidemia), hospital and type of multivitamin use. Patients undergoing VLRL-RYGB had slightly but significantly lower levels of calcium (beta -0.027, 95%CI -0.047; -0.007, p=0.008), iron (beta -2.285, 95%CI -3.669; -0.901, p=0.001) and vitamin D (beta -8.935, 95%CI -13.422; -4.448, p<0.001) at one year postoperative compared to patients undergoing standard RYGB. Also, patients undergoing VLRL-RYGB had significantly

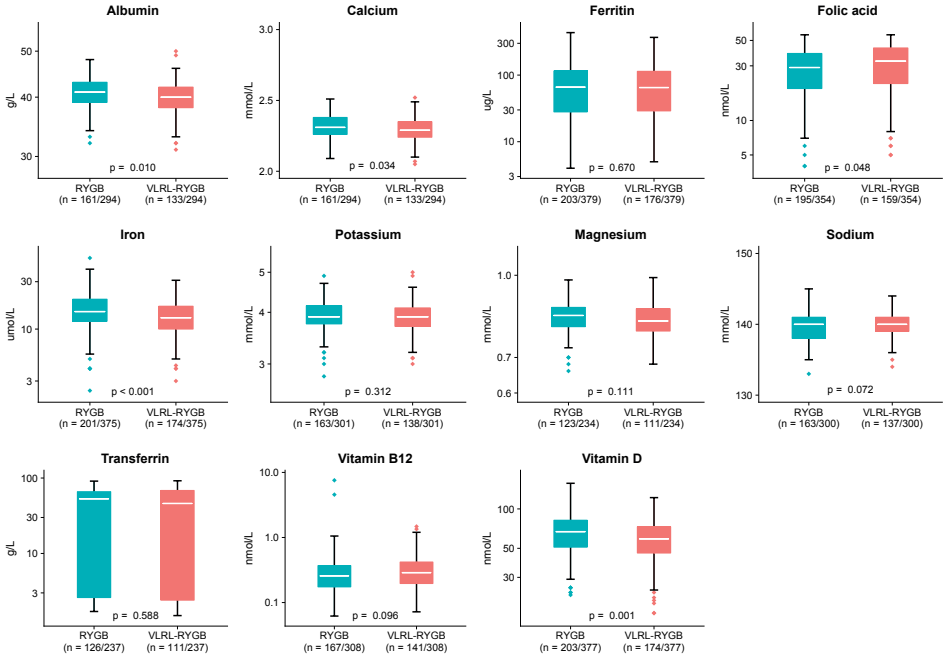


Figure 2: Laboratory results on nutrients and vitamins at 1 year postoperative in two groups.
* Data was missing for 10.4-44.0%, depending on the specific laboratory value.

higher levels of folic acid (beta 3.698, 95%CI 0.763; 6.632, p=0.014) and sodium (beta 0.507, 95%CI 0.045; 0.970, p=0.032) compared to patients undergoing standard RYGB.
Reoperation rates due to malabsorption were not significantly different between the RYGB group (2/227, 0.9%) and the VLRL-RYGB group (7/196, 3.6%) (p=0.088). All of these patients experienced severe diarrhea, which was the main reason for reoperation.

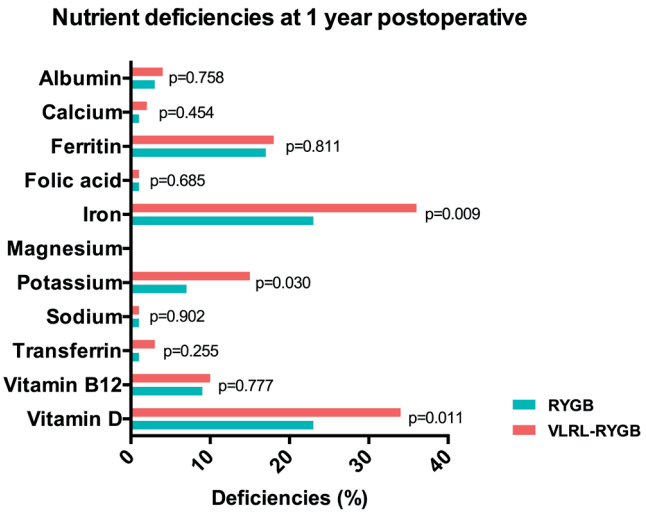


Figure 3: Deficiency rates in nutrients and vitamins at 1 year postoperative in two groups

Table 3: Linear regression analysis of nutrients and vitamins at 1 year postoperative on type of surgery, corrected for baseline value of nutrients and vitamins, patient characteristics, presence of comorbidities and multivitamin use

Nutrient	Estimate*	95% CI	p-value
Albumin	-0.687	-1.426 ; 0.052	0.068
Calcium	-0.027	-0.047 ; -0.007	0.008
Ferritin	6.676	-4.207 ; 17.560	0.228
Folic acid	3.698	0.763 ; 6.632	0.014
Iron	-2.285	-3.669 ; -0.901	0.001
Potassium	-0.003	-0.089 ; 0.082	0.942
Magnesium	-0.008	-0.022 ; 0.005	0.226
Sodium	0.507	0.045 ; 0.970	0.032
Transferrin	-0.606	-2.771 ; 1.559	0.581
Vitamin B12	-24.382	-184.782 ; 136.018	0.765
Vitamin D	-8.935	-13.422 ; -4.448	<0.001

* beta-coefficient VLRL-RYGB versus Standard RYGB
Abbreviations: CI, confidence interval. VLRL-RYGB, very long roux limb roux-en-Y gastric bypass. RYGB, roux-en-Y gastric bypass.

DISCUSSION

This study aimed to compare the presence of nutrient deficiencies in patients undergoing a standard RYGB versus a VLRL-RYGB. For both standard RYGB and VLRL-RYGB, most common deficiencies that occurred at one year postoperative were Ferritin, Iron, Potassium, Vitamin B12 and Vitamin D. Patients undergoing VLRL-RYGB had significantly lower levels of calcium, iron and vitamin D compared to patients undergoing standard RYGB at one year postoperative. However, levels of folic acid and sodium were significantly lower in patients undergoing standard RYGB compared to VLRL-RYGB. Although not significantly different, there were more reoperations because of malabsorption/severe diarrhea in the VLRL-RYGB group compared to the standard RYGB group.

Vitamin deficiencies were significantly more manifest in the VLRL-RYGB group. However, the absolute differences in mean nutrient and vitamin levels between the two procedure types were very small and all mean postoperative results remained within the normal range. Furthermore, the clinical relevance of these slightly lower levels of nutrients and vitamins is debatable. Albumin is considered to be associated with malnutrition[9] and median levels of albumin were well above the lower reference limit for both procedure types.

Previous studies suggest that the preoperative levels of micronutrients also influence the postoperative nutrient status[7, 10]. In our study, baseline laboratory values were comparable between the standard RYGB group and the VLRL-RYGB groups on all laboratory values but potassium. However, the absolute difference in median potassium value between the groups was very small. After correcting for the baseline laboratory results and for patient and other characteristics, significant differences were found in levels of calcium, iron and vitamin D. Once again, the clinical relevance of these statistically significant but very small absolute differences is questionable.

The most common nutrient deficiencies in our cohort are in line with the results from previous studies[4, 6, 7, 11-15]. Nutrient deficiencies after metabolic surgery can exist due to several reasons. First, pre-existing deficiencies can persist or worsen after surgery, such as iron deficiency caused by impaired expression of transporter proteins due to chronic inflammation. Pre-operatively, patients often have inappropriate eating behavior, their diet containing high energy density and few micronutrients[16]. Also, different procedures can cause specific alterations to digestion and absorption and result in small intestinal bacterial overgrowth (SIBO), which can cause pain, watery diarrhea, dyspepsia and weight loss. This causes malabsorption of thiamine, vitamin B12 and fat-soluble vitamins[17]. After surgery, prolonged nausea and vomiting, food intolerance, dietary and non-adherence to eating behavior, meal pattern and supplement recommendations can play a crucial role in the cause of nutrient deficiencies[17]. Patients in our study requiring reoperations all experienced severe diarrhea, most likely caused by the alterations to digestion and absorption after a standard RYGB or VLRL-RYGB.

It is thought that the length of the common limb affects the malabsorption and herewith the amount of weight loss[18-21], but possibly also leading to nutrient and vitamin deficiencies[22-25]. A systematic review by Orci et al. in 2011 identified a trend supporting that the construction of a longer Roux-limb was more effective in super obese patients in terms of weight loss, and no differences were found regarding nutritional outcomes between groups[26]. Mahawar et al. published a systematic review in 2016, stating that a range of 100-200 cm for combined length of biliopancreatic or alimentary limb gives optimum results with RYGB in most patients, with a low degree of macronutrient malabsorption[27]. The most recent systematic review on this topic was published by Gan et al. in 2018, which concluded that a standard alimentary limb length (130-150 cm) could be preferred since long alimentary limb length (170-250 cm) may result in greater nutritional deficiencies[28]. In our study, patients with a long limb length had slightly greater nutritional deficiencies as well. However, the differences in deficiencies between the two procedure types were very small and therefore, the clinical relevance of these slightly lower levels of nutrients and vitamins is debatable.

Partly in line with our findings, recent RCTs comparing different lengths of the biliopancreatic limb showed significant differences in deficiencies of vitamin B12, folic acid and vitamin A at one year postoperative[29, 30]. However, one of these studies describes usage of multivitamin that are not specific for bariatric patients and the other study does not report on multivitamin usage at all. The usage of multivitamin supplements specifically manufactured for bariatric patients has been proven to result in less deficiencies of vitamin B12, vitamin D, folic acid and ferritin[31]. Additional micronutrient supplementation in addition to two daily multivitamins is recommended in the American Society for Metabolic and Bariatric Surgery (ASMBS) Guidelines[32]. The results from our study were corrected for the different types of multivitamins and therefore have additional value to the previous publications on this topic.

Although a limitation of this study is the missing data on multivitamin usage (13.9%) and laboratory results (10.4-44.0%), the numbers were sufficient to form reliable conclusions, as other RCTs on this matter analyze similar or even smaller patient numbers. Future research should focus on a longer follow up period.

CONCLUSION

Patients undergoing VLRL-RYGB had significantly lower levels of calcium, iron and vitamin D compared to patients undergoing RYGB at one year postoperative, but higher levels of folic acid and sodium. Also, there was no difference in the reoperation rates because of malabsorption between the groups. Close monitoring on nutrient deficiencies should be performed in patients undergoing VLRL-RYGB and the usage of multivitamins specific for bariatric patients should be encouraged.

REFERENCES

1. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg. 2014;24(1):42-55.
2. Neudecker J, Sauerland S,, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc. 2002;16(7):1121-43.
3. Gadiot RP, Grotenhuis BA, Biter LU, et al. Study protocol of the DUCATI-study: a randomized controlled trial investigating the optimal common channel length in laparoscopic gastric bypass for morbid obese patients. BMC Obes. 2015;2:28.
4. Lupoli R, Lembo E, Saldalamacchia G, et al. Bariatric surgery and long-term nutritional issues. World J Diabetes. 2017;8(11):464-74.
5. Obinwanne KM, Fredrickson KA, Mathiason MA, et al. Incidence, treatment, and outcomes of iron deficiency after laparoscopic Roux-en-Y gastric bypass: a 10-year analysis. J Am Coll Surg. 2014;218(2):246-52.
6. Dogan K, Aarts EO, Koehestanie P, et al. Optimization of vitamin suppletion after Roux-en-Y gastric bypass surgery can lower postoperative deficiencies: a randomized controlled trial. Medicine (Baltimore). 2014;93(25):e169.
7. Parrott J, Frank L, Rabena R, et al. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. Surg Obes Relat Dis. 2017;13(5):727-41.
8. O'Kane M, Parretti HM, Hughes CA, et al. Guidelines for the follow-up of patients undergoing bariatric surgery. Clin Obes. 2016;6(3):210-24.
9. Ziegler O, Sirveaux MA, Brunaud L, et al. Medical follow up after bariatric surgery: nutritional and drug issues. General recommendations for the prevention and treatment of nutritional deficiencies. Diabetes Metab. 2009;35(6 Pt 2):544-57.
10. Mohapatra S, Gangadharan K, Pitchumoni CS. Malnutrition in obesity before and after bariatric surgery. Dis Mon. 2019.
11. Fieber JH, Sharoky CE, Wirtalla C, et al. The Malnourished Patient With Obesity: A Unique Paradox in Bariatric Surgery. J Surg Res. 2018;232:456-63.
12. Gesquiere I, Foulon V, Augustijns P, et al. Micronutrient intake, from diet and supplements, and association with status markers in pre- and post-RYGB patients. Clin Nutr. 2017;36(4):1175-81.
13. Kuin C, den Ouden F, Brandts H, et al. Treatment of Severe Protein Malnutrition After Bariatric Surgery. Obes Surg. 2019.
14. Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition. 2010;26(11-12):1031-7.
15. Dogan K, Homan J, Aarts EO, et al. Long-term nutritional status in patients following Roux-en-Y gastric bypass surgery. Clin Nutr. 2018;37(2):612-7.
16. Frame-Peterson LA, Megill RD, Carobrese S, et al. Nutrient Deficiencies Are Common Prior to Bariatric Surgery. Nutr Clin Pract. 2017;32(4):463-9.
17. Stein J, Stier C, Raab H, et al. Review article: The nutritional and pharmacological consequences of obesity surgery. Aliment Pharmacol Ther. 2014;40(6):582-609.
18. Brolin RE, LaMarca LB, Kenler HA, et al. Malabsorptive gastric bypass in patients with superobesity. J Gastrointest Surg. 2002;6(2):195-203; discussion 4-5.
19. Pinheiro JS, Schiavon CA, Pereira PB, et al. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. Surg Obes Relat Dis. 2008;4(4):521-5; discussion 6-7.
20. Scruggs DM, Cowan GS, Jr., Klesges L, et al. Weight Loss and Caloric Intake after Regular

