Advances in colorectal surgery
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Perioperative strategy in colonic surgery; \textit{LA}paroscopy and/or \textit{FA}st track multimodal management \textit{versus} standard care (LAFA trial) - design and rationale of a randomised controlled multicentre trial -

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Abstract

Introduction
Recent developments in large bowel surgery are the introduction of laparoscopic surgery and the implementation of multimodal fast track recovery programmes. Both focus on a faster recovery and shorter hospital stay. The randomised controlled multicentre LAFA-trial (LAparoscopy and/or FAst track multimodal management versus standard care) was conceived to determine whether laparoscopic surgery, fast track perioperative care or a combination of both is to be preferred over open surgery with standard care in patients having segmental colectomy for malignant disease.

Methods
The LAFA-trial is a double blinded, multicentre trial with a two by two balanced factorial design. Patients eligible for segmental colectomy for malignant colorectal disease i.e. right and left colectomy and anterior resection will be randomised to either open or laparoscopic colectomy, and to either standard care or the fast track perioperative care programme. This factorial design produces four treatment groups; open colectomy with standard care (a), open colectomy with the fast track programme (b), laparoscopic colectomy with standard care (c), and laparoscopic surgery with the fast track programme (d). Primary outcome parameter is postoperative hospital length of stay including readmission within 30 days. Secondary outcome parameters are quality of life two and four weeks after surgery, overall hospital costs, morbidity, patient satisfaction and readmission rate. Based on a mean postoperative hospital stay of 9 +/- 2.5 days a group size of 400 patients (100 each arm) can reliably detect a minimum difference of one day between the four arms (alpha = 0.95, beta = 0.8). With 100 patients in each arm a difference of 10% in subscales of the Short Form 36 (SF-36) questionnaire and social functioning can be detected.

Conclusions
The LAFA-trial is a randomised controlled multicentre trial that will provide evidence on the merits of fast track perioperative care and laparoscopic colorectal surgery in patients having segmental colectomy for malignant disease (ISRCTN:79588422).
Introduction

Recent developments in large bowel surgery are the introduction of laparoscopic surgery and the implementation of multimodal fast track perioperative care programmes. Both focus on enhanced recovery and shorter hospital stay as compared to open surgery and traditional care. Laparoscopic colectomy was first described in 1991. Since then a lot of effort has been made to establish its feasibility and safety particularly in laparoscopic colectomy for cancer. Recently, several randomised trials comparing laparoscopic with open colectomy indicated that laparoscopic surgery can be applied safely both for malignant and benign diseases. Several systematic reviews that assessed the evidence on the laparoscopic approach for colorectal cancer reported that laparoscopic surgery, in a traditional perioperative care setting was associated with less morbidity, less postoperative pain, earlier recovery and shorter hospital stay. Furthermore, short term cancer related outcomes such as cancer free resection margins and the number of harvested lymph nodes, as well as long term cancer related outcomes such as disease free survival were comparable between laparoscopic and open surgery. These results stimulated many surgeons in the Netherlands to set up a laparoscopic colorectal programme.

At the same time, enthusiasm was raised for the so-called fast track perioperative care programme, also referred to as Enhanced Recovery After Surgery (ERAS®), which essentially is a modification of the programme initially developed by the Danish surgeon Henrik Kehlet. This multimodal programme, involving optimisation of several aspects of the perioperative management of patients undergoing colectomy, enables patients to recover earlier and therefore go home as early as three days after open colectomy. Furthermore, postoperative morbidity was reduced. The essence of a fast track perioperative care programme consists of extensive preoperative counselling, no bowel preparation, no sedative premedication, no preoperative fasting but carbohydrate loaded liquids until two hours prior to surgery, tailored anaesthesiology encompassing thoracic epidural anaesthesia and short acting anaesthetics, perioperative intravenous fluid restriction, minimally invasive surgery (i.e. through small incisions or laparoscopy), non-opioid pain management, no routine use of drains and nasogastric tubes, early removal of bladder catheter, standard laxatives and prokinetics, and early and enhanced postoperative feeding and mobilisation.

As these new developments have been introduced in clinical practice, time has come to evaluate their feasibility, safety, and cost-effectiveness in large bowel surgery in a randomised controlled setting. It can be hypothesized that fast track and/or laparoscopy are associated with less attenuation of the patient’s condition after surgery resulting in a shorter postoperative hospital stay, a faster recovery to full activity at home, and a better quality of life.

Since it has not been established which combination of perioperative management and surgical approach i.e. standard care, fast track care, laparoscopic surgery or open surgery is best in terms of postoperative hospital stay, quality of life, postoperative morbidity,
readmission rate, overall costs and patient satisfaction, this is the subject of the present study proposal.

