Mechanical bowel preparation in elective open colon surgery

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Cover design and layout:
Printed by FEBODRUK BV, Enschede, The Netherlands
Financial support for publication of this thesis was provided by: the Nederlands Antilliaanse Stichting voor Klinisch Hoger Onderwijs, Astra Zeneca and is humbly appreciated.

Mechanical bowel preparation in elective open colon surgery

Preoperatieve darmvoorbereiding bij electieve open colon chirurgie

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor Promoties
Te verdedigen op woensdag 24 Mei 2006
klokke 16.15 uur

door

Patrick Regnier Fa-Si-Oen
geboren te Groningen
in 1971

Promotiecommissie

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To my grandparents

Un pueblo no ta mas ku e kurason di su yiunan

Mechanical bowel preparation in elective open colon surgery

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Introduction

Parts of this chapter have been published as review articles

Preoperatieve darmvoorbereiding in de colorectale chirurgie: de stand van zaken

Nederlands Tijdschrift voor Heelkunde 2001;1:3-6.

De zin van darmvoorbereiding bij aneurysmachirurgie

Nederlands Tijdschrift voor Heelkunde 2001;3:87-89.

The practice of preoperative bowel cleaning

In many surgical centers the bowel is thoroughly cleaned before colorectal surgery with the aim to prevent wound infection and anastomotic leakage. The modern practice dates from the 1970's when surgeons like Cohn, Nichols and Condon emphasized that mechanical cleaning of the bowel should be an essential part of the preoperative routine[1,2,3,4]. For those supporting these views the concept of cleaning the colon preoperatively seems to have a variety of attractions to the surgeon. Reducing the fecal contents may decrease intraoperative contamination of the peritoneal cavity and surgical wound, leading to less wound infection and less anastomosis infection and breakdown. Second, reducing fecal bulk may prevent a mechanical disruption of the fresh anastomosis and lead to easier handling of the bowel intraoperatively.
Through the years a number of methods have been applied for the cleaning of the preoperative colon.

Conventional bowel preparation
This method which has been applied for many years requires a patient admission to the hospital 3-5 days preoperatively to receive a low residue diet which is replaced by fluid 1-2 days prior to surgery. Additional purgation with a laxative is given for a couple of days, followed by enemata and rectal lavage just before surgery. This method which provides excellent clearance of the colon, is exhausting for the patient, results in significant starvation and electrolyte loss and is macro-economically expensive with regards to hospitalization. This method of preoperative bowel preparation has largely been abandoned in Western medicine[5,6].

Elemental diets
These solutions are designed for total absorption in the small bowel to reduce colon residue, while preventing patient starvation.
However, these solutions do not empty the colon of remaining residue nor do they reduce the concentration of microorganisms within the colon.
As with conventional bowel preparation this method requires extensive hospitalization and thus has never found widespread application as a mode of bowel preparation[7].

Whole gut irrigation
This method, which consists of irrigation of the bowel with an electrolyte solution through a nasogastric tube the day before surgery until clear fluid is produced rectally, was first proposed for the treatment of cholera and later modified for preoperative bowel preparation in 1973. This method was recognized as rapid, economical and effective with an excellent cleaning of the bowel, although fluid shift remained a problem. Strict contraindications for this method are obstruction, perforation of the gastro-intestinal tract and a toxic megacolon. Relative contraindications are renal insufficiency, congestive heart failure and bowel stenosis[8,9,10].

Oral bowel preparation or mechanical bowel preparation
Although whole bowel irrigation produced a well-cleansed colon, problems of fluid retention and the imposing use of a nasogastric tube and special toilet facilities remained. By the end of the 1970's methods of orally administered solutions to clean the human colon preoperatively were introduced. This method is nowadays referred to as mechanical bowel preparation.

Mannitol
The first agent to be used was mannitol, which as an olichosacharide is not absorbed and in a 5, 10 or 20% solution draws fluid into the lumen of the bowel by osmotic action. Mannitol, however, is fermented by enteric organisms and this resulted in an increased postoperative rate of septic complications and bowel explosions[11].

Polyethylene glycol
By the 1980's oral agents were introduced which induce bowel cleansing through osmotic fluid shifting and a contact laxative effect. In 1980 Davis et al. introduced polyethylene glycol as a means of cleaning the colon. It is an isotonic solution that contains hyper osmotic macrogol and sulphate, which are resorbed and as such induce a water secretion of 60cc/h with electrolyte shifting.
Through the years it has been used in a balanced electrolyte solution (ranging from Golytely to Kleanprep) to clean the preoperative bowel. It is generally recommended that the patient should drink 4 litres to achieve a clean colon, although the addition of bisacodyl can reduce this amount. The solution however, has a salty taste due to the sulphate.
This impairment has been partially nullified by flavoring the solution. Patient discomfort in the form of abdominal cramping, nausea and vomiting remains, but polyethylene glycol solution is currently one of the agents for mechanical bowel preparation mostly used[12,13,14,15].

Sodium picosulphate
Other agents also used are sodium picosulphate which is hydrolized in the colon and induces a reduced water and electrolyte resorbtion. Added magnesium citrate causes an osmotic diarrhea. The impairments of this agent are possible dehydration that can aggravate cardiovascular disturbances and the possibility of formation of explosive gasses[16,17,18].

Sodium phosphate
Sodium phosphate is a powerful osmotic agent that reduces electrolyte secretion to the bowel lumen and water resorbtion. The advantage of this agent is the low volume of administered solution which makes it very suitable for preoperative bowel preparation.
The rate of electrolyte shifting is neglectable, although a potassium deficit can be induced. The high osmotic pressures on the mucosa of the stomach can induce nausea. This can be prevented by dilution of natrium phosphate with water [19,20].

On table colonic lavage

In emergency situations or when there is a contraindication for mechanical bowel preparation, such as an obstructive tumor with preoperative ileus, the surgeon has to decide during the operation whether a primary anastomosis is feasible. Next to vascularization of the bowel, inflammation and technical aspects, one of the criteria influencing this decision is the fecal bulk that is present. If fecal bulk is the only factor preventing a primary anastomosis an on table lavage can be performed. First introduced by Windberg in 1958 this method has been modified over the years by various authors, although the principle remains the same. The bowel content is evacuated from the colon proximal to the anastomosis during the operation. The current method sometimes requires a total mobilization of the colonic flexures and uses an ortogradic lavage through a large bore hose distally and a Foley catheter proximally through the appendix stump. The method is innervating and prolongs operation time, but it is thought to prevent a two or three stage procedure[21,22].

Selective bowel decontamination

The concept of selective bowel decontamination, introduced by Stoutenbeek et al.[23], to protect critically ill patients by reducing fecal flora by ways of antibiotics is different from the prophylactic measure of cleaning the bowel preoperatively. Therefore it will not be discussed in this study.

Current Practice

The current standard in preoperative prophylaxis in colorectal surgery is adequate mechanical bowel preparation and short antibiotic prophylaxis[24-29].

There is, however, a shift in the way this mechanical bowel preparation is achieved. A study done in 1990 amongst 500 colorectal surgeons in the U.S. showed that all surgeons performed some kind of mechanical bowel preparation; in 36% in a conventional way, in 58% with polyethylene glycol and in 5% with mannitol[24]. In a survey done amongst 808 surgeons these percentages shifted to 70.9% using polyethylene glycol and 28.4 % using sodium phosphate[25]. More recently, Zmora et al[26] indicated that colorectal surgeons in North America currently prefer sodium phosphate for preparation of the colon preoperatively. In the United Kingdom in 1990 enemas, purgatives and mannitol were the agents mostly used[27].

Mechanical bowel preparation in the Netherlands

In the Netherlands bowel preparation was initially achieved in the conventional way by a strict regime in which the patient was treated with a laxative diet and enemas during a number of days preoperatively.