and Extended Gastric Bypass. Obes Surg. 1993;3(3):233-8.
21. Sugerman HJ, Kellum JM, DeMaria EJ. Conversion of proximal to distal gastric bypass for failed gastric bypass for superobesity. J Gastrointest Surg. 1997;1(6):517-24; discussion 24-6.
22. Fox SR, e. The Gastric Bypass for Failed Bariatric Surgical Procedures. Obes Surg. 1996;6(2):145-50.
23. Kalfarentzos F, Skroubis G, et al. Biliopancreatic diversion with Roux-en-Y gastric bypass and long limbs: advances in surgical treatment for super-obesity. Obes Surg. 2011;21(12):1849-58.
24. Muller MK, Rader S, Wildi S, et al. Long-term follow-up of proximal versus distal laparoscopic gastric bypass for morbid obesity. Br J Surg. 2008;95(11):1375-9.
25. Thurnheer M, Bisang P, Ernst B, et al. A novel distal very long Roux-en Y gastric bypass (DVLRYGB) as a primary bariatric procedure--complication rates, weight loss, and nutritional/metabolic changes in the first 355 patients. Obes Surg. 2012;22(9):1427-36.
26. Orci L, Chilcott M, Huber O. Short versus long Roux-limb length in Roux-en-Y gastric bypass surgery for the treatment of morbid and super obesity: a systematic review of the literature. Obes Surg. 2011;21(6):797-804.
27. Mahawar KK, Kumar P, Parmar C, et al. Small Bowel Limb Lengths and Roux-en-Y Gastric Bypass: a Systematic Review. Obes Surg. 2016;26(3):660-71.
28. Gan J, Wang Y, Zhou X. Whether a Short or Long Alimentary Limb Influences Weight Loss in Gastric Bypass: a Systematic Review and Meta-Analysis. Obes Surg. 2018;28(11):3701-10.
29. Ruiz-Tovar J, Vorwald P, Gonzalez-Ramirez G, et al. Impact of Biliopancreatic Limb Length (70 cm vs 120 cm), with Constant 150 cm Alimentary Limb, on Long-Term Weight Loss, Remission of Comorbidities and Supplementation Needs After Roux-En-Y Gastric Bypass: a Prospective Randomized Clinical Trial. Obes Surg. 2019.
30. Shah K, Nergard BJ, et al. Limb Length in Gastric Bypass in Super-Obese Patients-Importance of Length of Total Alimentary Small Bowel Tract. Obes Surg. 2019;29(7):2012-21.
31. Schijns W, Schuurman LT, Melse-Boonstra A, et al. Do specialized bariatric multivitamins lower deficiencies after RYGB? Surg Obes Relat Dis. 2018;14(7):1005-12.
32. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring). 2013;21 Suppl 1:S1-27.

10 Sleeve Bypass Trial: Sweet eating and weight loss

Accepted: Obesity Surgery, 2020

ABSTRACT

Introduction

Laparoscopic Roux-en-Y gastric bypass(LRYGB) and laparoscopic sleeve gastrectomy(LSG) have shown different weight loss results. These differences might be partly due to dumping after LRYGB, forcing sweet-eaters to switch to a healthy diet. The Dutch Sweet Eating Questionnaire(DSEQ) is validated to measure sweet-eating. This study aims to investigate if sweet-eating measured with the DSEQ influences weight loss.

Methods

In this multicenter randomized controlled trial, patients were included between 2013-2017 in two Dutch high-volume hospitals, and randomized with a 1:1 ratio between LRYGB and LSG. Primary outcome measure was weight loss. Secondary outcome measure was sweet-eating behavior, measured with the DSEQ. Data was collected at baseline, 1-year and 2-years postoperatively.

Results

Data was analyzed of 623 patients who underwent LRYGB(n=308,49.4%) or LSG(n=315,50.6%). Follow-up rates at 2-years postoperative were 67.1% for weight and 35.3% for DSEQ. At 2-years postoperative, mean BMI was significantly higher after LSG than LRYGB(respectively 30.88 versus 28.87kg/m^2, $p<0.001$), and the percentage of sweet-eaters was significantly higher after LSG than LRYGB(respectively 8.6% versus 2.6%, $p=0.049$). None of the preoperative sweet-eaters were sweet-eaters 2-years after LRYGB(0.0%), versus 11.8% 2-years after LSG. No correlation was found between postoperative sweet-eating behavior and %EBMIL.

Conclusion

No significant correlation was found between preoperative- or postoperative sweet-eating measured with the DSEQ and weight loss. The decision-making for the procedure type is more complex than weight loss and dietary habits, and should also involve quality of life and presence of comorbidities. These factors should be addressed in future research, along with longer term results.

INTRODUCTION

Metabolic surgery is the only long-term solution for morbid obesity. Different types of metabolic procedures have shown different results in terms of weight loss over the years, but the laparoscopic Roux-en-Y gastric bypass (LRYGB) is regarded as the gold standard in bariatric surgery[1]. However, the laparoscopic sleeve gastrectomy (LSG) has been increasing in popularity due to the advantages of the procedure, such as the remained intact anatomy of the gastro-intestinal tract, shorter operative time and seemingly similar weight loss results[2-6].
The determination of the indication for bariatric surgery and the decision-making for the type of surgery takes place at the outpatient clinic in the preoperative phase. The official International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) guidelines for metabolic surgery state that there is insufficient evidence-based data to suggest how to assign a patient to a specific procedure[7]. Factors that can influence the decision-making of type of surgery can be for example the body mass index (BMI), sex, age, the presence of comorbidities such as type 2 diabetes (T2D) or dyslipidemia, or the presence of gastroesophageal reflux disease (GERD), known bowel complaints, or inflammatory bowel disease. Previous studies have suggested that sweet-eating can influence weight loss after bariatric surgery, and that sweet-eaters should therefore undergo LRYGB instead of LSG[8, 9].
Sweet-eating after a LRYGB can lead to dumping: a phenomenon that causes patients to experience abdominal symptoms and/or autonomic responses after ingestion of carbohydrates[10]. This results in hyperglycemia and subsequently in a reactive hypoglycemia, causing symptoms such as dizziness, extreme hunger, confusion, sweating, and blurred vision[11]. It is hypothesized that the positive weight loss results from a LRYGB are associated with dumping, as dumping forces the patient to avoid carbohydrates and switch to a healthy diet[12].
To measure sweet-eating behavior, the Dutch Sweet Eating Questionnaire (DSEQ) was constructed in 2011, defining sweet-eating as an eating behavior in which at least 50% of daily consumed carbohydrates consist of simple carbohydrates and which can be triggered by emotional factors (i.e. stress)[13]. The DSEQ was proven a valid and reliable questionnaire to measure sweet-eating. It is uncertain if patients with sweet-eating behavior benefit more from a LRYGB or a LSG in terms of long-term weight loss. This study aims to investigate the predictive value of the preoperative DSEQ for determining the optimal bariatric procedure (LRYGB or SLG) to reach long-term weight loss. Our hypothesis is twofold: Firstly, that patients who were sweet-eaters preoperatively, become non-sweet-eaters when undergoing a LRYGB due to the dumping syndrome. Secondly, we hypothesize that weight loss after a LRYGB is better due to this change in sweet-eating habits.

METHODS

Design and data collection

The current study was performed as a part of the Sleeve Bypass trial, a multicenter randomized controlled trial comparing LRYGB with LSG. In the Sleeve Bypass trial, 637 patients were included between 2013-2017 in high-volume hospitals in the Netherlands. These patients were randomized with a 1:1 ratio between two procedure types: LRYGB versus LSG. At randomization, patients were stratified for sex, presence of T2D and BMI >50 kg/m^2. All patients found suitable for bariatric surgery according to the IFSO guidelines were invited to participate in the trial. Exclusion criteria were no informed consent, symptomatic GERD with proton pomp inhibitor use, a diagnosed hiatal hernia with symptoms, prior bariatric surgery, prior major abdominal surgery (e.g. surgery which might jeopardize the technical feasibility of LSG or LRYGB) and the inability of reading or understanding the questionnaires. Power analysis for the sleeve bypass trial was performed based on the null hypothesis of the mean %EBMIL (LSG) was equal to the mean %EBMIL (LRYGB). To be able to reject the null hypothesis, at least 2x294 analyzable patients had to be included. The power analysis is more thoroughly described in the trial protocol[14]. The study protocol was approved by the institutional review board (IRB) and the regional Medical Research Ethics Committee TWOR, Rotterdam, the Netherlands (protocol number 2011-48).

Outcomes

Primary outcome measure was the excess weight loss at one year and two years postoperatively. The secondary outcome measure was intake of simple carbohydrates at baseline, one year and two years postoperatively, in order to separate the sweet-eaters from the non-sweet-eaters. Data was collected on patient characteristics, DSEQ results and complications.

Surgical intervention

All patients followed the Enhanced Recovery After Bariatric Surgery protocol (ERABS)[15]. The LSG is performed as described by Gadiot et al.: after full mobilization of the greater curvature and the posterior stomach, the sleeve is stapled and removed from the abdomen[4]. The LRYGB is performed with the antecolic linear technique, with a measured biliopancreatic limb of 60 cm and an alimentary limb of 150 cm. The mesenteric defects are closed. The operation techniques were described in more detail in the study protocol[14].

Questionnaires

The intake of simple carbohydrates was scored using the DSEQ, which defines sweet-eating as an eating behavior in which at least 50% of daily consumed carbohydrates consist of simple carbohydrates and which can be triggered by emotional factors. Patients were asked to fill out the DSEQ four times: once pre-operatively, and postoperatively after eight weeks,

one year and 2 years. Patients had the opportunity to fill in the questionnaire while waiting for their periodical appointments at the outpatient clinic on computers provided by the hospital. In other cases, printed questionnaires were sent to the patients' home address to obtain as many data as possible. To avoid information bias, the questionnaires were always completed by the patient in the absence of a doctor or nurse. In addition, analysis of this data was not performed until now.

Weight loss

Weight loss outcomes were reported as recommended by Brethauer et al.[16]: 1) Mean initial BMI, 2) change in BMI (delta-BMI), 3) Percent of total weight loss (%TWL), and 4) Percent excess BMI loss (%EBMIL).

Statistical analysis

Patients that were scheduled for LRYGB but underwent a LSG – or vice versa – because of technical difficulties or perceived unsafety were analyzed as cross-overs to the other group. The statistical analysis was performed according to the as-treated principle. For comparisons between groups, Chi square tests were used for categorical variables and one-way ANOVA for continuous variables. Multivariable linear regression analysis was performed for delta-BMI after one year and after two years, corrected for type of surgery, sweet-eating behavior, patient characteristics (sex, age and BMI at baseline) and presence of T2D at baseline. All analyses were performed using SPSS (PASW) 25 software (SPSS Inc., Chicago, Illinois, USA). Results were evaluated at a significance threshold of $p<0.05$ (two-sided).