Methods

Study objectives
The objective of this study is to determine whether laparoscopic surgery, fast track perioperative care or a combination of both is to be preferred over open surgery with standard care in patients undergoing segmental colectomy for malignant disease. The objective is subdivided in three research questions; first, how laparoscopic surgery compares to open surgery in terms of hospital stay, quality of life and costs? Second, how fast track perioperative care compares to standard care in terms of hospital stay, quality of life, and costs? Finally, what is the added benefit of the fast track perioperative care programme in laparoscopic surgery in terms of hospital stay, quality of life and costs?

Study design
The LAFA-trial is a randomised multicentre trial, designed as a two by two balanced factorial design. Patients are blinded for the type of intervention i.e. laparoscopic or open surgery. Patients eligible for segmental colectomy, for malignant colorectal disease i.e. right and left colectomy and anterior resection will be randomised to either open or laparoscopic colectomy, and to either standard care or the fast track programme. This factorial design results in four treatment groups; open colectomy with standard care (a), open colectomy with fast track perioperative care (b), laparoscopic colectomy with standard care (c), and laparoscopic surgery with fast track perioperative care (d) (see Figure 1).

Randomisation is performed by an Internet randomisation module. Block-randomisation is used and the randomisation is stratified for the randomising centres.

Primary and secondary endpoints
The primary endpoint of the LAFA-study is total postoperative hospital stay in days, including hospital stay of patients who are readmitted within 30 days after surgery. Secondary endpoints are quality of life at two and four weeks after surgery. Quality of life will be measured by two validated questionnaires; Short Form 36 (SF-36) and the Gastro-Intestinal Quality of Life Index (GIQLI). Further secondary endpoints are; medical and non medical costs, morbidity, and mortality within 30 days after surgery, patient satisfaction measured by standardised questionnaires, and readmission rate.

Participating centres
Nine Dutch hospitals of the LAFA-study group, including three academic centres and four non-academic centres, will enroll patients.
**Study population**

The study population consists of patients eligible for segmental colectomy for malignant colorectal disease, *i.e.* right and left colectomy and anterior resection. Inclusion criteria are: age between 40 and 80 years, colorectal cancer including colon and recto-sigmoid cancers, ASA I-III, and informed consent. Exclusion criteria are: prior midline laparotomy, ASA IV, laparoscopic surgeon not available, emergency surgery and a planned stoma.
**Ethics**

This study is conducted in accordance with the principles of the Declaration of Helsinki and ‘good clinical practice’ guidelines. The independent medical ethics committees of the participating hospitals have approved the study protocol. Prior to randomisation, written informed consent will be obtained from all patients.

**Study outline**

Informed consent will be obtained at the outpatient department if the patient fulfils the inclusion and exclusion criteria. Randomisation is performed instantly through the study website.

The randomisation produces four treatment groups; open colectomy with standard care (a), open colectomy with fast track perioperative care (b), laparoscopic colectomy with standard care (c), and laparoscopic surgery with fast track perioperative care (d) (see Figure 1). Patients that are randomised to fast track perioperative care will be informed by a “fast track” trial nurse and by the anaesthesiologist about the essence of the fast track programme. Appointments for these consultations will be made after consulting the surgeon and randomisation has been done. All patients randomised to have a fast track perioperative treatment will be admitted to a separate “fast track” ward, where the nurses and medical staff are trained in fast track perioperative management.

Patients who will receive standard treatment are not counselled by the fast track nurse and will have a standard preassessment by the anaesthesiologist. Patient and medical staff will be blinded for the surgical approach until the day of discharge by applying a covering abdominal bandage.

**Surgery**

Both open and laparoscopic surgery is done according to the technique applied by the local surgeon. Antibiotic prophylaxis is done according to hospital protocol. All patients will have two enemas before surgery (evening before and morning before). After surgery the surgical wounds are covered with an abdominal dressing in order to blind the medical staff for the type of approach. A requirement for the participating laparoscopic surgeons to perform laparoscopic colectomy for cancer is a minimum of 20 laparoscopic colectomies for benign disease as indicated by the proclamation of the American Society of the Colon and Rectum Surgeons in 2004.20,21

**Fast track and standard care**

Comparison of the different strategies is only possible when a fast track programme is running sufficiently and patients are nursed separately depending on the results of randomisation either on a standard care or fast track ward in order to avoid a bias towards fast track treatment by the nursing and medical staff. Patients that have standard care cannot be nursed by nurses that have experience with fast track care. Fast track multimodal management is done according to the protocol summarized in Table 1.
### Table 1. Differences between fast-track and traditional care protocol