At the end of the 1970's there was a shift towards the 'whole gut irrigation' method administering the laxative liquid through an oral catheter. For many years this method was considered as the indicated way of achieving a clean peroperative bowel.

Finally, for patient oriented reasons, the laxative was administered orally. Throughout the years the constituency of these oral laxatives has changed. One of the first products that was used was mannitol. Products used today are polyethylene glycol, sodium picosulphate and sodium phosphate which act as osmotic laxatives. Bowel preparation of the patient by ways of an elementary diet has rapidly been abandoned in the Netherlands[28,29].

Mechanical bowel preparation in vascular surgery

In the preoperative management of abdominal aortic surgery in many surgical centers mechanical bowel preparation is performed. In the Netherlands we conducted a questionnaire survey of all surgical centers. In 118 of the 125 centers elective abdominal aneurysmal aortic surgery was performed. The surgeons were asked if, why and which form of mechanical bowel preparation was routinely used. The response rate was 97%. Complete bowel preparation was performed in 60 centers (52%), partially by means of clysmata in 18(16%). In 37(32%) centers no form of mechanical bowel preparation was performed. (**Table 1**)

Complete bowel preparation was achieved in most centers by ways of 4 litres of polyethylene glycol orally. Although the choice to use mechanical bowel preparation is arbitrary, we couldn't find any evidence in literature to justify the use in vascular surgery. It is suggested that bowel preparation reduces the incidence of ischaemic colitis. However, there is no proof of this in literature[30,31,32].

COMPLETE PREPARATION (52%)	**CLYSMATA (16%)**	**NO PREPARATION (32%)**
By custom 55%	By custom 72%	By custom 86%
Better access 30%	Better access 6%	Not evidence based 8%
Less ileus 28%	Reducing bulk 6%	Never bowel preparation 3%
Possible GI surgery 10%	Reducing passage problems 11%	'We don't cause bowel lesion' 3%
Less endo-infection 10%	Less complications 6%	Shorter hospital stay 5%

Table 1 *Reasons for mechanical bowel preparation in abdominal aortic surgery in 115 surgical centers in the Netherlands.*
More then one reason could be given as ratio. Percentages are presented for the whole group. Total percentage can therefore exceed 100%.

Mechanical bowel preparation in miscellaneous procedures

Mechanical bowel preparation is also given in oesophageal surgery, where a colon interposition might be needed. There exists no literature to validate the use of bowel preparation for the prevention of infection or anastomotic leakin oesophageal surgery. However, considering the post-operative distance between the oropharynx and the colon interposition it is believed that cleaning the colon preoperatively increases patient comfort by reducing postoperative oral fecal material. Mechanical bowel preparation is also used in the workup of patients undergoing extensive pancreatic surgery such as the Whipple procedure, without validating literature. In urologic diversion surgery mechanical bowel preparation is still used in many centers, although the value is currently under discussion[33,34].

Additional measures: Antibiotic prophylaxis in colorectal surgery

In the prevention of anastomotic leakage and wound infection in colorectal surgery next to the use of mechanical bowel preparation the use of antimicrobial prophylaxis is advocated.
There are a number of ways to administer antibiotics perioperatively; although oral and intraperitoneal antibiotics have not proven worthwhile, the intravenous prophylaxis with adequate antibiotics is thought to be indispensable in colorectal surgery[35,36,37]. Antimicrobial prophylaxis in colorectal surgery was first reported by Garlock and Seley[38] in 1939. They reported one wound infection in 21 patients receiving oral sulfonamides before elective colorectal surgery. A meta-analysis by Baum et al[39] was reported in1981 covering 26 clinical trials over a 15 year period. They compared various antimicrobial regimes in addition to mechanical bowel preparation and mechanical bowel preparation alone, revealing higher mortality and infection rates in patients not receiving antibiotic prophylaxis.
It was concluded that it is inappropriate to include -no treatment- arms in future antimicrobial trials.

Causal bacteriology
Peritoneal and wound infection after colorectal surgery is almost invariably caused by endogenous bacterial flora. Infections are almost invariably polymicrobial as more than 400 different bacterial species contaminate the peritoneal cavity after perforation or fecal spill of the bowel. Development of a bacterial peritonitis is a biphasic process which relies on bacterial simplification and synergism. Endotoxin generating facultative anaerobes such as *Escherichia coli* and obligate anaerobes such as *Bacteroides fragilis* predominate in the occurrence of peritonitis. *Escherichia coli* is responsible for the acute phase of infection and causes septicaemia by seeding the systemic circulation. *Bacteroides fragilis* is more involved in the later phases of infection with formation of abscesses [40,41,42,43].

In the total surgical field in recent years a slight shift has portrayed itself in the percentages of causal microorganisms of surgical infection. The main causal organisms of surgical infection remain *Stafylococcus aureus, gram-negative Staphylococci, Entorococcus species* and *Escherichiae coli* but an increasing number of surgical wound infections is caused by anti-microbial resistant pathogens such as *methicillin-resistant Stafylococcus aureus* (MRSA) or by funghi such as *Candida albicans.* This shift may reflect increasing numbers of severely ill and immunocompromised surgical patients and the impact of nosocomial broad spectrum antibiotics.
There have also been outbreaks reported of infection with unusual pathogens such as *Clostridium perfringens, Rhizopus oryzae, Nocardia farcinica, Legionella pneumophila, Rhodoccus bronchialis* and others. Most of these outbreaks could be traced back to a source of contamination within the operating theatre [44,45,46].

Antibiotic prophylaxis should be given according to the kind of operation performed as classified by the American College of Surgeons. In this classification surgical procedures are defined as clean, clean-contaminated, contaminated or dirty. Antibiotic prophylaxis is recommended for all clean-contaminated, contaminated and dirty procedures and is considered optional for clean procedures.
According to this classification all surgical procedures examined in our study were either clean-contaminated or contaminated. In our study antibiotic regime was uniform to what the guidelines regarding antibiotic prophylaxis issued by the U.S. Department of Health and Human Services advocate; a form of cefalosporine or aminoglycoside with the addition of metronidazole for colorectal procedures directed at the above mentioned causal bacterial agents. Concerning the dose and timing of the antibiotic gift the consensus is to give an adequate dose to maintain serum levels that secure a sufficient Minimum Inhibitory Concentration (MIC) during the procedure. In the case of cefalolosporines this is e.g cefazoline 1-2 grams no longer than half an hour prior to surgery or at induction[47,48]. When regarding these boundaries the MIC is secured up to 3-4 hours of surgery. In the duration of the surgical procedure re-administration is recommended at one or two half lives of the antibiotic given. In our studies we adhered to these guidelines of dose and timing although it was not necessary to give additional antibiotics. All colorectal procedures stayed within the boundaries of three hours as the included operations were only high colectomies.

There is an indication that continuing antibiotic prophylaxis beyond the operation has a beneficial effect in a subgroup of patients which are clinically thought to have a greater chance of postoperative septic complication[49]. To identify this group no clear predictor besides the clinical eye of the surgeon has been formulated. In chapter 4.1 of this study a trial is presented which ascertains the value of the intra-operative bacterial swab in defining this subgroup.
Previous study by Rusca et al[50] suggests that the microorganisms leading to anastomotic rupture are seeded during the appliance of the anastomosis and do not leak through it afterwards. We examined the correlation between the pathogens outside the anastomosis, the pathogens in the subcutis layer and subsequent infection in patients receiving mechanical bowel preparation and those who had not received any kind of preoperative colon cleansing.

