

**PREPARATION WITH MECHANICAL BOWEL CLEANSING  
OR ORAL ANTIBIOTICS AND MECHANICAL BOWEL PREPARATION  
FOR ELECTIVE RESECTION OF RECTUM**

A Two Arm Multicentre Randomised Controlled Study

The **MECCLANT-R** Trial

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## **INTRODUCTION**

During almost the whole of the 20<sup>th</sup> century and practically based on observational studies and experts opinion, mechanical bowel cleansing (MBC) has been considered as necessary prior to colorectal surgery, in order to remove gross faecal and bacteria colonic load and thus to prevent anastomotic leakage and reduce septic postoperative complications [1-7]. However, several more recent randomised clinical trials [8-16], meta-analyses, systematic reviews and surveys [17-25] have consistently shown that MBC does not prevent either anastomotic leakage or surgical site infection (SSI), and does not reduce immediate postoperative morbidity or mortality. Furthermore, MBC is costly, time consuming, harmful and unpleasant for the patient, and also impedes implementation of enhanced recovery programmes [26]. As a result of the aforementioned evidence, it is recommended that MBC for colorectal surgery must be abandoned.

However, even more recently, the interest in bowel preparation for colorectal surgery has been renewed, as when MBC combined with oral antibiotics seems to reduce postoperative morbidity, by preventing both anastomotic leakage and SSI, according to several clinical trials and reviews and meta-analyses [23,27-36]. Furthermore and according to three studies that analyzed data from the Colectomy-Targeted American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) of the years 2011 and 2012, it was shown that oral antibiotics bowel preparation with [37,38] or without [39] MBC in colorectal surgery is associated with reduced rates of anastomotic leakage, SSI and hospital readmissions as compared to no bowel preparation. According to the study by Morris et al [39], it is bowel preparation with oral antibiotics alone that results in reduced postoperative septic complications.

Most of the studies showing benefit for oral antibiotics bowel preparation i) are either retrospective clinical trials or analyses of large databases; ii) analyze cases with varying pathology involving malignant and benign neoplastic lesions and inflammatory diseases; iii) are heterogeneous as regards the exact antibiotic regime and time of administration; iv) do not report on the exact regime for mechanical bowel preparation; v) do not analyze according to procedure (left colectomy, right colectomy, low anterior resection of rectum) and site of anastomosis (ileo-transverse, colo-colic, colorectal, colo-anal); vi) mostly exclude cases with anastomosis and diverting stoma; and vii) do not report on the possible impact of enhanced recovery programmes (ERP) if they were implemented.

## **AIM-HYPOTHESIS**

The present study aims to compare the immediate postoperative outcomes of elective rectal resections, after preoperative MBC with or without preoperative oral antibiotics (OA) administration. It is hypothesized that preoperative OA administration, in the frame of an ERP, is the main preparative element that is associated with reduced immediate postoperative morbidity, in terms of SSI and, possibly, anastomotic leakage.

## **DESIGN – STUDY APPROVAL**

The MECLANT-R trial is a phase III prospective, randomized, two arm, comparative, multicenter study supported by the Gastro-Intestinal Cancer Study

Group (GIC-SG). A committee, under the guidance, coordination and secretarial support of the Colo-Rectal Cancer Study Group (CRC-SG) of the GIC-SG, is assigned for constant and systematic data monitoring (DMC). Participating centers register all data in a specifically designed database under the control of the DMC. Also, patients' randomization is provided by the DMC through the online data capturing system (REDCAP), to which serious adverse events and patients withdrawal from the study are reported.

## **PATIENS**

Inclusion and exclusion criteria are shown in tables 1 and 2 respectively. Primary pathology, demographic data, health status and comorbidities of eligible patients are shown in table 3 and should be registered. Eligible patients will be randomly allocated to one of the following two arms:

- Arm A: mechanical bowel cleansing (MBC)
- Arm B: mechanical bowel cleansing plus oral antibiotics (MBC+OA)

Randomization will be performed by the DMC, with stratification by participating centre.