<table>
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<tr>
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<th>Fast-track Care</th>
<th>Traditional Care</th>
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<tr>
<td><strong>Pre-operative phase</strong></td>
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| Outpatient department of Surgery | - Scheduling of operation  
- Information about FT  
- Informed consent | - Scheduling of operation |
| Outpatient department of anaesthesiology | - Pre-assessment for risk adjustment  
- Discussion focusing on placement of thoracic epidural catheter for management of perioperative analgesia | - Pre-assessment for risk adjustment  
- Open discussion about different possibilities for management of perioperative analgesia (i.e. placement of epidural catheter on any level, patient controlled analgesia with morphine (PCA-morphine) or continuous IV morphine infusion |
| Pre-admission guided tour on surgical ward | - Yes | - No tour |
| **Day of admission** |                                                                                |                                                                                |
| Pre-operative fasting | - Last meal 6 h before operation  
- Last clear drink (CHL) 2h before operation | - Last meal until midnight  
- No oral intake at the day of surgery |
| Pre-anaesthetic medication | - Lorazepam, 1 mg the evening before operation if necessary | - Lorazepam, 1 mg or temazepam 10 or 20 mg the evening before operation  
- Lorazepam 1mg, temazepam 10 or 20 mg, or midazolam 7.5 mg at the day of operation |
| **Day of Surgery** |                                                                                |                                                                                |
| Anaesthetic management | - Placement of thoracic epidural catheter (T6-T10, depending on the surgical resection); test-dose (bupivacaine 0.25% with adrenaline 1:200,000), top-up dose (bupivacaine 0.25% ±10 ml) with sufentanil 25 μg, followed by continuous infusion (bupivacaine 0.125% with fentanyl 2.5 μg.ml-1) until day 2 postoperative | - IV morphine loading (0.1 mg.kg-1) followed by continuous IV morphine infusion or PCA-morphine, OR placement of epidural catheter (T10-L1, test dose, top-up dose and continuous infusion in the same way as for fast track) when an open surgical procedure will be performed  
- IV morphine loading (0.05-0.1 mg.kg-1) followed by PCA-morphine or continuous IV morphine infusion when a laparoscopic surgical procedure is performed |
| - Combined with balanced general anaesthesia | - Restricted per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 6 ml.kg-1.h-1) | - Standard per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 10-12 ml.kg-1.h-1) |
| - Use of vasopressor drugs as 1st choice for management of mean blood pressure drop > 20% of baseline | - Use of extra fluid challenge as 1st choice for management of mean blood pressure drop > 20% below baseline |
### Surgical Management
- Minimal invasive incisions
- Supra-pubic urine catheter
- Infiltration of surgical wounds with bupivacaine
- Naso-gastric tube remain until day 1 after surgery
- Use of odansetron, dexamethasone or droperidol for PONV management according to attending anaesthesiologist

### Early post-operative management
- No standard use of abdominal drains
- Use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 is added
- Continuous IV morphine infusion or PCA-morphine OR use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 and/or diclofenac 3 x 50 mg.d-1 are added
- First oral drinks at 2 h post-surgery + IV infusion of RL 1.5 l.d-1
- Mobilisation in the evening (>2 h out of bed)
- First semi-solid food intake in the evening
- Bed rest

### Day 1 after Surgery
- Oral intake > 2.1 (including 4 units CHL drinks), offer solid food
- Stop IV fluid administration (leave canulla)
- Start laxative (MgO, 2 x 1g.d-1)
- Close supra-pubic urine catheter and remove when residue < 50 ml
- Expand mobilisation (> 6 h out of bed)
- Diet increased on daily basis when normal bowel sounds are examined
- IV fluid administration (2.5 l.d-1) is continued till adequate oral fluid intake
- Start laxative (MgO, 2 x 1 g.d-1)
- Close supra-pubic urine catheter and remove when residue < 50 ml

### Day 2 after surgery
- Offer solid food
- Expand mobilisation (> 8 hours)
- Plan discharge
- Continue as on day 1 until discharge criteria are fulfilled

### Day 3 after surgery
- Remove epidural catheter
- Continue Paracetamol 4x1000 mg
- Add NSAID
- Remove IV cannula
- Expand mobilisation (> 8 hours)
- Evaluating discharge criteria; discharge if fulfilled
- Continue as on day 1 until discharge criteria are fulfilled

### Day 4 after surgery
- Continue as on day 3 until discharge criteria are fulfilled
- Continue as on day 1 until discharge criteria are fulfilled

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FT: Fast-track; TC: Traditional care; CHL: carbohydrate loaded drink (Nutridrink®)
Discharge criteria

Since hospital stay is a primary efficacy parameter, the discharge criteria are defined. Every postoperative day will be noted whether the discharge criteria are met, and other reasons of prolonged hospital stay e.g. social environment or patient inacceptance. The discharge criteria include adequate pain control with oral analgesics, no nausea, ability to take solid foods, passage of flatus and/or stool, mobilisation and self support as compared to the preoperative level, and acceptance by the patient.