A number of patient characteristics have been associated with an increased risk of wound infection. Diabetes, nicotine use, steroid use, malnutrition, obesity, extreme age, prolonged preoperative stay, preoperative nares contamination with *Staphylococcus aureus* and perioperative transfusion have all be linked with an increased risk of surgical site infection although some of these factors still remain controversial [51,52,53,54].
In our clinical studies we scored all these factors except malnutrition, obesity and staphylococcal nares carriage.
The operative characteristics influencing surgical site infection outcome according to the guideline of prevention of surgical site infection issued by the U.S. Department of Health and Human Services, are preoperative antiseptic showering,

preoperative hair removal, patient skin preparation in the operating room, and operating room characteristics such as ventilation, sterilization of surgical instruments, surgical attire and scrubbing methods. All these factors were standardized in our randomized multi-center studies.

When analyzing the effect of prophylactic measures such as mechanical bowel preparation and prophylactic antibiotics a clear definition of the outcome parameters should be made. As explained elsewhere in this study in our clinical trials anastomotic leakage was divided into major leakage with abdominal signs and a relaparotomy as consequence and minor leakage for leakage without abdominal signs, confirmed with radiography and conservatively managed.
In the case of wound infection in all clinical trials in this study we upheld the definitions used by the National Center for Infectious Diseases (U.S. Department of Health and Human Services) as described in their guideline for prevention of surgical site infection of 1999 [55].
In this guideline a surgical site infection is defined as either superficial, deep, or deep with involvement of organs or spaces. Although in our study we used the same criteria for defining a wound infection, we made no subdivision into deep or superficial wound infection.

The effect of mechanical bowel preparation (MBP) on colonic tissue

There is little known about the detrimental effects the different agents for mechanical bowel preparation exert on bowel tissue.
From previous study we know their clinical effect in terms of efficacy in cleaning the colon, septic complications and patient comfort [4,25,56,57].
A study of Pockros et al [58] acknowledged that mechanical bowel preparation with polyethylene glycol before colonoscopy caused an increased influx of eosinophilic cells and edema in the lamina propria of the colonic tissue. However they concluded that in comparison with a standard colon preparation (48 hour liquid diet with 240 ml of magnesium citrate and senna derivative) polyethylene glycol did not induce histopathologic changes in colonic tissue. Recent studies of Bingol et al [59] and Coskun et al [60] show a detrimental effect of polyethylene glycol and sodium phosphate in colonic tissue in rats.
To date there is little known on the histopathologic effects of mechanical bowel preparation in a surgical setting. In chapter 5.1 a study is presented in which the histopathologic effects of mechanical bowel preparation with 4 litres of polyethylene glycol on colonic tissue are examined.
The damaging effects of the different osmotic agents used in mechanical bowel preparation are thought to be of a direct and indirect nature.

Direct effect of MBP on colon tissue
Mannitol, one of the first agents used for mechanical bowel preparation is fermented by endoluminal bacteria leading to colonic explosions with the use of diathermia. Edema of the lamina propria and bacterial overgrowth was also reported with the use of this agent [61].
The strong hyperosmotic effect of sodium phosphate causes damage to the superficial layers in the gastrointestinal tract accompanied by nausea in 15-20% of patients. Strong fluid shifts with the use of osmotic agents such as sodium picosulphate, sodium phosphate and polyethylene glycol cause an ischaemic and inflammatory effect which leads to local damage on the colonic tissue [62,63]. Liften [64] in 1984 argued that due to the systemic effects polyethylene glycol was even more harmful then mannitol in preparing the colon. Although these arguments have been refuted, none of the agents used for mechanical bowel preparation seem totally harmless.
In following of the article of Meisel et al [65] published in 1977 reporting on the histopathologic changes in the form of sloughing of surface epithelium in the colon attributed to the use of enema's and bisacodyl several authors such as Zwas et al [66] and Keefe et al [67] reported on mucosal damage due to mechanical bowel preparation prior to colonoscopy. These aphtous lesions may be wrongly diagnosed as a disease process at colonoscopy. Oxidative stress by the fluid shifts caused by the osmotic agents leading to disequilibrium in the oxidant-antioxidant

system is suggested by some authors to cause the damage in the different layers of the bowel tissue with the use of mechanical bowel preparation [68].

Indirect effect of MBP on colon tissue

By depleting the colon of butyrates and other short chain fatty acids (SFCA's) that act as fuel suppliers to the colonic mucosa a damaging effect is achieved.

The short chain fatty acids have recently been discovered to contain a number of important effects next to fuel supply for the colonic bowel. These effects are very diverse and as of yet not totally understood. Butyrate is produced by microbial fermentation of undigested dietary fiber, undigested starch, proteins and endogenously produced substrates reaching the colon. The fermentation rate varies depending on the site of the colon with a high concentration in the cecal portion and a lower concentration in the distal colon accompanying an increase in fecal pH towards the distal colon. On average 300-400mmol is produced per day with an intake of 32-42 grams of carbohydrate per day [69].

Effect of Short chain fatty acids (SFCA's)

Nutritional

In colonic tissue the preferable substance for oxydizable fuel is butyrate. The preference of colonocytes for butyrates as an energy substrate appears to be a tissue specific phenomenon with the highest usage in the distal colon and rectum. This nutritional effect is not only limited to a local uptake of metabolites in the colonocyte but SFCA's also affect gut mass and secretion of gut peptides that influence the partition of nutrients throughout the body such as glucose homeostasis and water, sodium and calcium absorption [70,71].

Hypertrophic effect on normal colonic tissue and a protective effect against colon cancer in vitro.

The discrepancy between these two effects is explained by the difference of metabolizing capacity in the degenerated colonocyte due to a shift from aerobic to anaerobic metabolism. This may lead to an accumulation and heightened sensitivity for butyrate in the neoplastic cells leading to growth arrest. The in vitro antineoplastic effects of butyrate occur at concentrations of 0.5 mM to 16 mM.

Intravenous infusion of butyrate has significant anti-tumor effects. In an in vivo murine model of colonic cancer metastatic to the liver McIntyre et al. and Wilson et al [72,73] reported on the protective effect of butyrate against colon carcinogenesis and the hyperthrophic effect of butyrate on colonic cells. In the distal colon, there is a relative shortage of carbohydrates; protein fermentation predominates leading to the formation of isoacids and valeric acids. This relatively high concentration of isoacids and valeric acids in combination with the decreased concentration of SFCA's in the distal colon may play a role in the association between high protein, low fiber diets and colon cancer.

Effects on motility of the colon

These seem to correlate with the functional parts of the colon, the cecum being the segment for fermentation, the mid-colon to keep faeces in the fermentation reservoir, and the distal part for extraction of fluids.

SFCA's influence motility to hold faeces bulk in the caecum leading to a high concentration of butyrate, and enhance motility for fecal excretion in the distal colon where high concentrations of iso-acids and valeric acids and low concentrations of butyrate are produced. The incidence of colonic cancer, being higher in the distal colon, seems to correlate with the concentration of these substances. In the small intestines SFCA shorten mouth to caecum transit time, with the least effect in the jejunal parts [74,75,76].

Healing effects on inflammated colonic tissue

Histopathologically there is little difference between lesions of diversion colitis and ulcerative colitis which suggests a connection between ulcerative colitis and a SFCA deprived state. Vernay et al in 1987 reported on decreased fecal concentrations of SFCA in patients with ulcerative colitis but not in those with Crohn's colitis. Positive results have been achieved by treating diversion colitis with topical SFCA. Scheppach in 1992 reported on patients with ulcerative colitis treated with butyrate enemas in a placebo controlled, single blinded, randomized

trial with positive results. It is postulated that the therapeutic effects of butyrate in the treatment of ulcerative colitis are due to the healing capacity by increasing protein production as a metabolic fuel [77,78,79].