## ***Discussion***

Theoretically, the question, of which sort of preoperative bowel preparation should achieve the lowest SSI rate, could be answered by a four-arm comparative study: In one Arm patients would have no preparation at all, in a second arm patients would have only MBC, in a third patients would have only oral antibiotics, and in the fourth patients would be given a combination of MBC and oral antibiotics. According to the current evidence [17-25,37-39], there is no significant difference in SSI rate between the first and the second treatment, while differences between the third and the fourth treatment are around 1 percent or less. Conceivably, a four-arm study would require an enormous number of patients to be recruited in the study, in order to be able to identify possible differences among groups. Therefore, between no preparation and preparation with only MBC, we chose MBC as the control arm, whilst between only oral antibiotics and combination of oral antibiotics and MBC we chose the latter as the experimental arm. The reason for adopting MBC in both arms is the need of a clear colon, as in the majority of the cases with resection of the rectum and anastomosis, a defunctioning stoma complements the operation in order to reduce the rate and severity of possible anastomotic leak.

## **DESIGN - METHODS**

All patients:

- enter an enhanced recovery programme (ERP) [40,41]. Included elements are shown in table 4.
- are instructed to low residue diet for 3-4 days prior to surgery, and beverages rich in carbohydrates, 2 hours prior to surgery.
- are given 500ml sodium phosphate solution as an enema, at 18:00 the day prior to surgery.
- are given antibiotics intravenously (1.5gr cefuroxime and 1gr metronidazole), on the day of operation, one hour prior to first abdominal incision. The regime of intravenous i.v. antibiotic prophylaxis can be adjusted according to the guidelines for prevention of surgical site infection set at each participating centre, or in case of patient's allergy to a specific antibiotic agent.

Patients allocated to Arms A or B consume per os 3-4 lt of either Klean Prep (Norgine Ltd, Uxbridge, UK) or Fortrans (Beaufour IPSEN Industry, Dreux, France) as MBC. MBC starts at 14:00 and ends by 18:00 on the day prior to surgery.

Patients allocated to Arm B are additionally given oral antibiotic prophylaxis as follows:

- 2gr of neomycin at 19:00 the day prior to surgery and
- 1,5gr of metronidazole at 21:00 the day prior to surgery

Compliance and any reactions to the MBC regime, namely intolerance, allergy, nausea, vomiting, dehydration, electrolytes disturbance or renal failure are recorded. Also, any intolerance, allergic reactions, gastrointestinal disturbances to the antibiotic regime, and clinical manifestation of pseudomembranous colitis (*clostridium difficile* infection) are recorded in detail.

### **Surgery**

Prior to surgery an epidural catheter for intra- and post- operative analgesia is placed at the level T6-T8. If placement of an epidural catheter is contraindicated or the anaesthetist considers epidural anesthesia unnecessary, postoperative analgesia is offered by means of patient controlled anaesthesia (PCA) with opioids. Optionally, analgesia can be offered with intravenous lidocaine. Recorded intraoperative elements should include mode of approach (open or laparoscopic), type of resection, site and method of anastomosis fashioning, intraoperative complications (bleeding, perforation of hollow viscera [large bowel or other], technical failure of anastomosis), prophylactic stoma, duration of operation etc.

### **END POINTS**

Primary end points are:

- Incisional surgical site infection (SSI)
  - Superficial wound infection
  - Deep wound infection
  - Intrabdominal infection (contaminated fluid or pus collection)

Secondary end points are:

- Anastomotic leakage 30-day mortality
- 30-day morbidity
- Paralytic ileus
- Length of hospital stay
- Readmission rate

Standard definitions for estimated of variables and outcomes are employed according to the Colectomy-Targeted American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) [42]. Specifically, the anastomotic leak is defined as:

- A leak of intraluminal contents (air, fluids, fecal material) through the anastomosis, that either drain or form a collection or
- A leak of intraluminal contrast medium through the anastomosis or

- Presence of infection or abscess, thought to be related to the anastomosis, even if anastomotic leak cannot be demonstrated by contrast medium extravasation [28].

All data on postoperative outcomes, including clinical manifestations and laboratory findings, are recorded.

#### **SAMPLE SIZE ESTIMATION - STATISTICAL ANALYSIS**

The SSI rate will be the primary end-point. Considering i) an  $\alpha=0.05$ , iii) a SSI rate of 0.12 for Arm A versus a SSI rate of 0.06 for Arm B, iii) randomization rate of 1:1 and iv) negligible drop-off rate, the sample size in each Arm should be 356 patients.