RESULTS

Between 2013 and 2017, 637 patients were randomized between the two groups. After excluding 14 patients because of consent withdrawals and taking into account crossing over for surgical reasons, 308 (49.4%) patients underwent a LRYGB and 315 (50.6%) patients underwent a LSG (Figure 1). Table 1 shows the baseline patient characteristics for the two types of surgery. The presence of sweet-eating behavior at baseline was similar in both groups: 19.0% in the LRYGB group versus 20.4% in the LSG group (p=0.683).

Figure 2 shows the mean postoperative BMI, divided by type of surgery. Mean BMI was similar at baseline (p=0.454), after eight weeks (p=0.498) and after one year (p=0.968). The mean BMI at two years postoperative was significantly higher in patients who underwent a LSG as compared to patients who underwent a LRYGB (30.88 vs 28.87 kg/m^2, $p<0.001$). Data on weight were available for 99.5% at baseline, 91.1% at one year, and 67.1% at two years postoperative.

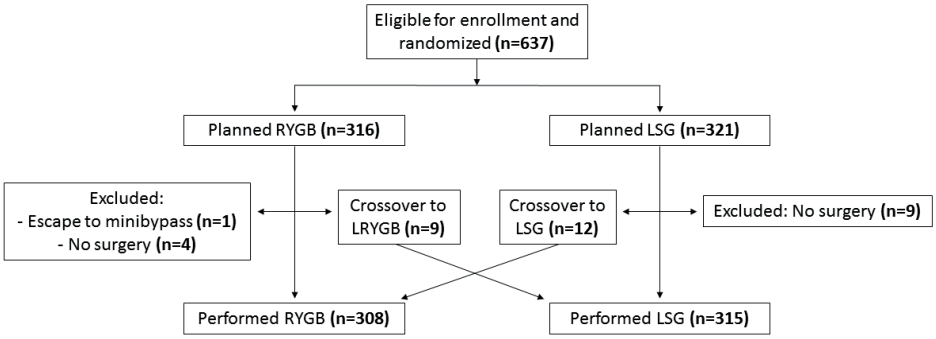


Figure 1: Study profile: patient selection and randomization

Table 1a: Baseline characteristics divided by type of surgery (n=623)

	LRYGB (n=308)	LSG (n=315)	Sig.
Female, n (%)	256 (83.1%)	252 (80.0%)	0.316
Age (years), mean ± sd	43 ± 11	43 ± 10	0.954
BMI (kg/m^2), mean ± sd	43.4 ± 4.7	43.6 ± 4.7	0.454
Presence of diabetes, n (%)	57 (18.5%)	64 (20.4%)	0.555
Presence of sweet-eating behavior, n (%)*	52/274 (19.0%)	57/280 (20.4%)	0.683

**Missing data on sweet-eating behavior for 34/308 (11.0%) in LRYGB group and for 35/315 (11.1%) in LSG group.*

Table 1b: Baseline characteristics divided by sweet-eating behavior (n=554)

	Sweet-eater (n=109)	Non-sweet-eater (n=445)	Sig.
Female, n (%)	96 (88.1%)	358 (80.4%)	0.064
Age (years), mean ± sd	42 ± 10	43 ± 10	0.254
BMI (kg/m^2), mean ± sd	43.3 ± 4.7	43.6 ± 4.7	0.529
Presence of diabetes, n (%)	15 (13.9%)	87 (19.6%)	0.174

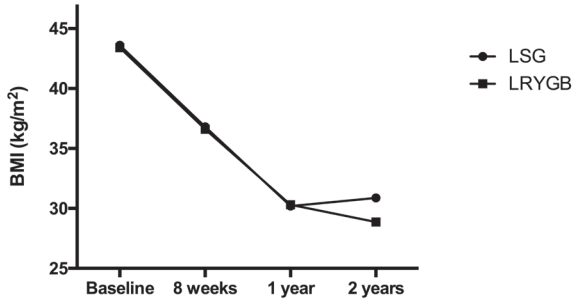


Figure 2: Percentage of sweet-eaters of laparoscopic roux-en-Y gastric by-pass (LRYGB) versus laparoscopic sleeve gastrectomy (LSG) after eight weeks, one year and two years post-operative

Figure 3 illustrates the percentage of sweet-eaters over the years, divided by type of surgery. At two years postoperative, the percentage of sweet-eaters was significantly larger in the LSG group as compared to the LRYGB group (respectively 8.6% versus 2.6%, p=0.049). Table 2 shows the percentage of preoperative sweet-eaters who are still sweet-eaters after one or two years postoperative. We found that there was a significant change in sweet-eating behavior between baseline and one year postoperative for both LRYGB (p=0.004) and LSG (p=0.006). After two years postoperative, these differences were no longer present. We also found that most of the postoperative sweet-eaters were already sweet-eaters preoperatively.

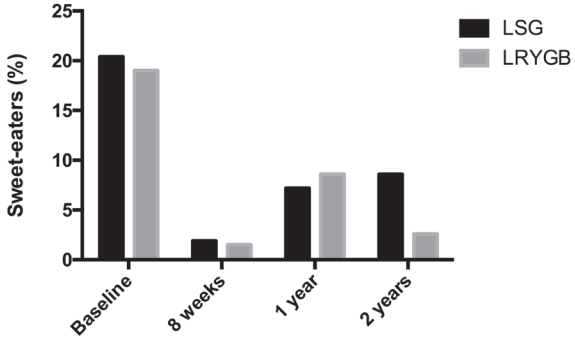


Figure 3: Body mass index (BMI) (mean ± sd) of laparoscopic roux-en-Y gastric bypass (LRYGB) versus laparoscopic sleeve gastrectomy (LSG) after eight weeks, one year and two years postoperative

Table 2: Sweet-eating behavior (n, %) over the years for LRYGB and LSG

LRYGB	**Sweet-eater at baseline**	**Non-sweet-eater at baseline**	**Sig.**
Sweet-eater at 1 year postop.	7 (17.9%)	7 (4.6%)	0.004
Non-sweet-eater at 1 year postop.	32 (82.1%)	146 (95.4%)	
Sweet-eater at 2 years postop.	0 (0.0%)	2 (2.4%)	0.481
Non-sweet-eater at 2 years postop.	20 (100%)	80 (97.6%)	

LSG	**Sweet-eater at baseline**	**Non-sweet-eater at baseline**	**Sig.**
Sweet-eater at 1 year postop.	6 (19.4%)	8 (5.1%)	0.006
Non-sweet-eater at 1 year postop.	25 (80.6%)	149 (94.9%)	
Sweet-eater at 2 years postop.	2 (11.8%)	6 (7.4%)	0.551
Non-sweet-eater at 2 years postop.	15 (88.2%)	75 (92.6%)	

When isolating the preoperative non-sweet-eaters, no significant difference was found in %TWL of patients who became sweet-eaters versus those who remained non-sweet-eaters at one year postoperatively (p=0.598) or two years postoperatively (p=0.326). Splitting these results for type of surgery, similar results were found after one and two years postoperative for LRYGB (respectively p=0.619 and p=0.412) and for LSG (respectively p=0.802 and p=0.302). An important aspect to take into account is the decreasing willingness of patients to complete the DSEQ over the years, starting at 88.5% preoperative, and decreasing to 83.4%

at eight weeks postoperative, 66.6% at one year postoperative and only 35.3% at two years postoperative.

Table 3 shows an overview of the weight loss expressed in BMI, delta-BMI, %TWL and %EBMIL, divided by type of surgery and preoperative sweet-eating behavior. For preoperative non-sweet-eaters, the BMI at two years postoperative was lower in the LRYGB group as compared to the LSG group (respectively 28.94 kg/m^2 versus 31.51 kg/m^2, p<0.001). For preoperative sweet-eaters, BMI at two years postoperative was similar for both types of procedure (29.68 kg/m^2 for LSG versus 28.68 kg/m^2 for LRYGB, p=0.352), although delta-BMI and %TWL at two years postoperative were significantly higher in the LRYGB group. For non-sweet-eaters, significant differences were found in BMI, delta-BMI, %TWL and %EBMIL at two years postoperative between the two procedure types, in favor of the LRYGB. Furthermore, sweet-eaters who underwent a LSG had a significantly lower BMI at one year postoperative (p=0.020), and significantly more %EBMIL at one year postoperative (p=0.007), as compared to sweet-eaters who underwent a LRYGB. In addition, Figure 4 illustrates how the %EBMIL at one year and two years postoperative relates for preoperative sweet-eaters (SE) versus non-sweet eaters (NSE) and LRYGB versus LSG.

Table 3: Weight loss expressed in BMI, delta-BMI, %TWL and %EBMIL, divided by preoperative sweet-eating behavior.

		Non-sweet-eater preop.		Sweet-eater preop.		Sig.
		Mean	*SD*	*Mean*	*SD*	
BMI preop.	*LSG*	43.91	4.76	42.63	4.34	0.066
	LRYGB	43.25	4.70	43.96	4.99	0.337
BMI 1 year postop.	*LSG*	30.76	4.83	29.02	4.66	**0.020**
	LRYGB	30.58	17.96	29.44	3.98	0.668
BMI 2 years postop.	*LSG*	31.51**	5.63	29.68	5.09	0.066
	LRYGB	28.94**	4.49	28.68	3.98	0.753
Delta-BMI 1 year postop.	*LSG*	13.06	4.07	13.66	3.29	0.325
	LRYGB	12.50	17.73	14.47	4.13	0.451
Delta-BMI 2 years postop.	*LSG*	12.41**	4.58	12.82*	3.80	0.603
	LRYGB	14.29**	4.30	15.48*	4.31	0.140
%TWL 1 year postop.	*LSG*	29.72	8.29	32.11	7.63	0.060
	LRYGB	29.02	39.77	32.71	7.78	0.527
%TWL 2 years postop.	*LSG*	28.26**	9.64	30.27*	8.88	0.239
	LRYGB	32.90**	8.47	34.80*	7.69	0.220
%EBMIL 1 year postop.	*LSG*	71.38	21.14	80.48	23.77	**0.007**
	LRYGB	72.14	92.09	78.01	19.45	0.665
%EBMIL 2 years postop.	*LSG*	68.07**	24.90	76.47	26.59	0.065
	LRYGB	80.68**	22.23	82.57	19.02	0.638

An asterisk indicates a significant difference between the two types of surgery; * <0.05, ** <0.001

To determine if postoperative sweet-eating behavior can explain the differences in %EBMIL between the types of surgery and sweet-eating behavior, a multivariable analysis was performed, correcting for type of surgery and sweet-eating behavior (Table 4). Analyzing the %EBMIL after one year, no significant effect was found for sweet-eating behavior at baseline (p=0.535), sweet-eating behavior after one year (p=0.852) or type of surgery (p=0.801). Analyzing the %EBMIL after two years, patients who underwent a LRYGB had significantly more %EBMIL than patients who underwent a LSG (p<0.001), and no significant effect was found on %EBMIL for sweet-eating behavior at baseline (p=0.867), sweet-eating behavior after one year (p=0.526), or after two years (p=0.554). In other words, patients who underwent a LRYGB had more weight loss, but we found no correlation between the weight loss and the DSEQ score.

Table 4: Multivariable linear regression analysis for %EBMIL after one year and after two years on sweet-eating behavior and type of surgery, corrected for patient characteristics (sex, age and BMI at baseline) and presence of T2D

%EBMIL – one year postop.	**Estimate**	**95% CI**	**Sig.**
Type of surgery: LRYGB vs LSG	-1.548	-13.632 ; 10.536	0.801
Sweet-eater preop.: yes vs no	4.726	-10.249 ; 19.701	0.535
Sweet-eater at one year postop.: yes vs no	-5.994	-69.003 ; 57.014	0.852

%EBMIL – two years postop.	**Estimate**	**95% CI**	**Sig.**
Type of surgery: LRYGB vs LSG	15.081	9.620 ; 20.542	<0.001
Sweet-eater preop.: yes vs no	0.594	-6.400 ; 7.588	0.867
Sweet-eater at one year postop.: yes vs no	9.679	-20.342 ; 39.700	0.526
Sweet-eater at two years postop.: yes vs no	3.284	-7.625 ; 14.193	0.554

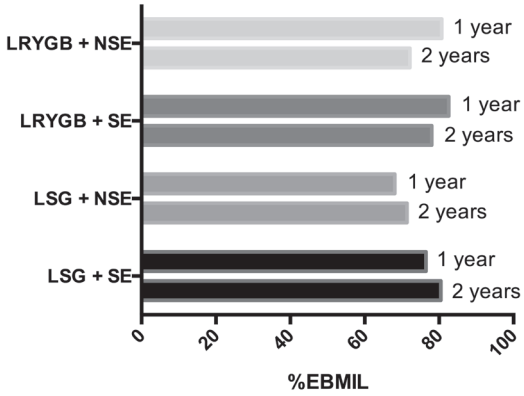


Figure 4: Percentage excess body mass index loss (%EBMIL) at one year and two years postoperative for sweet-eaters versus non-sweet eaters and laparoscopic roux-en-Y gastric bypass (LRYGB) versus laparoscopic sleeve gastrectomy (LSG)

DISCUSSION

The aim of this study was to investigate the predictive value of the preoperative DSEQ for determining the optimal bariatric procedure (LRYGB or SLG) to reach long-term weight loss in each individual patient. The results of this study suggest that sweet-eating behavior according to the DSEQ in the preoperative phase has no effect on weight loss after a bariatric procedure. We found that patients who underwent a LRYGB had significantly better weight loss results as compared to patients who underwent a LSG two years after the procedure. Our results also suggest that patients who underwent a LSG tend to relapse in sweet-eating behavior more often than patients who underwent a LRYGB at two years postoperative.