In seminal experimental studies in rats published in 1986 and 1997 Rollandelli et al. demonstrated that n-butyrate given intraluminally or intravenously enhance the colon anastomosis strength in rats [80,81,82,83].
In an experimental study in rats we examined the effects n-butyrate given intraluminally has on the properties of colonic tissue and on anastomotic strength in addition to mechanical bowel preparation.

Patient satisfaction and macro-economic effects of mechanical bowel preparation in elective open colon surgery

Patient satisfaction
Previous prospective randomized trials have compared the different agents for mechanical bowel preparation in terms of efficacy, and septic complications in a surgical setting and patient comfort and tolerance in a colonoscopy setting. Most of these studies show little difference or contradicting results between the various agents used in current mechanical bowel preparation. However in a surgical setting there is limited information on how well mechanical bowel preparation is tolerated by the patient. According to a large prospective randomized trial conducted in 1997 by Oliveira & Wexner et al [84] sodium phosphate seems to be better tolerated by patients in comparison to polyethylene glycol. A small retrospective study of 111 patients comparing polyethylene glycol with sodium phosphate by Chaleoykitti [29] in 2002 confirms these results. A large survey of the literature published from 1975 to 2000 conducted by Zmora et al [26] indicates that colorectal surgeons practicing in North America currently prefer sodium phosphate as an agent for mechanical bowel preparation.
The reason for better patient tolerance for sodium phosphate is probably due to the small volume that needs to be taken orally (75cc in comparison with 4 litres of polyethylene glycol). However, sodium phosphate seems to induce more histopathologic changes in the colonic bowel in experimental studies in rats [59, 60].

Health care costs
The cost of mechanical bowel preparation lays not so much in the products used. The most used osmotic agent in the Netherlands is polyethylene glycol which averages about 20 Euro for 4 litres of bowel preparation which is a small expense in comparison with total hospitalization costs [32].
The real costs lie in early hospitalization and supervision of the patient undergoing mechanical bowel preparation.
There is little known about the total percentage of daily workload for the nursing staff that is taken up by surveying a patient undergoing mechanical bowel preparation. This amount of workload automatically translates itself in staffing costs and macro-economical costs in healthcare.

The total amount of costs associated with the practice of mechanical bowel preparation in elective colorectal surgery is largely formed by the additional hospital stay (either to undergo the procedure or due to septic complications of the procedure). On this subject Frazee et al [85] in a randomized study conducted in 1992 found outpatient mechanical bowel preparation to be as effective as mechanical bowel preparation during hospitalization, thus reducing costs and hospital stay. Tuggle et al [86]. in 1987 found polyethylene glycol to be safe and effective in preparing the bowel for surgery in children, eliminating the need for multiple day hospitalization for conventional bowel preparation at the time. In 1989 an additional study by Tuggle et al [87] showed polyethylene glycol also to be effective and well tolerated in children in an outpatient setting. Shaffi et al [39] found bowel preparation given before urologic diversion surgery to lengthen

hospital stay and to have no advantage for the surgical outcome. Finally, a study conducted by Lee et al [88] in 1996 in which 180 patients were included, found no difference in hospital stay in patients receiving outpatient bowel preparation and patients that were hospitalized to undergo the procedure prior to colorectal surgery.

In order to lead a sound discussion on the benefits and setbacks of this culture based practice and verify the right of continuing mechanical bowel preparation in elective colorectal surgery, the macro-economical repercussions for the healthcare system have to be quantified and evaluated.

In chapter 6 through a multi-center, consecutive, questionnaire study we evaluated patient satisfaction, nursing workload and macro-economical costs for the practice of mechanical bowel preparation in elective open colon surgery.

Clinical comparative studies of the different methods of bowel preparation with regard to efficacy and patient tolerance

A number of comparative studies have been conducted over the past decade to compare the different oral solutions in terms of efficacy, septic complications and patient friendliness. Mostly little difference between the various agents was notified. In 1994 Wolters et al. compared Ringers lactate, polyethylene glycol and sodium phosphate (with bisacodyl) in 163 patients undergoing colorectal surgery [89]. The group receiving sodium phosphate had more overall postoperative complications. Also this group had the least effective cleaning of the bowel. Kohler et al [90] compared the effects of whole gut irrigation and mechanical bowel preparation by ways of sodium phosphate. The efficacy was 94 % in the group receiving whole gut irrigation in comparison with a 74% efficacy in the group receiving sodium phosphate. When receiving whole gut irrigation 54% of the patients complained of nausea and vomiting. In the group receiving sodium phosphate this was the case in 14% of the patients. In a blinded, prospective, randomized study comparing 4 litres polyethylene glycol (with or without metoclopramide) with sodium phosphate no difference in efficacy was seen in a cohort of 329 patients[91]. In this study sodium phosphate was experienced as least imposing by the patients. In a blinded, prospective, endoscopic study of 450 patients Cohen and Wexner et al [92] found a clean colon at colonoscopy in 90% of patients receiving sodium phosphate in contrast to 73% in patients receiving polyethylene glycol.
Also in this study, sodium phosphate was found to be least imposing.
In a small randomized group of 59 patients in a colonoscopy setting, Hamilton found a better patient tolerance for sodium picosulphate in comparison to polyethylene glycol [93]. In 2002 Chaleoykitti [94] presented the results of 111 patients in which sodium phosphate was compared to polyethylene glycol in a surgical setting. Patients fared better in the group receiving sodium phosphate as preparation agent.

Review of clinical studies on the value of mechanical bowel preparation in elective open colorectal surgery.

There are various controlled and uncontrolled patient series concerning the issue of mechanical bowel preparation in colorectal surgery.

Uncontrolled studies
Since the 1970's a number of retrospective and prospective series have been presented on the value of mechanical bowel preparation

Retrospective
In 1973 Schrock et al [95] reviewed 1703 colonic anastomoses and reported an overall leakage rate of 4.5% with as much as 10% leakage in emergency left colonic anastomoses in unprepared colons. In the same year Irvin and Goligher et al [96] reported on a series of 204 patients with small-bowel and colon anastomoses. They concluded that anastomotic leakage was significantly increased in the presence of fecal loading. In 1988 Mealy et al [97] reported on a series of 56 patients receiving a one-stage left colectomy in an emergency setting. They reported a 5.4% anastomosis leak and concluded that a primary anastomosis in the unprepared left colon was feasible. Recent review articles of Mackenzie et al. and Burch et al. reporting on the results of emergency surgery in civilian trauma centers indicate that the primary anastomosis of an injured unprepared colon is a safe option [98,99].
In 1990 Duthie et al [27] retrospectively reviewed a single surgeon's experience of 100 patients undergoing elective colorectal surgery without mechanical bowel preparation. The wound infection rate was 7% and there was only one anastomotic leak. A retrospective study by Memon et al [100] showed similar results.

Prospective
Goligher et al [101]. in 1970 presented a series of 73 patients receiving an elective anterior resection. They noted higher rates of anastomotic leakage in patients with fecal loading.
In 1971 Rosenberg et al [102] presented a series of 128 patients undergoing elective colorectal surgery. They found an increased rate of wound infection and anastomotic leak in the presence of gross fecal loading.
Irving et al [103] presented a series of 72 consecutive patients in 1987 that underwent colorectal surgery. In a heterogenic group of high and low anastomoses, a percentage of anastomotic leakage of 0 % and a wound infection rate of 8.3% was found.
In 1992 Mansvelt et al [104] reported on 189 patients undergoing elective colorectal surgery with just one or two enema's preoperatively. They reported a mortality rate of 1.6 %, a 0% anastomotic leak and a 2.6 % wound infection rate. The latter two series present excellent results for anastomotic leakage and wound infection rates compared to the averages found in literature [22, 96, 101].
However, these series give no indication as to patient selection.
In 2001 van Geldere et al [105] presented a series of 250 consecutive patients undergoing elective colorectal surgery without mechanical bowel preparation with

excellent results. The results are presented in chapter 2 of this study. Recently, two consecutive series were presented; Young Tabusso et al [106] presented the results on 47 consecutive patients undergoing colorectal surgery with and without mechanical bowel preparation and Jansen et al [107] presented the results of 102 consecutive patients. Both studies concluded that there is no advantage of preparing the colon preoperatively.
We conclude that the question can be raised if mechanical bowel preparation is still necessary in elective open colorectal surgery.