Statistical analysis

Intention to treat
The analysis will be performed in accordance with the intention to treat principle.

Sample size calculation
Since both, fast track care and laparoscopy focus on earlier recovery resulting in a reduction of hospital stay, the latter is used as primary efficacy parameter. The mean postoperative hospital stay for segmental bowel resection with standard care is nine days with a standard deviation of 2.5 days in the Academic Medical Centre Amsterdam. Using a 5% significance level, a total sample size of 400 would have a power of >95% to detect a minimum reduction of one day in hospital stay between laparoscopic surgery and open surgery, a one day reduction in hospital stay between fast track care and standard care, and a power of 80% to detect the same difference between the combination of fast track care with laparoscopic surgery and current treatment.
A much larger difference can be expected between the other treatment groups, for instance open surgery and standard care compared to fast track perioperative care and laparoscopic surgery. In order to obtain results with adequate precision we have calculated group size using a difference of one day rather than the expected 2-4 days. With a group size of one hundred patients per arm it is possible to find a significant difference (alpha=0.05, beta=0.1) of at least 10% in subscales of the SF-36, a validated quality of life questionnaire, at two weeks after surgery. Liem et al. demonstrated 20-30% differences in subscales of the SF-36 between laparoscopic versus open hernia repair one week after surgery. Maartense et al. found a 10% difference in physical and social function two weeks after surgery comparing laparoscopic versus open ileocolic resection in a randomised study from our institution.

Economic evaluation
The marginal direct medical, non-medical and time cost differences will be calculated for the four treatment strategies. These will include the additional costs of laparoscopy, of fast track care, as well as the differences due to complications and readmissions.
Data collection and monitoring

Data are collected via a secured internet module which is specially designed for the LAFA-study. Data are collected daily until the day of discharge. Preoperatively, and at two and four weeks postoperatively the questionnaires (SF-36 and GIQLI) are filled in by the patient. One month postoperatively, the general practitioner is contacted to inform whether he/she was contacted by the patient for problems related to the operation. There will be regular contact between the study coordinators and the participating centres. One research fellow will monitor the included data of every patient.

Discussion

Fast track programmes in colonic surgery have been introduced more than a decade ago with favourable early results. Many elements of these fast track programmes are based on solid evidence derived from randomised trials and systematic reviews. However, it is quite surprising, that implementation in daily practice has so far stayed behind.\textsuperscript{26-28} This can partly be explained by the necessity to break with long-standing traditions, such as preoperative fasting, slow postoperative advancement of oral feeding, and delayed mobilisation. In a recent systematic review including six comparative single centre studies, fast track programmes were found to reduce the time spent in the hospital and were found to be safe in major abdominal surgery. However, this systematic review demonstrated that the evidence on fast track colonic surgery was scarce.\textsuperscript{29} Both, laparoscopic surgery and fast track programmes are costly and require extensive expertise. Laparoscopic surgery is costly due to expensive disposables and additional operating time. Furthermore, a considerable learning curve must be mastered. Only 5-8\% of the colectomies are therefore done laparoscopically in the Netherlands. Fast track multimodal perioperative care requires additional personnel trained in several aspects of the fast track programme to make the programme work. It is clear that both, laparoscopic surgery and fast track programmes enhance recovery and thereby reduce hospital stay.\textsuperscript{2,8,29-32} Shortening hospital stay and reduction of morbidity are attractive, since both increase the availability of beds and might reduce the overall cost of hospital stay. However, despite the current enthusiasm and implementation into daily practice of fast track care and laparoscopic surgery, there are few data available that provide evidence on the optimal combination (laparoscopic or open surgery and fast track or standard care) in terms of shorter hospital stay, reduced morbidity and cost effectiveness. The largest reduction in hospital stay can probably be achieved by a combination of fast track programmes and laparoscopic surgery. However, it is not known what the additional costs of laparoscopic surgery or fast track programmes are compared to the reduction in hospital stay that can be achieved with these programmes. Since the average postoperative hospital stay after segmental colectomy is still considerable in the Netherlands as well as throughout Europe, an enormous improvement can be expected applying fast track
programmes and/or laparoscopy. The relative contribution to the reduction in hospital stay of both methods is unknown. This must be assessed in a setting where patients are blinded for the approach of surgery. The randomised controlled LAFA-trial was conceived to determine whether laparoscopic surgery, fast track perioperative care or a combination of both is to be preferred over open surgery with standard care in patients undergoing segmental colectomy for malignant disease.

Reference List


Part 2

Complications in colorectal surgery