Several studies have investigated the correlation between sweet-eating behavior and weight loss after a bariatric or metabolic procedure, mostly after gastric banding. Some studies found a strong correlation[17, 18], others found no correlation between sweet-eating behavior and postoperative weight reduction[19-21]. In the study of Angrisani et al. there was a correlation between sweet-eating behavior and weight loss; failure rate was higher in women ($p<0.01$) and in sweet-eaters ($p<0.05$)[17]. Busetto et al. stated that sweet-eaters had a lower relative risk of failure (%EWL <20%) after gastric banding, and that the relationship between sweet-eating and failure rate disappeared after adjusting for gender[18]. This outcome was explained by the fact that the prevalence of sweet-eating behavior was higher in women than in men. In our cohort, no difference in weight loss was observed between sweet-eaters and non-sweet-eaters at baseline. Furthermore, the percentage of women was not significantly different in the sweet-eaters group as compared with the non-sweet-eaters group at baseline.

In 2010, the sleeve gastrectomy was described as a safe, effective and by the patients well accepted bariatric procedure, but associated with weight regain and quite often with reflux symptoms in the long-term follow-up[22]. Ever since, the working mechanisms of weight loss after a sleeve gastrectomy have become clearer: as the ghrelin levels lower, the hunger reduces, while the normal gastro-intestinal tract is preserved[4]. Nowadays, the LSG is considered to be equally effective as the LRYGB in terms of weight loss[2, 7]. The amount of weight loss and the preservation of weight loss, however, can be influenced by multiple factors, and the eating pattern seems to be a very important one. Kafri et al. found that patients were able to maintain a healthy diet beyond the first year after laparoscopic sleeve gastrectomy[12]. Sioka et al. found that the postoperative eating pattern seems to have impact on excessive weight loss[23]. Ammon et al. reported that LSG reduced the preference for calorically dense foods high in fat, sugar and complex carbohydrate, changes that may contribute to the weight loss[24]. In the current study, the percentage of sweet-eaters was similar between the two types of surgery, up until one year postoperative. At two years postoperative, the percentage of sweet-eaters was significantly larger in the LSG group as compared to the LRYGB. Due to the high rates of lost-to-follow up on sweet-eating behavior at two years postoperative, the

patient numbers were too small to conclude that the higher percentage of sweet-eaters caused the difference in weight loss.

One theory on type of surgery and sweet-eating suggests that sweet-eaters will benefit more from a LRYGB than from a LSG, because of the dumping phenomenon that occurs after sweet-eating in patients with a LRYGB. The dumping phenomenon would discourage patients to eat carbohydrates and is mainly present in the early postoperative phase. Therefore, it was interesting to find that postoperative sweet-eating in patients who underwent a LRYGB was relatively high at one year postoperative, and later – after two years – decreased. This finding leads us to believe that dumping might not influence sweet-eating behavior as much as we thought.

With respect to dumping, it is important to take into account the difference between early and late dumping. Early dumping occurs within one hour after carbohydrate ingestion and causes gastrointestinal and vasomotor symptoms due to a release of gastrointestinal hormones. Late dumping occurs between 1 and 3 hours and is caused by hypoglycemia due to an exaggerated insulin release, resulting in hypoglycemia[25].

A study by Laurenius et al. describing early dumping found that although the symptoms are unpleasant, patients in their cohort considered the dumping syndrome as a positive protection against over-consumption[26]. Varma et al. focused on late dumping (post-bariatric hypoglycemia) and found evidence that the presence of post-bariatric surgery hypoglycemia symptoms was associated with weight regain[27]. No studies were found on the correlation between sweet-eating behavior and early and/or late dumping.

Therefore, the presence of dumping may actually impede weight loss after LRYGB. Unfortunately, we have no data on dumping episodes in our patient population. It would be interesting to collect data on early and late dumping episodes in the future. The influencing factors for sweet-eating behavior after surgery are still uncertain and require further investigation.

Official guidelines on the preoperative decision-making for the type of bariatric or metabolic procedure have not yet been conducted. In the participating hospitals, the following items are taken into account in order to determine which type of surgery is preferred: the presence of GERD; the presence of pre-existent bowel complaints such as diarrhea or constipation; previous surgery of the intestines; the presence of T2D; and, the preference of the patient. The results of the current study suggest that the LRYGB seems the superior choice for long-term weight loss. However, in patients who have bowel complaints or a medical history of intestinal surgery, a LRYGB would not be the procedure of preference. The results of this study can support in the expectation management of this patient population and might be used as a motivation for these patients to fully dedicate themselves to the prescribed diet, especially in the long term.

An important limitation of this study is the high lost-to-follow-up rate on sweet-eating behavior, especially at two years postoperative (64.7%). Filling in the questionnaires was not mandatory for patients visiting the outpatient clinic. Patients have stated that their eating

behavior had not changed, and that therefore they did not want to fill in the questionnaire again. Unfortunately, we could not use this statement to analyze postoperative sweet-eating behavior. Data at two years postoperative on weight loss results was missing in a smaller percentage (32.9%), which is comparable to other follow-up rates in metabolic surgery. All available data on weight loss results were analyzed to determine the correlation with baseline sweet-eating behavior. Follow up has always been challenging in bariatric surgery and remains an item that requires attention, as this will provide important data to optimize bariatric surgery worldwide. Future research should therefore focus on adequate follow up on eating behavior and weight loss.

CONCLUSION

This study suggests that the preoperative sweet-eating behavior does not influence postoperative weight loss. Therefore, we conclude that sweet-eating measured with the DSEQ is not sufficient to select the optimal procedure type to reach long-term weight loss after bariatric surgery. No correlation was found between postoperative sweet-eating and weight loss. This finding suggests that the suspected dietary change due to dumping in LRYGB is not the reason for the higher %TWL after LRYGB as compared to LSG. The decision-making for the type of procedure is more complex than weight loss and dietary habits, and should also involve quality of life and the presence of comorbidities. These factors should be addressed in future research, along with longer term results.

REFERENCES

1. Buchwald, H. and D.M. Oien, Metabolic/bariatric surgery worldwide 2011. Obes Surg, 2013. 23(4): p. 427-36.
2. Colquitt, J.L., et al., Surgery for weight loss in adults. Cochrane Database Syst Rev, 2014(8): p. Cd003641.
3. Zellmer, J.D., et al., Is laparoscopic sleeve gastrectomy a lower risk bariatric procedure compared with laparoscopic Roux-en-Y gastric bypass? A meta-analysis. Am J Surg, 2014. 208(6): p. 903-10; discussion 909-10.
4. Gadiot, R.P., et al., Laparoscopic sleeve gastrectomy with an extensive posterior mobilization: technique and preliminary results. Obes Surg, 2012. 22(2): p. 320-9.
5. Peterli, R., et al., Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. Jama, 2018. 319(3): p. 255-265.
6. Poelemeijer, Y.Q.M., et al., Gastric Bypass Versus Sleeve Gastrectomy: Patient Selection and Short-term Outcome of 47,101 Primary Operations from the Swedish, Norwegian, and Dutch National Quality Registries. Ann Surg, 2019.
7. Fried, M., et al., Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg, 2014. 24(1): p. 42-55.
8. Sugerman, H.J., J.V. Starkey, and R. Birkenhauer, A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. Ann Surg, 1987. 205(6): p. 613-24.
9. Wilson-Perez, H.E., et al., The effect of vertical sleeve gastrectomy on food choice in rats. Int J Obes (Lond), 2013. 37(2): p. 288-95.
10. Wijma, R.B., et al., Prevalence and pathophysiology of early dumping in patients after primary Roux-en-Y gastric bypass during a mixed-meal tolerance test. Surg Obes Relat Dis, 2019. 15(1): p. 73-81.
11. Ahmad, A., et al., Prevalence of Dumping Syndrome After Laparoscopic Sleeve Gastrectomy and Comparison with Laparoscopic Roux-en-Y Gastric Bypass. Obes Surg, 2019. 29(5): p. 1506-1513.
12. Kafri, N., et al., Health behavior, food tolerance, and satisfaction after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis, 2011. 7(1): p. 82-8.
13. van den Heuvel, M., et al., Sweet eating: a definition and the development of the Dutch Sweet Eating Questionnaire. Obes Surg, 2011. 21(6): p. 714-21.
14. Biter, L.U., et al., The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC Obes, 2015. 2: p. 30.
15. Mannaerts, G.H., et al., Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obes Surg, 2016. 26(2): p. 303-12.
16. Brethauer, S.A., et al., Standardized outcomes reporting in metabolic and bariatric surgery. Surg Obes Relat Dis, 2015. 11(3): p. 489-506.
17. Angrisani, L., et al., The Italian Group for LAP-BAND: predictive value of initial body mass index for weight loss after 5 years of follow-up. Surg Endosc, 2004. 18(10): p. 1524-7.
18. Busetto, L., et al., Outcome predictors in morbidly obese recipients of an adjustable gastric band. Obes Surg, 2002. 12(1): p. 83-92.
19. Hudson, S.M., J.B. Dixon, and P.E. O'Brien, Sweet eating is not a predictor of outcome after Lap-Band placement. Can we finally bury the myth? Obes Surg, 2002. 12(6): p. 789-94.
20. Korenkov, M., et al., Laparoscopic gastric banding as a universal method for the treat-

ment of patients with morbid obesity. Obes Surg, 2004. 14(8): p. 1123-7.
21. Livhits, M., et al., Preoperative predictors of weight loss following bariatric surgery: systematic review. Obes Surg, 2012. 22(1): p. 70-89.
22. Himpens, J., J. Dobbeleir, and G. Peeters, Long-term results of laparoscopic sleeve gastrectomy for obesity. Ann Surg, 2010. 252(2): p. 319-24.
23. Sioka, E., et al., Influence of eating profile on the outcome of laparoscopic sleeve gastrectomy. Obes Surg, 2013. 23(4): p. 501-8.
24. Ammon, B.S., et al., Short-term pilot study of the effect of sleeve gastrectomy on food preference. Obes Surg, 2015. 25(6): p. 1094-7.
25. Emous, M., et al., The short- to mid-term symptom prevalence of dumping syndrome after primary gastric-bypass surgery and its impact on health-related quality of life. Surg Obes Relat Dis, 2017. 13(9): p. 1489-1500.
26. Laurenius, A. and M. Engstrom, Early dumping syndrome is not a complication but a desirable feature of Roux-en-Y gastric bypass surgery. Clin Obes, 2016. 6(5): p. 332-40.
27. Varma, S., et al., Weight regain in patients with symptoms of post-bariatric surgery hypoglycemia. Surg Obes Relat Dis, 2017. 13(10): p. 1728-1734.

PART III

General discussion, summary, appendices

11 General discussion and future perspectives

DISCUSSION

Fast-track protocols are designed to aid in the optimization of surgical pathways, focusing on three key points: safety, patient-friendliness and efficiency. Many study groups have already described the positive results of implementation of an Enhanced Recovery After Bariatric Surgery (ERABS) program in their hospitals. The general conclusion was that implementation of ERABS protocols had positive effects on patient outcome(1-6).
Due to the high amount of medical research in the area of metabolic surgery, many suggestions have been made to revise and improve the ERABS protocol. Also, as our hospital is a high-volume center for metabolic surgery, our experience leads us to new research questions. The answers to these questions may lead to changes in the ERABS protocol, which could result in further optimization of patient outcome.
This thesis focuses on metabolic surgery in a fast-track setting. The first aim was to evaluate and change the protocols used in metabolic surgery, and herewith improve the surgical treatment of morbid obesity. This was described in Part I. The second aim of this thesis was to evaluate the outcomes after metabolic surgery in a fast-track setting, as described in Part II.