Controlled studies
The excellent results of the uncontrolled series of Irving and others have lead to a total of eight randomized prospective trials to date.

In 1972 Hughes [108] reported on a randomized trial in which 46 patients who received mechanical bowel preparation fared no better than 51 patients who received no preparation. Anastomotic leakage was 13% in the group receiving bowel preparation versus 9.8% in the group without preparation while the wound infection rate was 15.2% versus 19.6 %.

In 1990 Baker et al [109] reported on 389 patients (mostly healthy young men) who after an abdominal trauma underwent a colorectal resection and were randomized into two groups. One group had on table colonic lavage and the other group did not. There was no difference in mortality and wound infection rate (7.2% mortality with on table lavage versus 6.6% without, 19.3 % wound infection with on table lavage versus 16.2% without).

In 1992 Brownson et al [110] presented a randomized series of 179 patients who received mechanical bowel preparation by ways of polyethylene glycol or not. All patients received antibiotic prophylaxis. The percentage of wound infection was not significantly different (5.8% with bowel preparation versus 7.5% without mechanical bowel preparation). However, the number of anastomotic leakages was significantly higher in the group receiving mechanical bowel preparation (12 % versus 1.5%; 134 patients who received a primary anastomosis were included for statistical analysis).

In 1994 the study of Burke et al [111] was published in which 186 patients undergoing left colorectal resection were randomized between receiving mechanical bowel preparation with sodium picosulphate or not. After exclusion of 17 patients, operative results of 169 patients were included for statistical analysis.
Both groups received antibiotic prophylaxis. The percentages in anastomotic leakage and wound infection were not significantly different (3.7% anastomotic leakage in the group receiving bowel preparation versus 4.6% in the group without bowel preparation, with 4.9 % wound infection versus 3.4 % wound infection respectively).

In 1994 Santos et al [112] compared an imposing regime of bowel preparation consisting of 5 days of clymata with additional oral mannitol, with the complete omission of mechanical bowel preparation. All patients received antibiotic prophylaxis. In the group with bowel preparation the percentages of anastomotic leakage and wound infection were significantly higher (10 % anastomotic leakage versus 5% and 24 % wound infection versus 12 %).

In 2000 Miettinen et al [113] presented a study of 267 randomized patients either receiving polyethylene glycol preoperatively or no bowel preparation. They observed 4% anastomotic leak and a 9% surgical site infection rate in the group receiving polyethylene glycol versus a 2% anastomotic leak and an 8% surgical site infection rate in the group without bowel preparation. There were no deaths recorded.

In 2003 Zmora et al [114] presented the results of a randomized trial of 380 patients undergoing elective colorectal surgery with and without mechanical bowel preparation. The rate of anastomotic leak was 3.7% in the group of patients with mechanical bowel preparation and 2.1% in the group without. Wound infection rate was 6.4% with bowel preparation and 5.7% without.

Recently the results of a second large Dutch multicenter trial conducted by Contant and Weidema et al [115] which included 1260 patients have been presented at the Dutch Surgical Days. Also, with these large inclusion numbers of a heteregenous surgical group there was no significant difference in patients receiving mechanical bowel preparation or not. The reported rate of anastomotic leak was 4.9% in patients receiving mechanical bowel preparation and 5.1% in patients receiving no preparation. Also there was no difference in septic complications with a total wound infection rate of 9.4% in patients receiving mechanical bowel preparation and 10% in patients without preparation.

The results of the most relevant published prospective series concerning the evaluation of the value of mechanical bowel preparation in colorectal surgery to date are shown in **Table 2**.

AUTHORS (NR.OF INCLUDED PATIENTS)	YEAR OF PUBL.	TYPE OF TRIAL	WOUND INFECTION RATE (%)		ANASTOM. LEAK (%)	
			MBP	**No MBP**	**MBP**	**No MBP**
Hughes (97)	1972	RCT	7/46 (15.2)	10/51(19.6)	6/46(13)	5/51(9.8)
Irving (72)	1987	Prospective **§**	-	6/72 (8.3)	-	0/72 (0)
Duthie (100)	1990	Retrospective	-	7/100 (7)	-	1/100 (1)
Baker (389)	1990	RCT **§, #**	(19.3)	(16.2)		
Brownson (179)	1992	RCT[@]	5/86 (5.8)	7/93 (7.5)	8/67 (11.9)	1/67 (1.5)*
Burke (186)	1992	RCT[&]	4/82 (4.9)	3/87 (3.4)	3/82 (3.7)	4/87 (4.6)
Santos (149)	1994	RCT	17/72 (23.6)	9/77 (11.7)*	7/72 (10)	4/77 (5)*
Mansvelt (189)	1998	Prospective	-	5/189 (2.6)	-	0/189 (0)
Miettinen (267)	2000	RCT	13/138 (9)	10/129 (8)[$]	5/138 (4)	3/129 (2)
Zmora (380)	2003	RCT	12/187(6.4)	11/193(5.7)	7/187(3.7)	4/193(2.1)

Table 2 *Published series of elective open colorectal resections with and without mechanical bowel preparation (except on table lavage in trial by Baker et al.)*
MBP= Mechanical bowel preparation; RCT= Randomized clinical trial; *= Significant difference **§=**Including emergency colectomies; #= On-table lavage; &=17 patients excluded; @=134 patients with primary anastomosis; $= Surgical site infection rate.

Discussion

The results of Irving, Mansvelt and van Geldere are remarkable but they are achieved by a single experienced colorectal surgeon. This differs from the daily surgical practice in which, especially in training centers, the experience with colorectal surgery varies considerably.

The criticism on the previously mentioned clinical trials (with the exclusion of the trial reported by Miettinen), is a lack of a solid trial design with a clear definition of outcome variables. Although antibiotic prophylaxis was given in all trials a number of different substances and methods were used for bowel preparation, sometimes even within one trial [112]. Moreover, the patient populations, including M.Chagas, M.Hirshprung and young males with traumata completely differs from the mean patient population undergoing elective open colorectal surgery.

A meta-analysis of the studies of Brownson, Burke and Santos done by the group of Platell et al [116] showed a higher incidence of wound infections in the group receiving mechanical bowel preparation. There was no significant difference in anastomotic leakage between the two groups [55]. Recently published meta-analyses by Slim et al [117] (which includes the results of the study presented in chapter 3) and Bucher et al [118] even show that there are significantly more anastomotic leakages after MBP compared to a no preparation regimen. Other endpoints like wound infection also favored the no-preparation groups. Although mechanical bowel preparation is still routine practice in elective open colorectal surgery, the question remains if this procedure achieves the desired reduction in anastomotic leakage and wound infection. This basic thought is more based on culture than on clear evidence. The pivotal consideration in mechanical bowel preparation is that a decreased fecal load may induce a decreased number of bacterial colonies and as such lead to a decreased risk of complications such as anastomotic leakage and infection. It is thought that an increased bacterial load leads to an increased risk of infection, with a concentration of 10^6 colony forming units needed for wound sepsis [119].
Previous studies have demonstrated that the concentration of the micro-organisms in the intra-operative remaining fecal residue does not decrease with the various forms of mechanical bowel preparation [120]. Bowel preparation changes the physical characteristics of feces, which, by some authors is seen as a protective factor against the pressure of the fecal bulk against the fresh anastomosis. Others consider the newly formed soluble form less manageable and therefore more dangerous because of easy leakage through the fresh anastomosis, leading to fecal spill, subsequent peritonitis and fistulous tract forming [103] [121]. Mechanical bowel preparation disturbs the endoluminal bowel homeostasis. The mucosa is known to be dependent on endoluminal fuel delivery. The fecal butyrates and other short chain fatty acids are essential for cellular proliferation of colonic mucosa [122, 123]. Mechanical bowel preparation leads to a depletion of these basic fuels, with suboptimal preoperative bowel tissue as a result. This may increase the chance of postoperative anastomotic necrosis and susceptibility for postoperative infection