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**TABLE 1. Inclusion Criteria**

Patients to Undergo Surgery for Rectal Cancer With or Without Protective Stoma

Patients to Undergo Surgery for Rectal Benign Polyps (Solitary, Multiple)

Implementation of an Enhanced Recovery Programme (ERC)

Patient' s Informed Consent

**TABLE 2. Exclusion Criteria**

Patients Younger Than 18 Years of Age or Older Than 85 Years of Age  
Patients With Preoperative Hospital Stay >2 Days  
Patients to Undergo Non-Elective (Emergency) Operation  
Patients with Contraindication for Mechanical Bowel Preparation  
Patients Physically Unstable Requiring Intensive Preoperative Resuscitation  
Sepsis, Septic Shock, Systemic Inflammatory Response Syndrome (SIRS)  
Acute Respiratory Failure Requiring Mechanical Ventilation  
Acute Renal Failure  
American Society of Anesthesiologists (ASA) Physical Status Classification of 4  
or 5  
Patients With Infection at the Site of Abdominal Incision  
Patients with a History of Colo-Rectal Surgery  
Patients to Undergo Defunctioning Stoma Only  
Patients Incapable to Communicate and Provide Informed Consent  
Patients with a known allergy or intolerance to the aforementioned antibiotics  
(Neomycin, Cefuroxime and Metronidazole)

### **Table 3. Primary Pathology, Demographic Data, Health Status and Comorbidities of Eligible Patients**

#### ***Demographics***

Age, Sex  
Body Weight, Height, Body Mass Index (BMI)  
Race, Nationality

#### ***Primary Pathology***

Rectal Cancer, Location of Lesion  
Disseminated Rectal Cancer  
Benign Lesions (Solitary or Multiple Polyps- Location)  
FAP

#### ***Past Medical History***

Large Bowel Neoplasia  
Neoplasia Other Than Large Bowel  
Familial History of Large Bowel or Other Organ Neoplasia

#### ***Health Status***

American Society of Anesthesiologists (ASA) Classification  
General Status (at Admission) – ECOG

#### ***Comorbidities***

Diabetes Mellitus  
Chronic Obstructive-Restrictive Pulmonary Disease (CO-R-PD)  
Cardiac Failure – Congestive Heart Failure  
Hypertension  
Ischemic Heart Disease  
Renal Failure  
Cachexia  
Active Smoking  
Chronic Use of Steroids  
Chronic Use of Immunosuppressant  
Neo-Adjuvant Chemo- or/and Radio- Therapy  
Bleeding Disorders, Treatment with Anticoagulants

#### ***Laboratory Investigations***

Full Blood Count  
Liver Function Tests  
Serum Albumin  
Serum Electrolytes  
Serum Urea  
Serum Creatinine

## **Table 4. Elements of the Enhanced Recovery Programme**

### ***From Days -3-4 Until Day -1 Preoperatively***

Low residue diet

### ***Day -1 Preoperatively***

Oral and written information of patient and relatives by surgeon and head nurse

Visit of anesthetist and explanation about epidural pump

Oral nutrition with high-calorie carbohydrate drinks until 2h prior to surgery

### ***Day 0 (Surgery)***

Limited intravenous administration of colloids

Placement of epidural catheter unless contraindicated

Placement of urethral catheter

Placement of nasogastric tube after intubation (optional)

Removal of nasogastric tube before extubation

High-calorie drinks a few hours after surgery

Mandatory 1-hour mobilization out of bed

Offer of 60% O<sub>2</sub> for 8h after extubation

Intraoperative active warming of patient

### ***Day 1 Postoperatively***

Beginning of oral solid diet

Mandatory 4-hour mobilization out of bed

Epidural analgesia: continuous infusion of local anesthetics and according to patient's needs (epidural-PCA) or i.v. opioids according to patient's need (PCA), or i.v. lidocaine

### ***Day 2 Postoperatively***

Removal of epidural catheter

Analgesia with NSAID drugs or paracetamol intramuscularly

Full mobilisation

### ***Day 3 Postoperatively***

Removal of urethral catheter if urine output >40 ml/h

### ***Days 4-5 Postoperatively***

Planned discharge, if general conditions and domiciliary environment permit