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Preparation with Mechanical Bowel Cleansing or/and Oral Antibiotics or Nothing for Elective Colorectal Surgery: Two-Two-Arm Multicentre Randomised Controlled Studies (MECCLANT –C and –R Trials)

Evaghelos Xynos[1], Nikolaos Gouvas[2*], Christos Agalianos[3], Ioannis Balogiannis[4], Manoussos Christodoulakis[5], Dimitrios Korkolis[6], Dimitrios Manatakis[6], Dimitrios Lytras[7], Ioannis Papakonstantinou[8], Costas Stamou[9], Ioannis Triantaphyllidis[10], Georgios Tzovaras[11] and Georgios Zacharioudakis[12]

[1]*Creta Interclinic, Heraklion, Crete, Greece*

[2]*Acute Hospitals, Worcester, UK*

[3]*Naval and Veterans Hospital of Athens, Greece*

[4]*University Hospital, Larissa, Greece*

[5]*Venizeleion Hospital, Heraklion, Crete, Greece*

[6]*Agios Savvas Hospital, Athens, Greece*

[7]*Achillopouleion Hospital, Volos, Greece*

[8]*Aretaieion University Hospital, Athens, Greece*

[9]*Bioclinic, Athens, Greece*

[10]*General Hospital, Florina, Greece*

[11]*University Hospital, Larissa, Greece*

[12]*Hippokrateion University Hospital, Thessaloniki, Greece*

[*]**Corresponding author:** Nikolaos Gouvas, Acute Hospitals, UK, Tel: 00447946469727; E-mail: nikos.gouvas@gmail.com

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Abstract

Background: Based on sound evidence, traditional mechanical bowel preparation for elective colorectal surgery has mostly been abandoned during the last two decades. However, more recent evidence from USA large databases show that mechanical bowel preparation combined with oral antibiotics, reduces significantly surgical site infections (SSI) after elective colorectal surgery.

Hypothesis-Aim: We hypothesise that administration of oral antibiotics only, and not mechanical bowel preparation, is the main factor that prevents SSI. Furthermore, we consider that rectal surgery for cancer differs from colon surgery in that the former is usually associated with defunctioning stoma, which requires an empty colon.

Patients-Methods: Patients to be subjected to elective colectomy for colonic neoplasms or diverticular disease will be randomised to two arms; Arm A: no bowel preparation; Arm B: mechanical bowel preparation combined with oral antibiotics (MECCLAND –C Trial). Patients scheduled for elective low anterior resection of the rectum for rectal cancer will be randomised to two arms; Arm A: mechanical bowel preparation only; Arm B: mechanical bowel preparation combined with oral antibiotics (MECCLAND –R Trial). All patients will receive intravenous antibiotics one hour prior to first surgical incision. Enemas at the day prior to surgery are optional. Participating centres are advised to implement enhanced recovery programmes in all patients.

Primary End-Points: The primary end point is surgical site infection (SSI), including (i) superficial wound infection, (ii) deep wound infection, and (iii) intrabdominal infection (contaminated fluid or pus collection).

Statistical Points: Considering a SSI rate of 0.12 for Arm A *vs.* a SSI rate of 0.06 for Arm B, a randomization rate of 1:1 and negligible drop-off rate, the sample size of either Arm of either Trial should be 356 patients.

Keywords: Bowel preparation; Oral antibiotics; Randomized trial; Colon cancer; Rectal cancer

Introduction

During almost all the 20th century and practically based on observational studies and experts opinion, mechanical bowel preparation (MBP) 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 MBP does not prevent either anastomotic leakage or surgical site infection (SSI), and does not reduce immediate postoperative morbidity or mortality. Furthermore, MBP 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.

Recently, the interest in bowel preparation for colorectal surgery has been renewed, as when MBP 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) do not report on the exact antibiotic regime and time of administration; (iv) do not report on the exact regime for mechanical bowel preparation; (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 with diverting stoma; and vi) 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:

(a) Elective colectomy for colonic neoplastic lesions (cancer, benign solitary or multiple polyps) and diverticular disease, 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 MECCLAND –C Trial) and

(b) Elective rectal resections, after preoperative MBP with or without preoperative 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 (MECCLAND –R Trial).

Design-Study Approval

The MECLLAND -C and –R trials are two phase III prospective, randomized, two-arm, comparative, multicentre studies 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, to which any serious adverse events or patients withdrawal from the study are reported. The trials ID are:

MECCLAND –C Trial: EudraCT number 2016-000254-35.

MECCLAND –R Trial: EudraCT number 2016-001404-32.

