PREPARATION WITH MECHANICAL BOWEL CLEANSING AND ORAL ANTIBIOTICS OR NOTHING FOR ELECTIVE COLECTOMY

A Two Arm Multicentre Randomised Controlled Study

The **MECCLANT- C** Trial

***Registration (ID) Number**: EudraCT number 2016-000254-35*

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INTRODUCTION

During almost the whole of the 20th 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 MBP 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 antobiotics 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 analysed data form 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] MBP 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) analyse 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 MBC; v) do not analyse 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 colectomy for colon cancer, after no preoperative preparation or after preoperative preparation with MBP and oral antibiotics (OA) administration. It is hypothesised 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 MECLLAND-C 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, randomization of patients is provided by the DMC, to which any serious adverse events or 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: no bowel preparation (NBP)
- Arm B: mechanical bowel cleansing plus oral antibiotics (MBC+OA)

Randomization will be performed by the DMC and it is designed to happen automatically through the online data capture system (REDCAP), with stratification by participating centre.

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, no preoperative preparation was chosen for the control arm in order to avoid the side effects of MBC, whilst between only oral antibiotics and combination of oral antibiotics and MBC we chose the latter as the experimental arm.

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 (could be omitted for right colectomy with planned ileal - transverse colon anastomosis).
- 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 Arm B:

i) 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.
ii) are 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
It is recommended that 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 lindocaine. 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 is:
- 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 are should be 356 patients.

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TABLE 1. Inclusion Criteria

Patients to Undergo Surgery for Colon Cancer
Patients to Undergo Surgery for Colonic Benign Polyps (Solitary, Multiple)
Patients to Undergo Surgery for Diverticular Disease
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 Surgery for Rectal Cancer With or Without Protective Stoma
Patients to Undergo Total Procto-Colectomy with Ileal-Pouch – Anal Anastomosis
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 known allergy or intolerance to the aforementioned Antibiotics (Cefuroxime, Neomycin, 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
Colon Cancer, Location of Lesion
Disseminated Colon Cancer
Benign Lesions (Solitary Polyp – Location, Polyposis Syndrome)
Diverticular Disease

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 the method of analgesia
Oral nutrition with high-calorie carbohydrate drinks until 2h prior to surgery

Day 0 (Surgery)
Limited intravenous administration of colloids
Placement of epidural catheter (if it is the chosen method of analgesia) 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_2 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. lindocaine

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