PART I

Before making new changes to the protocol, we aimed to analyze the effects of the protocol changes that had been made in the previous years. Chapter 2 reports the morbidity-related outcomes of patients undergoing bariatric surgery before and after revising the protocol in 2014. In this revised protocol, both the physical therapist and the dietician would visit each patient on the morning after the procedure and before discharge, to prepare them optimally for their recovery at home. After these changes, minor complication rates decreased significantly, most importantly resulting in less readmissions and unplanned hospital revisits. Interestingly, the major complication rates remained stable. An important question that arose was whether these changes were really caused by the revisions in the ERABS protocol, or if they were mainly influenced by the experience of the surgeon and the anesthesiology team. Those patients who did revisit the emergency ward or outpatient clinic, more frequently did have a complication that required treatment. Herewith, we improved the hospital revisit rates that had initially increased after the primary implementation of the ERABS protocol in our hospital(5).
In a teaching hospital, the procedures are performed by metabolic surgeons or by residents under the supervision of a metabolic surgeon. When conducting a study that includes patients over a period of multiple years, the learning curve of the operator could potentially influence the patient outcome. Also in this study, the surgeons that performed most of the procedures were in different stages of their learning curve and therefore their experience varied. How-

ever, the surgeon did not independently influence the complication rates. We hypothesized that the experience of the whole team of surgeons, scrub nurses and anesthesiology staff has a bigger impact than the experience of the primary operator.

At the moment, the involvement of residents in major abdominal surgery is a frequently discussed item. Most studies showed that resident involvement is safe(7-11). However, others state that procedures take longer when performed by residents, and that surgeons should be cautious in allowing residents to perform (parts of) a procedure(12, 13). To further analyze the hypothesis that experience of a whole team is more important than experience of the primary operator, we investigated the influence of the operator's level of experience on patient outcome in Chapter 3. We found that the experience of the operator was negatively correlated with the duration of surgery. Although duration of surgery was longer in the learning curve period this did not affect postoperative recovery or complication rates. Therefore, we conclude that it is safe to involve a resident training program in a fast-track setting. For a resident, involvement in metabolic surgery can be very valuable for their training to become a skilled surgeon. Residents should be allowed to perform (parts of) the procedure to enhance the quality of their education and without decreasing the quality or safety of the surgery.

For both residents as well as experienced surgeons, a proper surgical overview is of great importance. To achieve a surgical overview of good quality, higher intraabdominal pressures (IAP) up to 20 mmHg are used in laparoscopic surgery in morbidly obese patients(14). A disadvantage of such a high IAP could be more postoperative pain, as previous studies have suggested(15). Therefore, we wished to evaluate if the IAP could be lowered by using deep neuromuscular blockade (NMB) instead of the currently used moderate NMB, without deteriorating the surgical overview or increasing the duration of surgery or complication rates. Chapter 4 describes the results of a randomized pilot study to determine the feasibility, safety and tolerability of low IAP and deep NMB to reduce postoperative pain. In 40% of the procedures with low IAP, the surgical overview was insufficient. The postoperative pain in the week after the procedure was found to differ only slightly between the groups. We concluded that an IAP of 20 mmHg seems the best option, leading to an optimal surgical overview without any relevant increase in postoperative pain for the patient. An interesting side note on this matter is that earlier research showed that obese subjects might experience pain different from non-obese subjects and that obese subjects should receive higher opiates dosages until more research is produced(16). However, the side-effects of opiates such as sleepiness are unwanted in a fast-track setting. We advise to refrain from prescribing patients opiates back at the ward. In our hospital, patients undergoing metabolic surgery only receive opiates in the hour(s) after the procedure. Once back on the ward, patients are prescribed acetaminophen solely as analgesia, Patients are encouraged to get out of bed and mobilize in order to recover faster and, importantly, to prevent venous thromboembolic events (VTE).

Prevention of VTEs such as deep venous thrombosis (DVT) or pulmonary embolism (PE) in the obese patient is important, because the relatively high mortality rates of PE in obese

subjects. In the past, extended chemical thromboprophylaxis up to six weeks in combination with mechanical prophylaxis such as compression stockings or intermittent pneumatic compression were advised(17). The rates of DVT and PE after metabolic surgery reported in 2014 were moderate, respectively 0.3-2.2% and 1% within one month postoperatively(18). However, the official ERABS guidelines that were published in 2016 still encouraged extended use of thromboprophylaxis for three to four weeks(6). In our hospital, severe morbidity or mortality due to VTE was rare. Therefore, the standard thromboprophylaxis in patients undergoing metabolic surgery with no or few risk factors besides their obesity was updated. These patients would only receive chemical thromboprophylaxis during their hospital admission. A VTE was observed in none of the patients managed according to the new restricted thromboprophylaxis protocol (Chapter 5). We concluded that it was safe to administer thromboprophylaxis for low-risk patients only during hospital admission. This means that it is no longer necessary for patients to self-administer thromboprophylaxis for several weeks after surgery.

Moreover, over time it seemed that the problem of developing DVT had withdrawn to the background, and that postoperative hemorrhage played a more important role regarding postoperative complications. Also in literature, the incidence of major bleeding seems to increase(1, 19). A possible solution for this problem could be administration of tranexamic acid(20, 21). To investigate this, we drafted the trial protocol for a double-blinded placebo-controlled randomized trial, which aims to determine whether peroperative administration of tranexamic acid reduces the peroperative and postoperative hemorrhage rates in laparoscopic sleeve gastrectomy (Chapter 6). The results of this trial should determine if administration of tranexamic acid should be included in the ERABS protocol, to aid in the prevention of postoperative complications.

As for the detection of postoperative complications, it remains challenging to identify those patients who should not be discharged from the hospital on day-one postoperative. Our group previously demonstrated that a standardized postoperative checklist of clinical parameters and laboratory findings proved useful in predicting post-operative complications(22). A hemoglobin decrease of more than one point and the unwillingness of a patient to go home were significant predictive factors of postoperative complications. C-reactive protein (CRP) was used in or hospital with a cut-off value of 50 to aid in deciding if patients were ready for discharge. However, there was need for a more sensitive biomarker of postoperative complications. In other surgical areas, the neutrophil-to-lymphocyte ratio (NLR) had shown promising results as a marker of postoperative complications(23-27). We decided to add the complete blood count to the standard laboratory tests of patients in the pre- and postoperative phase for one year. As described in Chapter 7, we found that the postoperative NLR and the delta-NLR (postoperative NLR minus preoperative NLR) showed a stronger correlation to postoperative complications than CRP or leukocyte count. The calculated cutoff points of

6.5 for postoperative NLR and 3.74 for delta-NLR will be implemented in our postoperative checklist, to aid in the decision-making for discharge on day-one postoperative.

PART II

Publications about metabolic surgery suggest greater improvement in weight loss outcomes and weight associated comorbidities compared with non-surgical interventions(28). Also, patients with type 2 diabetes who underwent metabolic surgery had better remission and lower risks of microvascular and macrovascular disease and mortality than patients in the non-surgical treatment group after at least five years of follow-up(29). Furthermore, a substantial and significant improvement in physical and mental health was seen after metabolic surgery compared with non-surgically treated patients after 5-25 years after surgery(30). The success of metabolic surgery is published and it is important to improve the surgical techniques and treatment strategies further. In the second part of this thesis, the outcomes after metabolic surgery in a fast-track setting were evaluated.

As a part of the ASSISI study, data of 200 patients undergoing metabolic surgery was collected, yearly measuring the carotid intima media thickness (cIMT) and the pulse wave velocity (PWV). In Chapter 8 we described the significant improvement of the functional and structural vascular quality for a substantial percentage of the patients undergoing a metabolic procedure. The fact that these changes were already seen after one year after the procedure underlines the effectiveness of metabolic surgery in a group of patients at high risk for cardiovascular disease. The effects of metabolic surgery on the vascular quality were unexpectedly rapid, especially when comparing the changes to those caused by other interventions in cardiovascular medicine. Statin treatment for example showed a regression of cIMT in the general population, but only in intensive drug dosage and an adequate long term treatment period(31) or as secondary prevention(32). In our study, statin treatment was not correlated to the cIMT or PWV at baseline or at one year postoperatively. This study nicely illustrated how metabolic surgery does not only lead to weight loss, but can also improve the cardiovascular status.

However, not all outcomes correlated to weight loss after metabolic surgery are positive. One of the negative results of metabolic surgery is nutrient insufficiency. Chapter 9 reports the outcomes of the Dutch Common Channel Trial (DUCATI): a randomized controlled trial investigation the optimal length of the limbs of a laparoscopic Roux-en-Y gastric bypass (LRYGB). Patients with a longer roux-limb had lower levels of calcium, iron and vitamin D than patients with a standard LRYGB. There was a trend in more reoperations due to malabsorption for the patients with a longer roux-limb, but these results were not significant. The main reason for reoperations was severe diarrhea. Also in literature it is mentioned that postoperative prolonged nausea and vomiting, food intolerance, and non-compliance to

dietary recommendations can play a crucial role in the cause of nutrient deficiencies(33). Therefore, patients with this kind of complaints should be identified at the outpatient clinic during the postoperative follow-up and extra laboratory test could be useful. In our study, we found that the vitamin deficiencies which were more present in patients with a longer roux-limb were very small and therefore of little importance. It will be interesting to see if during longer follow-up, the reoperation rates because of malabsorption between patients with longer and standard limb lengths will become significant. Also, weight loss results are very interesting to analyze with respect to nutrient deficiencies. In case substantial weight loss after certain procedure types would go hand-in-hand with (severe) nutrient deficiencies and herewith cause new complaints or illnesses for the patient, we would not be on the right track.

Randomized controlled trials comparing two types of metabolic procedures such as the comparison of different limb lengths in the DUCATI are of substantial value. These studies can help us further in determining the ideal type of procedure for each individual patient, as guidelines state that there is insufficient evidence-based data to suggest how to assign a patient to a specific procedure(17). Another study that aimed to contribute in this matter is the Sleeve versus bypass trial. In this study, more than 600 patients were randomized between a LSG and a LRYGB collecting data on sweet-eating behavior and many other parameters. Chapter 10 investigates the predictive value of the preoperative Dutch Sweet Eating Questionnaire (DSEQ) on postoperative weight loss after LRYGB and LSG. Do patients who are sweet-eaters benefit more from a LRYGB? Or do patients with no sweet-eating behavior benefit more from a LSG? More than 30 years ago, Sugerman et al. already suggested that sweet-eaters would benefit more from a LRYGB(34). In our study, a strong correlation between sweet-eating behavior and weight loss for any type of procedure was not found. This finding once again makes it clear that the decision-making for the procedure type is complex. Dietary habits, quality of life, presence of comorbidities, and many other factors should play a role in the decision-making.

FUTURE PERSPECTIVES

A great amount of research has already been performed on the topic of fast-track metabolic surgery. However, there is still a lot more to discover and investigate with regard to the ERABS key points: safety, patient-friendliness and efficiency. Could we eventually offer the morbidly obese patient a treatment path in which they arrive at the hospital, undergo the procedure and return home after a couple of hours without developing complications or the need to revisit the hospital due to complaints?

Safety

Even though a lot of improvements have been made, safety remains the most important in fast-track metabolic surgery. Improvements in safety can be measured by the decrease of short term and long term complications. Over the years, the incidence of DVT has decreased and the number of postoperative hemorrhages has increased. The PATAS-trial should determine whether postoperative hemorrhage can be prevented by administering tranexamic acid in LSG. Besides prevention of complications, we should focus on the early detection of postoperative complications. The implementation of the NLR as a marker of early complications in the postoperative ERABS checklist can aid in this matter. Future research should determine whether the implementation of this new marker indeed reduced the hospital revisits or hospital readmission rates.

Patient-friendliness

The second key point of ERABS is patient-friendliness. Metabolic surgery is performed electively and in high numbers, so there is a lot of opportunity to improve the process. Future research could focus on optimizing for example perioperative analgesia, anti-emetics, or the preoperative diet. Collecting questionnaires such as Patient Reported Experience Measures (PREMs) could aid in identifying items that should be changed to make metabolic surgery more patient-friendly.