Patients

MECCLAND –C trial

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

- Arm A: no bowel preparation (NBP)
- Arm B: mechanical bowel preparation plus oral antibiotics (MBP +OA)

Randomization will be performed by the DMC, with stratification by participating centre. The allocation result will be returned to the participating centre on the same day.

All Patients	Implementation of an Enhanced Recovery Programme (ERC)
	Patients Informed Consent
MECCLAND -C Trial	Patients to undergo surgery for colon cancer
	Patients to undergo surgery for colonic benign polyps (solitary, multiple)
	Patients to undergo surgery for diverticular disease
MECCLAND –R Trial	Patients to undergo surgery for rectal cancer with or without protective stoma
	Patients to undergo surgery for rectal benign polyps (solitary, multiple)

Table 1: Inclusion criteria.

MECCLAND –R trial

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

- Arm A: mechanical bowel preparation (MBP)
- Arm B: mechanical bowel preparation plus oral antibiotics (MBP +OA)

Randomization will be performed by the DMC, with stratification by participating centre. The allocation result will be returned to the participating centre on the same day.

All Patients
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 undergoing surgery for IBD
Patients undergoing panproctocolectomy for Familial Adenomatous Polyposis (FAP)

Table 2: Exclusion Criteria.

Design-Methods

All patients:

• Enter an enhanced recovery programme (ERP) [40,41]. Included elements are shown in table 1.

• Are instructed to low residue diet for 3-4 days prior to surgery, and beverages rich in carbohydrates, 2 h prior to surgery.

• Are given 500 ml 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 (1.5 g cefuroxime and 1g 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.

MECCLAND –C trial

Patients allocated to Arm A have no other bowel preparation.

Patients allocated to Arm B:

Consume per os 3-4 L of either Klean Prep (Norgine Ltd, Uxbridge, UK) or Fortrans (Beaufour IPSEN Industry, Dreux, France) as MBP. MBP starts at 14:00 and ends by 18:00 on the day prior to surgery.

Are given oral antibiotic prophylaxis as follows:

2 g of neomycin at 19:00 the day prior to surgery and

1.5 g of metronidazole at 21:00 the day prior to surgery.

MECCLAND –R trial

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

In addition, patients allocated to Arm B are additionally given oral antibiotic prophylaxis as follows:

• 2 g of neomycin at 19:00 the day prior to surgery and

• 1.5 g of metronidazole at 21:00 the day prior to surgery

Compliance and any reactions to the MBP 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. Intraoperative elements are recorded in detail, and 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

The primary end point is surgical site infection (SSI), including (i) superficial wound infection, (ii) deep wound infection, and (iii) intrabdominal infection (contaminated fluid or pus collection).

Secondary end points are (i) anastomotic leakage, (ii) 30-day mortality, (iii) 30-day morbidity, (iv) paralytic ileus, (v) length of hospital stay, and (vi) 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, faecal 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 and registered in a specific proforma.

Sample size estimation-statistical analysis

The SSI rate will be the primary end-point. Considering (i) an α=0.05, (iii) a SSI rate of 0.12 for Arm A *vs.* a SSI rate of 0.06 for Arm B, (iii) randomization rate of 1:1 and (iv) negligible drop-off rate, the sample size of either Arm of either Trial should be 356 patients.

Discussion

Concerning MECCLAND –C, the theoretical question, of which sort of preoperative bowel preparation should achieve the lowest SSI rate in elective colon surgery, 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 MBP, in a third patients would have only oral antibiotics, and in the fourth patients would be given a combination of MBP and oral antibiotics. According to 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% or less. Conceivably, a four-arm study would require an enormous number of patients to be recruited in the study, in order differences between the four treatments to reach statistical significance. Therefore, between no preparation and preparation with only MBP, we chose no preoperative preparation as the control arm in order to avoid the side effects of MBP, whilst between only oral antibiotics and combination of oral antibiotics and MBP we chose the latter as the experimental arm.

Similarly, as regards MECCLAND -R, the theoretical question, of which sort of preoperative bowel preparation should achieve the lowest SSI rate in elective low anterior resection of the rectum, could be answered also by a four-arm comparative study: in one Arm patients would have no preparation at all, in a second arm patients would have only MBP, in a third patients would have only oral antibiotics, and in the fourth patients would be given a combination of MBP and oral antibiotics. Again, and according to 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% or less. Conceivably, a four-arm study would require an enormous number of patients to be recruited in the study, in order differences between the four treatments to reach statistical significance. Therefore, between no preparation and preparation with only MBP, we chose MBP as the control arm, whilst between only oral antibiotics and combination of oral antibiotics and MBP we chose the latter as the experimental arm. The reason for adopting MBP 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.

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