with fecal micro-organisms. Animal studies show that leaving faeces in situ has a beneficial effect on anastomotic healing; Okada et al[124] demonstrated that the bursting pressure in colonic anastomoses surrounded by micro-organisms in rats was higher than in those with preoperatively cleaned bowels. Little is known about the direct toxic effect of osmotic laxatives on the colonic tissue. However, bowel preparation may reduce colonization resistance leaving the bowel more susceptible to nosocomial infection and may inhance bacterial translocation by disrupting the mucosal barrier[125,126]. Namely in the older patients mechanical bowel preparation can lead to electrolyte- and fluid balance disturbances. Depending on the form of mechanical bowel preparation this can lead to a more katabolic state in such patients. It has been shown that a katabolic state can lead to an increased incidence of anastomotic leakage [127,128].

The outline of this thesis

In this thesis we will address the following aspects of the value of mechanical bowel preparation in elective open colon surgery.

1) The effect op MBP on clinical outcome in elective open colon surgery; in Chapter II a large consecutive trial is presented, in Chapter III a multi-center randomized clinical trial is presented.

2) The relevance of MBP in preventing bacterial translocation in patients undergoing elective open colon surgery. In Chapter IV.I and IV.II two bacteriological studies are presented.

3) The direct and indirect toxic effect of MBP on colonic tissue. In Chapter V.I and V.II two experimental studies are presented.

4) Patient satisfaction and macroeconomic effects of MBP in medical care. In Chapter VI a questionnaire study is presented.

All clinical trials and experimental studies used polyethylene glycol as the sole agent for bowel preparation. Such a single agent eliminates statistical confounding and gives a clearer view of factors surrounding the procedure of bowel preparation. Furthermore, a thorough examination of one single agent has greater value than a shallow examination of different agents. We opted for polyethylene glycol because it is thought to be the least harmful osmotic agent and nowadays one of the most used agents. In the Netherlands 4 litres of polyethylene glycol orally is the method most used to achieve a clean bowel.

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-Chapter II

Complications after open colorectal surgery without mechanical bowel preparation
A consecutive clinical study

A condensed form of this chapter has been published

Complications after colorectal surgery without mechanical bowel preparation

Journal of American College Of Surgeons 2002;194:40-7.

Abstract

Background: The current practice of mechanical bowel preparation (MBP) before colorectal surgery is questionable. MBP is unpleasant for the patient, often distressful and potentially harmful. The results are often less than desired, increasing the risk of contamination. Moreover, cleansing the colon and rectum before surgery has never been shown in clinical trials to benefit patients. In animal experiments MBP has a detrimental effect on colonic healing.
Patients and methods: To investigate the outcome of colorectal surgery without MBP, we prospectively evaluated a consecutive series of unselected patients who underwent resection and primary anastomosis of the colon and upper rectum, including emergency operations. Endpoints were wound infection, anastomotic failure and death. Late signs and symptoms that might be secondary to leakage of the anastomosis were considered as an anastomotic failure as well.
Results: Two hundred and fifty operations were performed of which 199 (79.6%) were elective. Colectomies were left-sided in 65.6 %. Anastomoses were ileocolic in 32 %, colocolic in 20.8 %, colorectal intraperitoneal in 34.4 % and extraperitoneal in 12.8 %. No patient suffered from fecal impaction. Seven patients (2.8 %; 95 % C.I.: 1.1 – 5.7) developed superficial wound infections. In three patients there was leakage from an extraperitoneal colorectal anastomosis, in two of them after hospital discharge. The overall anastomotic failure rate was 1.2 % (95 % C.I.: 0.3 – 3.5). The in-hospital mortality rate was 0.8 % (95 % C.I.: 0.1 – 2.9) and was not related to abdominal or septic complications.
Conclusion: Mechanical bowel preparation is not a *sine qua non* for safe colorectal surgery.

Introduction

Virtually all colorectal surgeons consider a mechanically cleansed and empty bowel as one of the prerequisites for a safe colonic resection and anastomosis.[1] The current practice of mechanical bowel preparation (MBP) before colorectal surgery, however, has been questioned in the past decade.

The purpose of preoperative MBP is to reduce the risk of septic complications and anastomotic dehiscence[2-5]. Mechanical bowel preparation, however, is unpleasant for the patient, often distressful and potentially harmful. It is associated with abdominal pain, nausea, vomiting, embarrassment, fear and fatigue[6,7]. In the elderly patient it carries the risk of electrolyte disturbance with fluid overload in the hours prior to surgery[5,8,9]. MBP may enhance bacterial translocation and may be responsible for the septic complications seen following colorectal surgery[10,11]. In animal experiments MBP has a detrimental effect on colonic healing[12-14]. Although the rigid regimen of whole bowel irrigation has been replaced by simpler regimens of MBP using oral solutions such as polyethylene glycol or sodium phosphate, patients still suffer from these preparations. Additionally, the results are often less than desired especially in patients with stenotic lesions. Solid stools are only converted to liquid masses that are difficult to control during surgery and more likely to contaminate the peritoneal cavity during open anastomosis[15,16]. In emergency procedures a loaded bowel is generally regarded as a contra-indication for anastomosis, although there is a trend towards one-stage procedures with peroperative colonic irrigation. The process of vigorously cleansing the colon and rectum before surgery has never been shown in clinical trials to benefit patients[17-19]. All this has resulted in a paradigm shift regarding the necessity of MBP prior to colorectal surgery.

We have omitted MBP in selected patients since the late 1980s, before omitting its practice completely in 1990. We prospectively studied the outcome of surgery in a consecutive series of unselected patients who underwent colonic resection and primary anastomosis without MBP.

Patients and Methods

Between January 1990 and March 1999 data were collected prospectively on a consecutive series of unselected patients who underwent colorectal surgery without MBP. All patients admitted to the care of a single surgeon (DvG) who were scheduled to undergo primary resection and anastomosis of the colon and upper rectum were eligible for inclusion of the study. Not eligible were patients on whom MBP had been carried out for colonoscopy, barium enema or other reasons in the week before operation, or patients scheduled for a low anterior resection with peroperative rectal washout with cytotoxic solutions.
Elective patients were admitted on the day before surgery and received a normal meal on the evening prior to surgery. Preoperative MBP with purgatives, enemas, irrigations or otherwise was not performed. In emergency patients the decision to mechanically cleanse the bowel and to perform a primary anastomosis was made during the operation.
Prophylactic antibiotics were given intravenously to all patients
-cefamandole 1 g and metronidazole 1.5 g - after induction of anesthesia, with three further doses of cefamandole administered 6, 12 and 18 hours after the procedure. Antibiotics were only continued in cases of sepsis.
Laparotomies were carried out through midline or right transverse incisions. The bowel was divided between non-crushing occluding clamps. The bowel ends were cleaned with swaps soaked in aqueous chlorhexidine. Occasionally stool was manipulated into the bowel segment to be resected, or gently removed. In case of fecal spill the abdominal or pelvic cavity was locally washed out with saline and chlorhexidine. Anastomoses were made end-to-end using a single serosubmucosal layer with continuous polydioxanon suture. In patients with localized and purulent peritonitis a primary anastomosis was performed. Anastomoses were wrapped in omentum when possible. In fecal peritonitis Hartmann's procedure was carried out. Drains were not routinely used. Diverting colostomies or ileostomies were never used. The abdominal wall was closed in one layer with running polydioxanon suture. In contaminated or dirty wounds the skin and subcutaneous tissues were left open.
Nasogastric suction was not routinely used, but oral intake was limited in the first postoperative days. Patients were mobilized early. They were visited daily until discharge and thereafter at two weeks, six weeks and one year. A microlaxative enema was given, when spontaneous defecation had not occurred by seven days postoperatively or when patients felt an urge to defecate without result.
Endpoints of the study were wound infection, anastomotic failure and death. Patients were considered to be healed when they had been asymptomatic for one year. Wound infection was defined as discharge of pus from the wound or a positive culture at any time. Anastomotic leakage was defined as a fecal fistula from the abdominal wound, the drain tract or the vagina or an intraperitoneal abscess or peritonitis along with an anastomotic dehiscence as seen by contrast enema, colonoscopy or laparotomy. Late signs and symptoms that might be secondary to a contained disruption of the anastomosis were considered as an anastomotic failure as well. No effort was made to screen for asymptomatic leakage. When a leak was suspected a water-soluble contrast enema was