Patient experience of the treatment is important, but the long-term effects of the treatment on quality of life are possibly even more important. These results should be evaluated using Patient Reported Outcome Measures (PROMs). Over the years, questionnaires on quality of life were filled in by all patients undergoing metabolic surgery in our hospital. It would be interesting to determine if there is a difference between the procedure types, or if the patient satisfaction is correlated to for example weight loss or to other parameters such as for example gastro-esophageal reflux disease.

Efficiency

With the increasing rates of morbid obesity, optimal efficiency in metabolic surgery is important in order to be able to help as many patients per day as possible. Future research can monitor if we will be able to perform more surgeries per day, as the experience of the whole team of surgeons, scrub nurses and anesthesiologists keeps increasing. Also, the length of hospital stay could be investigated further; is metabolic surgery in day-care a patient-friendly option, and do the benefits of this very short length of hospital stay weigh up to the risks?

Answering these research questions will guide us in our pursuit of perfection of the surgical treatment of morbidly obese patients. But, although metabolic surgery has been shown to be superior to non-surgical treatment in terms of weight loss, resolution of comorbidities and improving the quality of life, not all patients benefit from a metabolic procedure. Weight regain is not uncommon, and can lead to the recurrence or worsening of the comorbidities.

Another reason for failure of bariatric surgery is inadequate weight loss, meaning that the procedure never seemed to have any effects on the weight of the patient. Those patients for whom metabolic surgery was not successful also deserve to be the subject of future research. It is important to find ways to identify those patients at risk of weight regain and/or the recurrence of comorbidities and to get more insight into how to prevent this from happening in the postoperative phase. Just as important would be knowing how to preoperatively select patients with a high chance of inadequate responding to metabolic surgery. This knowledge could possibly lead to a more strict selection of patients eligible for metabolic surgery or at least to improved preoperative counselling.

REFERENCES

1. Blanchet MC, Gignoux B, Matussiere Y, Vulliez A, Lanz T, Monier F, et al. Experience with an Enhanced Recovery After Surgery (ERAS) Program for Bariatric Surgery: Comparison of MGB and LSG in 374 Patients. Obesity surgery. 2017;27(7):1896-900.
2. Dogan K, Kraaij L, Aarts EO, Koehestanie P, Hammink E, van Laarhoven CJ, et al. Fast-track bariatric surgery improves perioperative care and logistics compared to conventional care. Obesity surgery. 2015;25(1):28-35.
3. Elliott JA, Patel VM, Kirresh A, Ashrafian H, Le Roux CW, Olbers T, et al. Fast-track laparoscopic bariatric surgery: a systematic review. Updates in surgery. 2013;65(2):85-94.
4. Malczak P, Pisarska M, Piotr M, Wysocki M, Budzynski A, Pedziwiatr M. Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis. Obesity surgery. 2017;27(1):226-35.
5. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrun M, de Quelerij M, Verbrugge SJ, et al. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obesity surgery. 2016;26(2):303-12.
6. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
7. D'Souza N, Hashimoto DA, Gurusamy K, Aggarwal R. Comparative Outcomes of Resident vs Attending Performed Surgery: A Systematic Review and Meta-Analysis. Journal of surgical education. 2016;73(3):391-9.
8. Doyon L, Moreno-Koehler A, Ricciardi R, Nepomnayshy D. Resident participation in laparoscopic Roux-en-Y gastric bypass: a comparison of outcomes from the ACS-NSQIP database. Surgical endoscopy. 2016;30(8):3216-24.
9. Iordens GI, Klaassen RA, van Lieshout EM, Cleffken BI, van der Harst E. How to train surgical residents to perform laparoscopic Roux-en-Y gastric bypass safely. World journal of surgery. 2012;36(9):2003-10.
10. Kuckelman J, Bingham J, Barron M, Lallemand M, Martin M, Sohn V. Advanced laparoscopic bariatric surgery Is safe in general surgery training. American journal of surgery. 2017;213(5):963-6.
11. Major P, Wysocki M, Dworak J, Pedziwiatr M, Malczak P, Budzynski A. Are bariatric operations performed by residents safe and efficient? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2017;13(4):614-21.
12. Chan MM, Hamza N, Ammori BJ. Duration of surgery independently influences risk of venous thromboembolism after laparoscopic bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(1):88-93.
13. Krell RW, Birkmeyer NJ, Reames BN, Carlin AM, Birkmeyer JD, Finks JF. Effects of resident involvement on complication rates after laparoscopic gastric bypass. Journal of the American College of Surgeons. 2014;218(2):253-60.
14. Mulier JP, Dillemans B, Van Cauwenberge S. Impact of the patient's body position on the intraabdominal workspace during laparoscopic surgery. Surgical endoscopy. 2010;24(6):1398-402.
15. Donatsky AM, Bjerrum F, Gogenur I. Surgical techniques to minimize shoulder pain after laparoscopic cholecystectomy. A systematic review. Surgical endoscopy. 2013;27(7):2275-82.
16. Torensma B, Thomassen I, van Velzen M, In 't Veld BA. Pain Experience and Perception in the Obese Subject Systematic Review (Revised Version). Obesity surgery. 2016;26(3):631-9.

17. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obesity surgery. 2014;24(1):42-55.
18. Stein PD, Matta F. Pulmonary embolism and deep venous thrombosis following bariatric surgery. Obesity surgery. 2013;23(5):663-8.
19. Becattini C, Agnelli G, Manina G, Noya G, Rondelli F. Venous thromboembolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012;8(1):108-15.
20. Klaassen RA, Selles CA, van den Berg JW, Poelman MM, van der Harst E. Tranexamic acid therapy for postoperative bleeding after bariatric surgery. BMC obesity. 2018;5:36.
21. Hussain A, Al-Shoek I, El-Hasani S. The Use of Tranexamic Acid in Sleeve Gastrectomy. Obesity surgery. 2017;27(1):198-9.
22. van Mil SR, Duinhouwer LE, Mannaerts GHH, Biter LU, Dunkelgrun M, Apers JA. The Standardized Postoperative Checklist for Bariatric Surgery; a Tool for Safe Early Discharge? Obesity surgery. 2017;27(12):3102-9.
23. Cho KI, Ann SH, Singh GB, Her AY, Shin ES. Combined Usefulness of the Platelet-to-Lymphocyte Ratio and the Neutrophil-to-Lymphocyte Ratio in Predicting the Long-Term Adverse Events in Patients Who Have Undergone Percutaneous Coronary Intervention with a Drug-Eluting Stent. PloS one. 2015;10(7):e0133934.
24. Da Silva M, Cleghorn MC, Elnahas A, Jackson TD, Okrainec A, Quereshy FA. Postoperative day one neutrophil-to-lymphocyte ratio as a predictor of 30-day outcomes in bariatric surgery patients. Surgical endoscopy. 2017;31(6):2645-50.
25. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. American heart journal. 2007;154(5):995-1002.
26. Malietzis G, Giacometti M, Askari A, Nachiappan S, Kennedy RH, Faiz OD, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Annals of surgery. 2014;260(2):287-92.
27. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surgical oncology. 2014;23(1):31-9.
28. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. The Cochrane database of systematic reviews. 2014(8):Cd003641.
29. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications, and Mortality: a Systematic Review and Meta-Analysis. Obesity surgery. 2017;27(10):2724-32.
30. Driscoll S, Gregory DM, Fardy JM, Twells LK. Long-term health-related quality of life in bariatric surgery patients: A systematic review and meta-analysis. Obesity (Silver Spring, Md). 2016;24(1):60-70.
31. Riccioni G. Statins and carotid intima-media thickness reduction: an up-to-date review. Current medicinal chemistry. 2009;16(14):1799-805.
32. Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. Journal of atherosclerosis and thrombosis. 2013;20(1):108-21.
33. Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. Alimentary pharmacology & therapeutics. 2014;40(6):582-609.

34. Sugerman HJ, Starkey JV, Birkenhauer R. A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. Annals of surgery. 1987;205(6):613-24.

Fast-track protocols are designed to aid in the optimization of surgical pathways, focusing on three key points: safety, patient-friendliness and efficiency. Many study groups have already described the positive results of implementation of an Enhanced Recovery After Bariatric Surgery (ERABS) program in their hospitals. The general conclusion was that implementation of ERABS protocols had positive effects on patient outcomes(4-9).

12 Summary in English and Dutch

ENGLISH SUMMARY

This thesis focuses on the enhanced recovery after bariatric surgery (ERABS) protocol. We studied on how to improve this protocol by continuous evaluation, aiming for optimal safety, efficacy and patient satisfaction of the bariatric patient.

Part I of this thesis describes the first aim of this thesis: to evaluate and change the protocols used in metabolic surgery, and herewith improve the surgical treatment of morbid obesity.

Chapter 2 describes the morbidity-related outcomes of patients undergoing bariatric surgery before and after revising the protocol in 2014. In this revised protocol, both the physical therapist and the dietician would visit each patient on the morning after the procedure and before discharge, to prepare them optimally for their recovery at home. After these changes, minor complication rates decreased significantly, most importantly resulting in less readmissions and unplanned hospital revisits. Interestingly, the major complication rates remained stable.

In **Chapter 3**, we investigated the influence of the operator's level of experience on patient outcome to analyze the hypothesis that experience of a whole team is more important than experience of the primary operator. We found that the experience of the operator was negatively correlated with the duration of surgery. Although duration of surgery was longer in the learning curve period this did not affect postoperative recovery or complication rates. Therefore, we conclude that it is safe to involve a resident training program in a fast-track setting.

Chapter 4 describes the results of a randomized pilot study to determine the feasibility, safety and tolerability of low intraabdominal pressure (IAP) and deep neuromuscular blockade to reduce postoperative pain in laparoscopic Roux-en-Y gastric bypass (LRYGB). In 40% of the procedures with low IAP, the surgical overview was insufficient. The postoperative pain in the week after the procedure was found to differ only slightly between the groups. We concluded that an IAP of 20 mmHg seems the best option, leading to an optimal surgical overview without any relevant increase in postoperative pain for the patient.

The results of a comparative study on the occurrence of venous thromboembolic events (VTEs) after metabolic surgery are described in **Chapter 5**. In our hospital, severe morbidity or mortality due to VTE was rare. Therefore it was decided to alter the standard thromboprophylaxis in patients undergoing metabolic surgery with no or few risk factors besides their obesity. These patients would only receive chemical thromboprophylaxis during their hospital admission. A VTE was observed in none of the patients managed according to the new restricted thromboprophylaxis protocol. We concluded that it was safe to administer thromboprophylaxis for low-risk patients only during hospital admission.

Chapter 6 describes the trial protocol for a double-blinded placebo-controlled randomized trial, which aims to investigate whether peroperative administration of tranexamic acid reduces the peroperative and postoperative hemorrhage rates in laparoscopic sleeve gastrectomy

(LSG). The results of this trial should determine if administration of tranexamic acid should be included in the ERABS protocol, to aid in the prevention of postoperative complications.
Chapter 7 describes the study that assessed the predictive value of the neutrophils-to-lymphocyte ratio (NLR) on postoperative complications. We found that the postoperative NLR and the delta-NLR (postoperative NLR minus preoperative NLR) showed a stronger correlation to postoperative complications than C-reactive protein (CRP) or leukocyte count. The calculated cutoff points of 6.5 for postoperative NLR and 3.74 for delta-NLR will be implemented in our postoperative checklist, to aid in the decision-making for discharge on day-one postoperative.
Part II of this thesis describes the second aim: to evaluate the outcomes after metabolic surgery in a fast-track setting. In **Chapter 8**, we describe the significant improvement of the functional and structural vascular quality for a substantial percentage of the patients undergoing a metabolic procedure. The fact that these changes were already seen after one year after the procedure underlines the effectiveness of metabolic surgery in a group of patients at high risk for cardiovascular disease.
Chapter 9 reports the outcomes of the Dutch Common Channel Trial (DUCATI): a randomized controlled trial investigation the optimal length of the limbs of a LRYGB. Patients with a longer roux-limb had lower levels of calcium, iron and vitamin D than patients with a standard LRYGB. There was a trend in more reoperations due to malabsorption for the patients with a longer roux-limb, but these results were not significant.
In **Chapter 10**, we investigate the predictive value of the preoperative Dutch Sweet Eating Questionnaire (DSEQ) on postoperative weight loss after LRYGB and LSG. A strong correlation between sweet-eating behavior and weight loss for any type of procedure was not found. We conclude that dietary habits, quality of life, presence of comorbidities, and many other factors should play a role in the decision-making for the procedure type.

