Perioperative selective decontamination of the digestive tract and standard antibiotic prophylaxis versus standard antibiotic prophylaxis alone in elective colorectal cancer patients

A multicentre randomized clinical trial, the SELECT Trial

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ABSTRACT

INTRODUCTION: Infectious complications and especially anastomotic leakage (AL) severely impede the recuperation of patients following colorectal cancer (CRC) surgery. When the normal gut barrier fails, as in AL, pathogenic microorganisms can enter the circulation and may cause severe sepsis which is associated with substantial mortality. Moreover, AL has a negative impact on the CRC prognosis. Selective decontamination of the digestive tract (SDD) employs oral nonabsorbable antibiotics to eradicate pathogenic microorganisms before elective tumour resection.

METHODS: In this multicentre randomised clinical trial, perioperative SDD in addition to standard antibiotic prophylaxis is compared with standard antibiotic prophylaxis alone in patients with CRC who undergo elective surgical resection with a curative intent. The SDD regimen consists of colistin, tobramycin and amphotericin B. The primary objectives of this randomised clinical trial are to evaluate if perioperative SDD reduces the incidence of clinical AL and its septic consequences as well as other infectious complications. A main secondary objective is improvement of the cancer-free survival. A total of 762 patients will be included in total for sufficient power.

CONCLUSION: It is hypothesised that SDD will reduce clinical AL thereby reducing the morbidity and the mortality in CRC patients.

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TRIAL REGISTRATION: The trial is registered at ClinicalTrials.gov: NCT01740947.

In Western countries, approximately 5% of men and women will be diagnosed with colorectal cancer (CRC) during their lifetime [1]. Surgery remains the mainstay for curative treatment of CRC. During the post-operative phase, infectious complications are an important clinical problem with an incidence of 20-40% [2, 3]. Anastomotic leakage (AL) is a particularly severe and potentially devastating complication with an incidence ranging from 4% and 28%, depending on definitions, but generally considered to average 8-10%. AL is associated with substantial additional morbidity and considerable mortality rates ranging from 6% to 37% [4, 5]. Treatment of complications requires specialised care and is associated with major health-care costs. In addition to these short-term consequences for patients, there is mounting evidence linking AL with increased tumour recurrence and poor survival. AL has been shown to be an independent risk factor associated with poor cancer-specific survival after resection of CRC [4, 5]. AL implicates insufficiency of the gut barrier function and allows potentially pathological microorganisms (PPM) that colonise the digestive tract to enter the peritoneal cavity or the blood circulation. Furthermore, blood-borne Gram-negative bacteria and their endotoxins (also known as lipopolysaccharides (LPS)) contribute to the pathogenesis of sepsis and are associated with shock and multiple organ failure [6]. Limiting exposure to these specific endogenous PPM and their endotoxins during the post-operative phase may be a rational way of diminishing infectious complications, including the clinical consequences of AL. Aerobic Gram-negative bacteria expressing LPS on their cell surface can be eradicated by means of selective decontamination of the digestive tract (SDD). SDD is based on the application of oral nonabsorbable antibiotics [7, 8]. As an antimicrobial prophylaxis regime, it is designed to prevent or minimise the impact of endogenous infections by PPM. This group of microorganisms originates from the patient's digestive tract and consists predominantly of aerobic Gram-negative bacteria and fungi. Selective eradication of oropharyngeal and gastro-intestinal carriage of PPM is achieved by oral administration of the non-absorbable SDD suspension. SDD is effective against PPM such as aerobic Gram-negative bacteria, including *Enterobacteriaceae (Escherichia coli* species, *Klebsiella, Proteus* and *Enterobacter* species) and *Pseudomonas aeruginosa*, but also *Staphylococcus*

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TABLE 1

Definition of endpoints.

	Description
Primary endpoint *Clinical AL*	Clinical and/or radiological evidence of anastomotic dehiscence requiring surgical or radiological (re)intervention An intra-abdominal abscess localised) in the proximity (or same abdominal quadrant) of the anastomosis is considered clinical AL if it requires intervention
Secondary endpoints	
Other post-operative infectious complications	Pneumonia, urinary tract infections, surgical-site infections, wound dehiscence, remote intra-abdominal abscess
Disease-free survival at 3 and 5 yrs	
Non-infectious complications	Including cardiac failure, cerebrovascular events, deep venous thrombosis
Perioperative mortality	Defined as deaths occurring during hospitalisation or within 30 days of discharge
Readmission rate	
Reintervention rate	
Duration of hospital stay	
Quality of life (quality-adjusted life years)	Euro-Qol 5D, SF-36, GIQLI questionnaires
Cost-effectiveness	SF-H&L

AL = anastomotic leakage; Euro-Qol 5D = European Quality of Life 5D; GIQLI = Gastrointestinal Quality of Life Index; SF-36 = Short Form 36; SF-H&L = Short Form Health and Labour.

aureus and yeasts. The indigenous anaerobobic flora that protect against overgrowth of potentially pathogenic microorganisms, also known as colonization resistance, is left undisturbed by SDD [9].