carried out. Mortality was defined as in-hospital death. Other complications were also noted.
The hospital's ethical committee approved the study.

Results

Of 353 consecutive patients admitted for primary colorectal surgery 266 patients were eligible for the study. Not eligible were 75 patients with tumorls in the middle and lower part of the rectum, and 12 other patients who had their bowel emptied for several reasons: starvation for initial conservative treatment (n=3), colonoscopy or barium enema in the days before operation (n=3), MBP because of gastrocolic, colovesical or colocutaneous fistulas (n=3), scheduled peroperative colonoscopy (n=1) or clerical error (n=2). Of the study group of 266 patients eventually 16 patients were excluded for the following reasons: Hartmann's procedure (n=9), peroperative bowel irrigation for bowel obstruction and massive fecal loading (n=3), palliative colostomy only (n=2) and laparotomy only (n=2). The study group that underwent colorectal resections and anastomosis without MBP thus consisted of 250 patients, 104 males and 146 females. The median age was 70 years (range 17 – 91; mean 67). All patients gave informed consent.

Colorectal cancer (n = 156) was the most common diagnosis, followed by diverticular disease (n = 62) , inflammatory bowel disease (n = 18), benign adenoma (n =8), volvulus (n = 2) and sarcoma, appendicitis, fibrosis and a retained surgical sponge (each n = 1).

Emergency resection and anastomosis was carried out in 51 cases (20.4 %): for bowel obstruction (n=28), for acute inflammation (n=13), for perforation (n=5) and for bleeding (n=5).

The operations performed and the types of anastomosis are summarized in **Tables 1** and **2**. Two-thirds of the resections were left-sided (65.6 %) and almost half of the anastomoses were colorectal (47.2 %).

Intraoperative fecal spill occurred in seven patients (2.8 %); it was moderate in six and severe in one. Operations were classified as clean-contaminated in 208 cases (83.2%), contaminated in 39 (15.6 %) and dirty in three (1.2 %).

In 58 patients additional procedures were carried out: small bowel resection (n=15), ovarian resection (n=13), appendectomy (n=8), cholecystectomy (n=5), liver metastasectomy (n=2), splenectomy (n=2), partial cystectomy (n=6), herniorrhaphy (n=6), partial resection of the abdominal wall (n=5), and miscellaneous (n=6).

Postoperative recovery was uneventful in 208 patients (83.2 %). The first postoperative defecation occurred after a median of 4.5 days (range 0 – 10 days). No patient suffered from fecal impaction.

Seven patients (2.8 %; 95 % confidence interval [C.I.] 1.1 – 5.7) developed early superficial wound infections (**Table 2**). Additional wound infections after hospital discharge were not found.

Anastomotic failures occurred in three patients (**Table 2**). The overall anastomotic failure rate was 1.2 % (95 % C.I. 0.3 – 3.5) The first failure was in a 77-year-old woman who underwent acute sigmoid resection and primary extraperitoneal colorectal anastomosis for perforated diverticulitis with localized peritonitis and a paracolic abscess; she was very obese and had undergone hysterectomy. Postoperatively a pelvic abscess was evacuated, but no anastomotic dehiscence could be visualized. After discharge she developed a

colovaginal fistula four weeks postoperatively. She recovered after a defunctioning colostomy. The second anastomotic failure was in a 55-year-old woman who underwent high anterior resection for carcinoma of the upper rectum. She had fever for four days postoperatively without any abdominal sign or symptom. Radiology revealed no leakage. She received amoxicillin for suspected pneumonia, recovered well and was discharged after eleven days. Gradually she developed stenosis of the anastomosis and was eventually reoperated seven months later. The stenotic segment was removed successfully. Histologic examination revealed signs that might be secondary to a contained disruption at the colorectal anastomosis. The third failure occurred in a 34-year-old obese man. Anastomotic leakage occurred six days after urgent sigmoidectomy for phlegmonous diverticulitis with a pericolic abscess. At relaparotomy the extraperitoneal colorectal anastomosis was partially necrotic at a site with possibly too many suture bites.

There was a localized purulent peritonitis. Faeces had not escaped from the bowel, nor was there fecal impaction. Hartmann's procedure was performed. A superficial wound infection occurred. Bowel continuity was restored three months later, together with incisional hernia repair.

Six other patients underwent a contrast enema for suspected leakage with negative findings. All were symptom free one year later.

There were two in hospital deaths (overall mortality rate: 0.8 %; 95 % C.I. 0.1 – 2.9), both after right hemicolectomy for carcinoma. A 72-year-old man with massive liver metastasis died 24 days after operation. An 81-year-old woman died seven days postoperatively of myocardial infarction. Neither of these patients had abdominal complications.

Reintervention was necessary in two patients (0.8 %) for postoperative hemorrhage.

General postoperative complications were pulmonary in 15 patients (6%), cardiac in nine (3.6 %), thrombo-embolic in one (0.4%) and urologic in eleven (4.4 %). Two patients (0.8 %) developed decubitus ulcers.

The median hospital stay was 10 days (range 5 – 72 days, mean 11.8 days). In the first postoperative year seven patients (2.8 %), all with an uneventful recovery, were lost to follow up, 18 patients (7.2 %) died of cancer and one patient (0.4 %) died of myocardial infarction. An incisional hernia developed in seven (3.2 %) of the 222 patients at risk after one year.

In the non-eligible group of patients that underwent low anterior resection five of 57 patients (8.7 %) suffered from anastomotic leakage. In 15 other patients who were not eligible or who were excluded there was no anastomotic leakage, although one patient suffered from the sequelae of rupture of the ascending colon during attempted intraoperative colonic irrigation.

OPERATION	ELECTIVE	EMERGENCY	TOTAL PATIENTS
Right-Sided:	72 (28.8)	14 (5.6)	86 (34.4)
Ileocecal Resection	12 (4.8)	6 (2.4)	18 (7.2)
Right Hemicolectomy	60 (24)	8 (3.2)	68 (27.2)
Left-Sided:	127 (50.8)	37 (14.8)	164 (65.6)
Transverse Colectomy	7 (2.8)	3 (1.2)	10 (4.0)
Left Hemicolectomy	21 (8.4)	10 (4.0)	31 (12.4)
Sigmoid Colectomy	80 (32)	23 (9.2)	103 (41.2)
High Anterior Resection	19 (7.6)	1 (0.4)	20 (8.0)
Total	199 (79.6)	51 (20.4)	250 (100)

Table 1 *Distibution of operations*
Values in parentheses are percentages.