NEDERLANDSE SAMENVATTING

Deze thesis concentreert zich op het enhanced recovery after bariatric surgery (ERABS) protocol. Wij bestudeerden hoe wij dit protocol verder konden verbeteren door continue evaluatie, erop gericht om de bariatrisch patiënt zo veilig, efficiënt en patiëntvriendelijk mogelijk te behandelen.

Deel I van deze thesis beschrijft het eerste doel van de thesis: om de protocollen die gebruikt worden in metabole chirurgie te evalueren en aanpassen, en hiermee de chirurgische behandeling van morbide obesitas te verbeteren. **Hoofdstuk 2** beschrijft de morbiditeit-gerelateerde uitkomsten voor patiënten die bariatrische chirurgie ondergaan voor en na de protocolaanpassingen in 2014. In dit gereviseerde protocol bezochten zowel de fysiotherapeut als de diëtist de patiënten op de ochtend na de operatie, net voor ontslag uit het ziekenhuis, om hen optimaal voor te bereiden op hun herstel thuis. Na deze wijzigingen daalden de aantallen 'minor' complicaties significant, met name leidend tot minder heropnames en ongeplande herbezoeken aan het ziekenhuis. Een interessant gegeven was dat het aantal 'major' complicaties gelijk bleef.

In **Hoofdstuk 3** onderzochten wij de invloed van de ervaring van de operateur op de uitkomst voor de patiënt. De hypothese was dat de ervaring van het gehele operatieteam belangrijker is dan de ervaring van alleen de eerste operateur. Wij zagen dat de ervaring van de operateur negatief gecorreleerd was met de operatieduur. Ondanks dat de operatieduur langer was in het begin van de leercurve beïnvloedde dit niet het postoperatieve herstel of de complicatiecijfers. Daarom concludeerden wij dat een trainingsprogramma voor chirurgen in opleiding in fast-track metabole chirurgie veilig is.

Hoofdstuk 4 beschrijft de resultaten van een gerandomiseerde pilot studie waarin de haalbaarheid, veiligheid en tolerantie van lage intra-abdominale druk en diepe neuromusculaire blokkade bepaald werden om de postoperatieve pijn na een Roux-en-Y gastric bypass (LRYGB) te verminderen. In 40% van de operaties met lage druk was het chirurgisch overzicht onvoldoende. Er was maar een minimaal verschil in postoperatieve pijn in de week na de operatie tussen de groepen. Wij concludeerden dat een druk van 20 mmHg de beste optie lijkt, resulterend in een optimaal chirurgisch overzicht en zonder relevante toename in postoperatieve pijn voor de patiënt.

De resultaten van een comparatieve studie naar het optreden van veneuze trombo-embolische events (VTEs) na metabole chirurgie zijn beschreven in **Hoofdstuk 5**. In ons ziekenhuis was ernstige morbiditeit of mortaliteit door VTE zeldzaam. Daarom werd besloten om het beleid van standaard tromboseprofylaxe te wijzigen voor patiënten die metabole chirurgie ondergingen en die geen of weinig risicofactoren hadden op het ontwikkelen van een VTE. Deze patiënten kregen alleen medicamenteuze tromboseprofylaxe gedurende de opname in het ziekenhuis. Geen van de patiënten die tromboseprofylaxe kregen volgens dit nieuwe beperkte protocol volgen ontwikkelden een VTE. Wij concludeerden dat het veilig is om

laag-risico patiënten slechts te behandelen met tromboseprofylaxe gedurende opname in het ziekenhuis.

Hoofdstuk 6 beschrijft het studieprotocol voor een dubbelblinde placebo-gecontroleerde gerandomiseerde trial, waarin onderzocht zal worden of de peroperatieve toediening van tranexaminezuur het aantal per- en postoperatieve bloedingen kan verminderen in laparoscopische sleeve gastrectomieën (LSG). De resultaten van deze trial moeten bepalen of toediening van tranexaminezuur opgenomen moet worden in het ERABS protocol om het aantal postoperatieve complicaties te verminderen.

Hoofdstuk 7 beschrijft de studie die onderzocht heeft wat de voorspellende waarde is van de neutrofielen-lymfocyten ratio (NLR) voor postoperatieve complicaties. Wij zagen dat de postoperatieve NLR en de delta-NLR (postoperatieve NLR min preoperatieve NLR) een sterkte correlatie hadden met postoperatieve complicaties, sterker dan C-reactive protein (CRP) of het leukocyten getal. De berekende afkapwaarden van 6.5 voor postoperatieve NLR en 3.74 voor delta-NLR zullen geïmplementeerd worden in onze postoperatieve checklist om zo van toegevoegde waarde te zijn in de beslisvorming rondom ontslag op dag 1 postoperatief.

Deel II van deze thesis beschrijft het tweede doel: om de uitkomsten van metabole chirurgie in een fast-track setting te evalueren. In **Hoofdstuk 8** beschrijven wij de significante verbetering van de functionele en structurele kwaliteit van de bloedvaten in een substantieel percentage van de patiënten die metabole chirurgie ondergingen. Het feit dat deze veranderingen reeds te zien waren na 1 jaar na de operatie benadrukken de effectiviteit van metabole chirurgie in een groep patiënten met een hoog risico op cardiovasculaire ziekten.

Hoofdstuk 9 beschrijft de uitkomsten van de Dutch Common Channel Trial (DUCATI): een gerandomiseerde gecontroleerde trial die onderzoekt wat de optimale lengtes van de darmlissen zijn in een LRYGB. Patiënten met een langere roux-lis hadden lagere waarden van calcium, ijzer en vitamine D in het bloed dan patiënten met een standaard LRYGB. Er was een trend in het aantal reoperaties wegens malabsorptie bij patiënten met een langere roux-lis, maar deze resultaten waren niet significant.

In **Hoofdstuk 10** onderzochten wij de voorspellende waarde van de reoperatieve Dutch Sweet Eating Questionnaire (DSEQ) voor postoperatief gewichtsverlies na LRYGB en LSG. Er werd geen sterke correlatie gevonden tussen ‘sweet-eating’ en gewichtsverlies voor geen van beide operaties. Wij concludeerden dat eetgewoonten, kwaliteit van leven, aanwezigheid van comorbiditeiten en vele andere factoren een rol moeten spelen bij de beslisvorming rondom het type metabole operatie.

A

PhD portfolio
List of publications
Curriculum Vitae
Dankwoord

PHD PORTFOLIO

Name PhD student:	Marjolijn Leeman
Erasmus MC department:	Surgery
Research School:	Netherlands Institute of Health Sciences
PhD period:	July 2017 – June 2020
Promotor:	Prof. dr. C. Verhoef
Supervisor:	dr. M. Dunkelgrun (Franciscus Gasthuis & Vlietland)

General courses	**Year**	**ECTS**
Good Clinical Practice	2017	1.0
Biostatistical Methods I: Basic Principles	2017	2.0
Research integrity	2019	0.6
Biomedical English Writing Course	2019	2.5

Oral presentations	**Year**	**ECTS**
NASO Spring meeting (NL)	2018	1.0
ASSISI		
DSMBS conference (NL)	2018	1.0
ERABS 2.0		
IFSO world congress (Dubai, United Arab Emirates)	2018	2.0
ERABS 2.0, ASSISI		
Wetenschapsdag Franciscus Gasthuis & Vlietland (NL)	2018	1.0
ASSISI		
DSMBS conference (NL)	2019	1.0
Thromboprophylaxis		
Chirurgendagen (NL)	2019	1.0
Thromboprophylaxis		
IFSO world congress (Spain)	2019	3.0
Thromboprophylaxis, Bar Press, PATAS		
Regionale bariatrie refereeravond	2019	1.0
Overview of PhD project		

Poster presentations	**Year**	**ECTS**
Wetenschapsdag Franciscus Gasthuis & Vlietland (NL)	2018	1.0
ERABS 2.0		
IFSO European chapter 2018 (Greece)	2018	0.3
ERABS 2.0		

Wetenschapsdag Franciscus Gasthuis & Vlietland (NL)	2019	2.0
Thromboprophylaxis, Bar Press		

Symposia, seminars & workshops	**Year**	**ECTS**
Wetenschapsdag Franciscus Gasthuis & Vlietland (NL)	2018	1.0
DSMBS congres (NL)	2018	1.0
Chirurgendagen (NL)	2018	1.0
IFSO European chapter (Greece)	2018	1.0
Nederlands Obesitas Symposium (NL)	2018	1.0
IFSO world congress (United Arab Emirates)	2018	1.0
Wetenschapsdag Franciscus Gasthuis & Vlietland (NL)	2019	1.0
DSMBS congres (NL)	2019	1.0
Chirurgendagen (NL)	2019	1.0
Regionale bariatrie refereeravond (NL)	2019	1.0
IFSO world congress (Spain)	2019	1.0

Clinical meetings/projects	**Year**	**ECTS**
Wetenschapsvergadering bariatrie	2017-2020	3.0
Franciscus research meeting	2019-2020	2.0

Teachings activities	**Year**	**ECTS**
Supervision of medical students' research project	2018-2019	2.0

LIST OF PUBLICATIONS

This thesis

1. Leeman M, van Mil SR, Al-Ghanam I, Biter LU, Dunkelgrun M, Castro Cabezas M. Structural and functional vascular improvement 1 year after bariatric surgery: a prospective cohort study. Surgery for Obesity And Related Diseases. 2019.
2. Leeman M, Biter LU, Apers JA, Birnie E, Verbrugge SJ, Verhoef C, et al. A single-center comparison of extended and restricted thromboprophylaxis with LMWH after metabolic surgery. Obesity Surgery. 2020.
3. Leeman M, Vijgen G, Apers JA, Zengerink JF, Verhoef C, Dunkelgrun M, et al. The Influence of Surgical Experience on Postoperative Recovery in Fast-Track Bariatric Surgery. Obesity Surgery. 2020.
4. Leeman M, van Mil SR, Biter LU, Apers JA, Verhoef K, Dunkelgrun M. Reducing complication rates and hospital readmissions while revising the enhanced recovery after bariatric surgery (ERABS) protocol. Surgical Endoscopy. 2020.
5. Leeman M, Huisbrink J, Wijnand JMA, Biter LU, Verbrugge SJC, Dunkelgrun M, et al. Trial protocol: preoperative administration of tranexamic acid in sleeve gastrectomy (PATAS) to reduce haemorrhage rates. A randomised controlled trial. BMJ Open. 2020.
6. Leeman M, Gadiot RPM, Wijnand JMA, Birnie E, Apers JA, Biter LU, et al. Effects of standard versus very long roux limb Roux-en-Y gastric bypass on nutrient status: A 1 year follow-up report from the DUCATI study. The British Journal of Nutrition. 2020.
7. Leeman M, Biter LU, Friskes I, der Kinderen M, Apers JA, Dunkelgrun M, et al. The Prognostic Value of the Dutch Sweet Eating Questionnaire on Weight Loss After Metabolic Surgery: a Randomized Controlled Trial. Obesity Surgery. 2020.
8. Leeman M, Biter LU, Apers JA, Birnie E, Verbrugge SJC, Dunkelgrun M. Low-pressure pneumoperitoneum with deep neuromuscular blockade in metabolic surgery to reduce postoperative pain: a randomized pilot trial. Surgical Endoscopy. 2020.

Other

9. Lammers WJ, Leeman M, Ponsioen CI, Boonstra K, van Erpecum KJ, Wolfhagen FH, et al. How the concept of biochemical response influenced the management of primary biliary cholangitis over time. The Netherlands Journal of Medicine. 2016.
10. Leeman M, Burgers P, Brehm V, van Brussel JP. Psoas abscess after bacille Calmette-Guerin instillations causing iliac artery contained rupture. Journal of Vascular Surgery. 2017.
11. Gadiot RPM, Leeman M, Biter LU, Dunkelgrun M, Apers JA, Van ‘t Hof G, Feskens PBGM, Mannaerts GHH. Does the length of the common channel as part of the total alimentary tract matter? One year results from the multicenter Dutch Common Channel Trial (DUCATI) comparing standard versus distal Roux-en-Y gastric bypass with similar biliopancreatic bowel limb lengths. Obesity Surgery, 2020.