Here, we present the SELECT trial protocol. The aim of this trial is to investigate a possible protective effect of perioperative SDD in elective CRC patients who undergo elective surgery.

METHODS

Study objectives and hypothesis

The primary objective of the present study is to evaluate whether perioperative SDD is effective in reducing clinical AL rates and, secondarily, the incidence of other post-operative infectious complications following elective CRC surgery. We hypothesise that restricting exposure to specific endogenous PPM and their endotoxins during the post-operative phase could be a realistic way to decrease infectious complications including the clinical consequences of AL. PPM are predominantly composed of aerobic Gram-negative bacteria expressing LPS, and they can be eliminated by means of selective decontamination of the digestive tract (SDD) using oral non-absorbable antibiotics.

Another secondary objective is to investigate oncological outcome in terms of disease-free survival and overall survival. As AL has been shown to negatively influence long-term survival, we hypothesise that reducing this severe infectious complication may improve the oncological outcome. In addition, by decreasing these complication rates we aim to reduce health-care costs substantially as we anticipate a significant decrease in the reoperation/re-intervention rate, intensive care unit (ICU) admission rates and hospital days, which will all be analysed as well (**Table 1**). We also hypothesise that the use of perioperative SDD will improve the quality of life of patients, which will also be evaluated. A reduction of both severe infectious complications after surgery and the risk of developing post-surgical metastases are of the utmost significance for the well-being of CRC patients.

Design

This trial is a randomised multicentre study comparing perioperative SDD combined with standard antibiotic prophylaxis (n = 381) with standard antibiotic prophylaxis alone (n = 381) in elective CRC surgery patients. Clinical decision-making is identical in the two groups in the post-operative period.

Patient recruitment and randomisation

Patients will be recruited by the participating hospitals of the SELECT trial group, which is comprised of one academic and seven teaching hospitals in The Netherlands. Inclusion and exclusion criteria are shown in **Table 2**. Scheduled inclusion will take place during a 24-month period. After all inclusion and exclusion criteria have been verified and informed consent has been obtained, randomisation will be performed via an internet-based randomisation programme at the SELECT Trial website. Allocation will be stratified according to participating centre and tumour localisation (colon or rectum).
A unique patient identification code is generated and corresponds with either the allocated intervention or the standard treatment regimen. A standardised online case record form (CRF) will be used and is available online at the study location. This CRF is web-based via a secured internet module.

Study drug

SDD is a 10 ml suspension containing 5 ml amphotericine B (500 mg) suspension and 5 ml colistin sulphate (100 mg) and tobramycin (80 mg) suspension. The suspension is applicable for oral administration.

Intervention group

The intervention group receives the study drug orally four times daily, starting three days before surgery, and medication is continued until either normal bowel passage or a minimum of three days after surgery. In case of a post-operative nasogastric tube for gastroparalysis or post-operative ileus, the nasogastric tube will be oc-

cluded for thirty minutes when administering SDD. Normal bowel passage is defined as toleration of a normal diet and oral intake of more than one litre of fluids per 24 hours. In addition, a single preoperative parenteral dose of cefazoline (Kefzol) 1,000 mg and metronidazole (Flagyl) 500 mg is given. A peroperative rectal swap will be taken in all patients.

Control group

The control group routinely receives a single parenteral dose of cefazoline 1,000 mg and metronidazole 500 mg preoperatively. Also, a peroperative rectal swap will be taken from all patients.

Rectal swab

A peroperative rectal swap will be taken in all patients and analysed with the interspace-profiling method (IS-pro) technique in order to confirm the effectiveness of the decontamination. IS-pro is a new polymerase chain reaction (PCR)-based profiling technique for high-throughput analysis of the human intestinal microbiota [10].

Data collection

Baseline characteristics including age, gender, co-morbidity, American Society of Anesthesiologists physical status (ASA classification), smoking habits, alcohol intake, body mass index, surgical history and preoperative radio(chemo)therapy are obtained. Preoperative blood samples are taken and haemoglobin, white blood cell count (WBC), carcino-embryonic antigen (CEA) and C reactive protein (CRP) are determined. In addition, intraoperative data including tumour localisation, type of surgical procedure (laparoscopy or open), duration of surgery, blood loss, type of anastomosis and diverting ileostomy will be documented. Post-operative blood samples (standard day +1 and +3, including inflammatory parameters), histopathological classification of the tumour, tumour-node-metastasis classification (TNM classification), use of non-steroidal anti-inflammatory drugs (NSAID), radicality and (type of) adjuvant therapy will be recorded.

Statistics

A power analysis on anastomotic leakage as primary endpoint was performed using a power of 80% at a confidence level of 95%. Assuming a 9% anastomotic leakage rate in the control group (H0 = 9%) and an estimated 4% in the intervention group, 381 patients need to be included per treatment arm for a total of 762 patients. All data will be collected in an online OpenClinica database, and statistical analyses will be performed using SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA).