CURRICULUM VITAE

Marjolijn Leeman werd op 22 augustus 1991 geboren te Vlaardingen. In 2008 slaagde zij voor het eindexamen VWO-gymnasium aan het Stedelijk Gymnasium Schiedam. Direct daarna startte zij met de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Gedurende het eerste jaar van haar studententijd werkte zij als voedingsassistente op de afdeling interne geneeskunde in het Vlietland Ziekenhuis in Schiedam. Daarna werd zij afdelingsassistente op de Dialyse afdeling van het Erasmus Medisch Centrum, waar zij ook de taken van teamleider en afdelingssecretaresse vervulde. In 2015 volgde zij een keuze-coschap op de Trauma Unit in het Groote Schuur Hospitaal in Kaapstad, Zuid Afrika. Haar oudste coschap volgde zij op de afdeling Chirurgie van het Franciscus Gasthuis & Vlietland te Rotterdam. In het voorjaar van 2016 behaalde zij haar artsenbul en startte zij als ANIOS chirurgie in het Franciscus Gasthuis & Vlietland. Na ruim een jaar, zette zij haar tijd in dit ziekenhuis voort als arts-onderzoeker metabole chirurgie, in het kader van een promotieonderzoek met als hoofdonderwerp “ERABS”: Enhanced Recovery After Bariatric Surgery. Dit heeft geresulteerd in dit proefschrift.

Marjolijn Leeman was born on August 22nd 1991 in Vlaardingen. She graduated high school in 2008 at the Stedelijk Gymnasium Schiedam, after which she started to study Medicine at the Erasmus University in Rotterdam. During the first year of her student life, she worked as a nutrition assistant at the department of internal medicine in the Vlietland Hospital in Schiedam. Later, she joined the team of medical students assisting on the Dialysis department of the Erasmus Medical Center, where she also became team manager and department secretary. In 2015, she did a residency on the Trauma Unit of the Groote Schuur Hospital in Cape Town, South Africa. She did her eldest residency on the surgical department of the Franciscus Gasthuis & Vlietland in Rotterdam. She graduated med school in the spring of 2016 and started to work as a surgical resident not in training in the Franciscus Gasthuis & Vlietland. After more than a year, she continued her time in this hospital as a fulltime researcher metabolic surgery with the subject “ERABS”: Enhanced Recovery After Bariatric Surgery. This has led to the writing of this thesis.

DANKWOORD

Het voelt als de dag van gisteren dat ik solliciteerde voor de functie van arts-onderzoeker Bariatrische chirurgie. Het was nooit echt mijn passie om arts-onderzoeker te worden, maar ik dacht: promoveren is altijd goed. Achteraf gezien was het de beste keuze die ik had kunnen maken. Ik heb veel geleerd en daarnaast een fantastische tijd gehad. En dat heb ik natuurlijk te danken aan een heleboel mensen, die ik hier graag wil noemen.

Allereerst prof. dr. Verhoef, beste **Kees**. Het was niet altijd gemakkelijk voor mij om iemand die zo veel langer en zo veel wijzer is dan ik, aan te spreken met 'je' en 'jij'. Ook al zat ik een stukje verderop in het Franciscus en is de bariatrische chirurgie niet direct jouw hobby, heb ik altijd veel gehad aan jouw begeleiding. Elke paar maanden kwam ik even langs om te vertellen wat ik zoal had uitgevoerd en ik vertrok altijd weer met een enorme glimlach en hernieuwde motivatie. Bedankt voor al je support en adviezen, niet alleen op het gebied van de wetenschap, maar ook voor mijn toekomstplannen.

Dr. Dunkelgrun, beste **Martin**. Als co-promotor nam jij je taak als 'dagelijks begeleider' serieus. Tijdens je poli-dagen kwam je minimaal 1 keer per dag het onderzoekshok binnengestapt om even te kletsen of op zijn minst te vragen of er nog "research" gedaan werd. Ik vond het fijn dat we elke vrijdag even een momentje gepland hadden om de voortgang te bespreken en dat we dat combineerden met lunch, koffie of het opzoeken van foto's van vakantiebestemmingen. Bedankt voor al je steun in de afgelopen jaren, de vrijheid die je me gaf tijdens het onderzoeken en de fijne samenwerking.

Drs. Biter en drs. Apers, beste **Ulas** en **Jan**, jullie kwamen minstens even vaak het onderzoekshok binnen om even te kletsen. Gelukkig was ik meestal net op tijd om Whatsapp desktop of Zalando weg te klikken, of deden jullie alsof jullie het niet zagen. Ulas, als ik was vastgelopen in een stuk wist jij het altijd op zo'n simpele manier te verwoorden dat ik niet meer inzag waarom ik het in eerste instantie niet doorzag. Jan, op congressen was jij misschien wel degene die het hardst klapte na mijn praatje. Verder ken ik maar weinig mensen die zo kunnen genieten van lekker eten of alleen al de gedachte daaraan! Bedankt voor jullie goede begeleiding, het meedenken voor mooie artikelen en voor de mooie momenten op de congressen.

Ik wil graag **prof.dr. Hazebroek**, **prof.dr. Greve** en **prof.dr. Lange** bedanken voor het plaatsnemen in de kleine commissie. Verder wil ik de overige leden bedanken voor het plaatsnemen in de grote commissie.

Graag wil ik alle **patiënten** bedanken die hun gegevens beschikbaar stelden voor het onderzoek of die hebben deelgenomen aan de opgezette studies.

Aan alle **chirurgen** van het Franciscus Gasthuis & Vlietland, heel veel dank voor jullie interesse in mijn promotieonderzoek en voor de gezelligheid tijdens de lunch of werkuitjes. Ik heb veel van jullie geleerd! In het bijzonder drs. Zengerink, **Hans**; bedankt voor je betrokkenheid en interesse bij de bariatrische onderzoeken, ondanks dat tegelijkertijd zo veel andere

dingen je aandacht vragen. Dr. Vijgen, **Guy**, gedurende mijn onderzoekstijd kon ik je altijd vragen stellen over van alles en had je altijd goede adviezen over congressen en publiceren. Daarnaast heb je me mooie tips gegeven voor mijn carrière-plannen en voor vakanties in Costa Rica. Drs. Gadiot, **Ralph**, "Dio", we hebben veel gelachen op werk en congressen en ook nog hoogstaande research verricht. Dankjulliewel!

Muchas gracias a dr. Castro Cabezas. Beste **Manuel**, ik heb altijd erg genoten van onze samenwerking en ik heb veel van je geleerd. Bedankt voor jouw begeleiding bij de internistische kant van de bariatrie.

Stefanie, jij was mijn voorganger als full-time arts-onderzoeker bariatrie. Toen ik nog ANIOS was zag ik jou dag in, dag uit, enorm geconcentreerd werken achterin de assistentenkamer. De lat lag hoog! Dank dat je me op weg hebt geholpen. **Judith**, bedankt dat je het stokje van me wilt overnemen, ik heb er alle vertrouwen in dat je er iets moois van zult maken!

Veel dank aan de anesthesiologie: **dr. Verbrugge, Henneke, Joeri, Niels**. Jullie hebben me enorm geholpen in het opzetten en uitvoeren van de studies. Tante Hen, jij in het bijzonder bedankt! Ook wil ik het dedicated bariatrie OK team bedanken. **Patricia, Rianne, Iris,** we hebben het erg gezellig gehad op de OK en tijdens de congressen! Ook veel dank aan **Nadine Pouw** (Klinische Chemie) en **Jeannine Huisbrink** (Apotheek) voor hun bijdrage aan verschillende onderzoeksprojecten.

Lieve **Zenaida** en **Heleen**, jullie waren er altijd om te helpen met de praktische kant van mijn onderzoeken en waren altijd in voor een praatje. **Irene**, dank voor je hulp bij verschillende projecten en voor de gezelligheid.

Aan alle **arts-assistenten** van het Franciscus Gasthuis & Vlietland: heel veel dank voor jullie adviezen, de welkome dagelijkse afleiding en de koffie-traktaties. Ik heb ervan genoten dat jullie me elke ochtend en middag vroegen waarom ik nou eigenlijk bij de overdracht zat; soms wist ik zelf eigenlijk ook even niet meer waarom. Lieve **Mathilde**, bedankt voor alle dingen die je in een handomdraai voor me hebt geregeld en voor de leuke koffie-momentjes.

Beste medewerkers van het **Wetenschapsbureau**, dank voor jullie hulp en begeleiding. Ook veel dank aan **dr. Birnie** voor het controleren van mijn statistische pogingen en de waardevolle revisies van mijn manuscripten.

Lieve **Julíe**, ongeveer een week nadat wij elkaar voor het eerst hadden gesproken deelden wij een kamer tijdens een congres in Londen. Sindsdien zijn we op elk congres onafscheidelijk en zijn we ontelbaar veel cappuccino's en etentjes verder. Ik ben enorm blij dat we ook buiten het ziekenhuis (en buiten Europa) vriendinnetjes zijn. Bedankt voor je luisterend oor, je hulp, je nuchtere blik en je gezelligheid de afgelopen jaren.

Lieve **Elles**, mijn paranimf. Hoe kan het ook anders? Het eerste jaartje was even lastig, maar sinds jij naast mij plaatsnam was het promoveren ineens één groot feest. We konden samen lachen, huilen, serieus praten en discussiëren over onderzoek… maar het allerbeste konden we salades en cappuccino's maken, online shoppen en DJ'en. De favoriet voor de vrijdag middag: **Scooter** – Weekend.

Lieve clubgenootjes, lieve **Binkies**. Wat ben ik blij dat we elkaar leerden kennen in 2008 en dat we nu, 12 jaar later, elkaar nog steeds zien. Bedankt voor jullie interesse in mijn onderzoek. Lieve **Abi**, **Karlijn** en **Madelon**, wij geneeskunde-Binks zijn blijkbaar echt voorbestemd om onderzoek te doen. En **Nina** natuurlijk vanuit de neuropsychologie! Ik vond het altijd heel fijn om het met jullie te hebben over de onderzoeksperikelen en toekomstplannen. Lieve **Renee**, **Isabel** en **Stefanie**, wie had gedacht dat studiegroepje 1.12 zo'n goede basis zou zijn voor vriendschappen? Zo veel jaren later hebben wij het nog steeds zo leuk met elkaar. Wat ben ik altijd blij om jullie te zien en om te praten over geneeskunde-dingen, planten verzorgen, de gevaren van katten en barometers en andere gekkigheid. Hopelijk kunnen we elkaar in de toekomst nog heel vaak in consult vragen of eindelijk met z'n allen op mini-vakantie!
Lieve oud-huisgenootjes, lieve **Tetters**. De tijd van Happy-Inn op vrijdagochtend is helaas voorbij, maar gelukkig zien we elkaar nog af te toe om terug te denken aan die mooie periode. Lieve **Sara**, bedankt dat je zo'n lief vriendinnetje bent en voor je adviezen over mijn PhD en andere dingen. Sorry dat ik al je planten heb verpest toen je op vakantie was. Lieve **Barbara**, gelukkig woon je weer aan de Noordkant van de Maas. Ik hoop dat we elkaar nog veel gaan zien en weer eens een nieuwe serie kiezen om samen te kijken.
Lieve **Annemiek**, Miek, Girl. Jij bent altijd mijn grote voorbeeld geweest. Als arts-onderzoeker en eigenlijk ook als mens op zich. Ik ben ongelofelijk blij dat jij mijn zus en paranimf bent. Bedankt dat jij en **Jaime** er altijd zijn om voor me te zorgen en met me te lachen. Gelukkig gaat er bijna geen week voorbij waarin we niet kunnen zussen en daarna slechte films kunnen kijken. Een alinea is te kort om uit te leggen hoe belangrijk die momenten voor mij zijn!
Lieve **pap en mam**, jullie hebben mij altijd gesteund in mijn keuzes en me vrijgelaten om te doen wat ik wilde. Met wijsheden als 'jouw tijd komt nog' en 'spinnen komen altijd met z'n twee' ben ik toch best een eind gekomen. Lieve mama, bedankt voor de prachtige ontwerpen die je voor mijn proefschrift hebt gemaakt. Lieve papa, bedankt voor je motiverende woorden en je steun. Beiden, bedankt voor alles.
Lieve **Sergio**, toen ik jou leerde kennen had ik eigenlijk geen idee wat ik wilde in het leven. Jij hebt mij laten inzien dat het echt niet erg is als niet alles tot in de puntjes is uitgedacht en voorbereid en dat geluk zit in de kleine dingen. Me haces muy feliz. Gracias por estar tan increíble.