Percentage differences in baseline values between groups will be compared using the Pearson's χ^2-test or Fisher's exact test. Comparison of continuous data will be done by use of the Mann Whitney test. The logrank test is used to make univariate comparisons. Disease-free survival and overall survival are depicted as Kaplan Meier curves. Multivariate analyses of primary endpoints and survival outcomes will be done by use of Cox regression analysis. p-values ≤ 0.05 are considered statistically significant. 95% confidence intervals (CI) are reported as well. The main analyses will be based on an intention-to-treat basis.

The economic evaluation will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis. The main analyses include costs per day reduction to achieve full recovery and costs per quality-adjusted life year (QALY) gained. Additional sensitivity analyses of differences in possible subgroups will be performed. This will include different age groups, gender groups and colon versus rectal cancer patients. All related costs will be estimated based on the actual input terms of resource use and personnel in the in-hospital period. For all cost-items such as hospital admission,

TABLE 2

Inclusion and exclusion criteria.

Inclusion criteria
Elective colon and/or rectal cancer surgery with primary anastomosis
Elective colorectal surgery for suspected carcinoma with primary anastomosis
No evidence of distant metastases (preoperative CT-abdomen and X-thorax or CT-thorax)
Procedure either with or without diverting stoma
Both laparoscopic and open surgery
Informed consent
Aged ≥ 18 yrs
Exclusion criteria
Previous colorectal malignancy
Synchronous malignancy currently undergoing treatment
Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
Previous surgery for diverticular disease
Performance status ASA ≥ 4
Expected adverse reactions/allergies for study medication
Prednisone use > 5 mg/day
FAP coli (Lynch syndrome), HNPCC
Mental disorder/unable to give informed consent
Pregnancy
Post-randomization:
No resection/unresectable
No anastomosis constructed
Macroscopic (R2) or microscopic (R1) incomplete tumour resection (for secondary endpoint oncological outcome)
No adenocarcinoma (in resected specimen) (for secondary endpoint oncological outcome)

ASA = American Society for Anaesthesiologists; CT = computed tomography; FAP = familial adenomatous polyposis; HNPCC = hereditary non-polyposis colorectal cancer.

ABBREVIATIONS

AL = anastomotic leakage
CRC = colorectal cancer
CRF = case record form
ICU = intensive care unit
LPS = lipopolysaccharide
PPM = potentially pathological microorganisms
SDD = selective decontamination of the digestive tract

medication used, and diagnostic tests, unit costs will be derived from the Dutch costing manual or determined in cooperation with the hospital administration. Direct medical costs will be recorded in the case record forms. Indirect costs arising from losses in productivity will be assessed by means of the Health and Labour questionnaire and will be calculated by means of the friction cost method [11].

Ethics

The study will be conducted according to the principles of the Declaration of Helsinki (6. rev, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and acts as well as good clinical practice. The Vrije Universiteit (VU) medical centre Medical Ethics Committee and The Central Committee on Research Involving Human Subjects have approved the study.

Trial registration: The trial is registered at ClinicalTrials.gov, identifier: NCT01740947. Acronym: SELECT.

DISCUSSION

The multicentre randomised SELECT trial aims to reduce clinical AL rates. We presume that by limiting exposure to specific endogenous PPM and their endotoxins during the post-operative phase, infectious complications including clinical AL and its consequences will be reduced. Endotoxin, an LPS and constituent of the cell wall of Gram-negative bacteria, is an important mediator in sepsis and associated with shock and multiple organ failure [6]. We previously demonstrated that either abdominal surgery or LPS injection increased adherence of circulating tumour cells in the livers of rats [12-14]. Furthermore, perioperative exposure to LPS has been implicated in accelerated metastatic tumour growth in several experimental tumour models [15, 16]. Moreover, continued and repetitive exposure to LPS such as during abdominal sepsis results in reduced (cellular) immune responsiveness or even immune paralysis. This immunosuppression may impede an effective antitumor response and may contribute to the development of metastases following CRC resection [13, 14]. These mechanisms may explain the enhanced recurrence rates observed in CRC patients that have had AL after curative resection [4, 5].

So far, SDD has shown encouraging results in terms of significantly reducing infectious complications and AL in several studies in which oesophagogastric cancer surgery was performed [17, 18]. Furthermore, Roos et al recently published a retrospective case controlled study and a monocentre randomised controlled trial on SDD treatment in digestive surgery patients [19, 20]. Both studies supported a significant decrease in infectious complications and AL rates for CRC surgery patients. Length of hospital stay and mortality did not differ between groups in this population. These results, however, are only from studies with small samples in a monocentre setting and not powered for AL [20]. In addition, several intensive care unit-related studies have shown that SDD does not seem to lead to development of resistance [8, 21].

The abovementioned promising results with regard to clinical AL and other post-operative infectious complications and, as a consequence, the hypothesised effects on oncological outcome prompted us to instigate this multicentre clinical trial in order to add a valuable improvement to CRC treatment.

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