CHARACTERISTIC	WOUND INFECTION	ANASTOMOTIC LEAKAGE	TOTAL
Number of patients	7 (2.8)	3 (1.2)	250 (100)
Timing			
Elective	4 (2.0)	1 (0.5)	199 (79.6)
Emergency	3 (5.9)	2 (3.9)	51 (20.4)
Side			
Right-Sided Resections	1 (1.2)	0 (0)	86 (34.4)
Left-Sided Resections	6 (3.7)	3 (1.8)	164 (65.6)
Contamination			
Clean-Contaminated	2 (1.0)	1 (0.5)	208 (83.2)
Contaminated	4 (10.3)	1 (2.6)	39 (15.6)
Dirty	1 (33.3)	1 (33.3)	3 (1.2)
Anastomosis			
Ileo-Colic	0	0	80 (32.0)
Colo-Colic	1 (2.0)	0	52 (20,8)
Colo-Rectal IP	3 (3.5)	0	86 (34,4)
Colo-Rectal EP	3 (9.4)	3 (9.4)	32 (12,8)

Table 2 *Wound infection and anastomotic leakage by distribution of operations*
Values in parentheses are percentages; IP, intra-peritoneal; EP, extra-peritoneal.

Discussion

This study confirms the results obtained from the few other series on colonic anastomoses without mechanical bowel preparation (Table 3).
Hughes reported on a small randomized trial in 1972. The 46 patients who underwent MBP fared no better than those 51 who did not[20,21]. Irving and Scrimgeour wrote a seminal article in 1987[15]. They reported on 72 consecutive elective and emergency colectomies with primary anastomosis where all mechanical preparation of the bowel was omitted and the patient was only covered by a single peroperative dose of cefuroxime and metronidazole. No anastomotic dehiscence was clinically apparent and wound infection was noted only in 8.3 % of patients[15]. Two retrospective studies show similar results[22,23] and Several randomized clinical trials were completed[17,18,24,25]. In 1998 Platell & Hall[19] gave an excellent review of the literature and performed a meta-analysis of three trials in patients undergoing elective colorectal surgery. It revealed a significantly greater incidence of wound infection in patients who received MBP (10.8 vs. 7.4 %). The incidence of anastomotic leakage was twice that of unprepared patients, but this difference was not significant (8.1 vs. 4 %).
In left colonic emergencies there is a strong trend towards one-stage resection and anastomosis[26-30]. Several studies have shown that primary anastomosis can be performed safely after gaseous decompression of the obstructed colon alone, without the need for intra operative colonic irrigation[31-36]. One randomized trial on emergency cases with colonic injuries showed that whether on table colonic lavage was performed or not, had no influence on morbidity or mortality[37]. However, all trial designs were weak[19].
In our study the total anastomotic leakage rate was 1.2 %. Since no effort was made to screen for asymptomatic dehiscence, we also included all the late complications of subclinical leakage during a follow up of one year. The results of this series compare favorably to previously published studies of colorectal surgery without MBP, as well as to reports of many other series where MBP was performed. The reported leakage rate of the latter varies greatly from 0 to 30%, but averages 5 %.[38]None of these series have included anastomotic failures after hospital discharge[39-46].
The wound infection rate of 2.8% in our study was similarly low. In a recent systematic review the overall rate of surgical wound infection was 11 % in patients undergoing colorectal surgery with antibiotic prophylaxis[19,47,48]. The use of prophylactic antibiotics is generally accepted[49].
No patient died of sepsis and the mortality rate of 0.8 % is in keeping with that of other studies, where total mortality ranges from 0 to 16 %, with an average of approximately 5 per cent[50]. Our results should be regarded with caution, since all surgery was performed by one single dedicated surgeon only[38-40,46,48,51-53].
All three anastomotic failures were after left-sided resections and after extraperitoneal colorectal anastomosis. There was no indication that the loaded bowel played a role. Other risk factors, such as complicated diverticular disease, associated peritonitis and previous hysterectomy may have contributed to the failure of these anastomoses[29,41,44,54,55].

Statistical analysis of subgroups was not performed. The studygroup and the number of events are not large enough to detect important clinical differences, although the trend shows more complications after contaminated and dirty operations and extraperitoneal anastomoses. The debate regarding resection and primary anastomosis in urgent or emergency procedures is beyond the scope of this article. We perform staged procedures only in extreme circumstances.

During elective operations the loaded bowel was seldom a nuisance. When carefully handled and gently occluded the bowel ends could easily be anastomosed without any drawback, although the cleansing is aesthetically unpleasant. During surgery for obstructed bowels control of the bowel contents was more difficult and failed in a few cases, resulting in fecal spill. This was not different from procedures in the past wherein subtotal colectomy was performed or where intraoperative colonic lavage was attempted. In our patients the distended bowel was partly emptied only for decompression of endangered bowel and to make anastomosis easier. Total cleansing was never an objective. When occluding bowel clamps were removed, the anastomosis and the distal colorectum were immediately loaded and on table defecation might occur, unhygienic but harmless.

The gentle manipulation of the bowel probably does not violate oncological principles. Some bowel contents were massaged towards the segment to be removed and thus add to the mechanical barrier around the tumorl, making early ligation of the bowel next to the tumorl unnecessary.

For the pathologist the faeces containing specimen is a nuisance - as is the bedpan for nurses - but otherwise the pathological examination is not influenced.

Since after surgery the large bowel is paralytic for a few days, the first defecation occurred after a median of 4.5 days. The loaded bowel apparently did not prolong the usual postoperative ileus. Fecal impaction proximal to the anastomosis was never observed.

The omission of MBP is cost effective. Patients do not need to be admitted the day before surgery and it saves nursing time. Our patients seemed to be uniformly happy not having to undergo MBP on the day before surgery, especially those who had undergone such a preparation earlier before colonoscopy, bowel enema or both.

Oral feeding of the patient until 12 hours or less before surgery maintains the intestinal integrity of the patient as long as possible. Starvation increases mucosal permeability and bacterial translocation, especially after surgical trauma[56,57].

An empty bowel may theoretically render anastomotic leakage less dangerous and facilitate its management if it occurs. However, anastomotic leakage usually occurs after seven to eighth days, by which time the previously prepared bowel is already loaded, regardless of the regimen of early oral feeding or traditional bowel confinement[45,58,59].

In certain cases, however, MBP remains mandatory. This is especially the case when intra-operative colonoscopy is undertaken, when blind stapling is performed, when control of the bowel contents will be difficult as in laparoscopic

surgery or when resection margins are limited and local irrigation is necessary for oncological reasons as in low anterior resection.
Why is it that faeces do not harm the healing process? Several factors may be responsible. The intestinal flora has important functions. The colonic mucosa derives most of its energy supply from the colonic lumen by bacterial metabolites of fermentable fiber, mainly short chain fatty acids like butyrate[60,61]. Furthermore, the endogenous microbial flora prevents the overgrowth of potentially pathogenic microorganisms; it stimulates the immune system, especially the gut-associated lymphatic tissue; it helps to eliminate toxins from the lumen; and it participates in intestinal regulation, mucus utilization, nutrient absorption, intestinal motility and blood flow[14,56]. We know that an empty bowel, deprived of its natural short chain fatty acid source may atrophy[62]. Animal experiments are inconclusive or conflicting. Interestingly, before the paradigm shift, experiments supported the view of an adverse effect of fecal loading on the healing of the intestinal wall[63-65]. Later the opposite was found. In recent experiments the presence of a normal intestinal flora enhances the healing of colonic anastomoses[12-14].
The disadvantages of MBP may outweigh the presumed advantages.
Although the results of this uncontrolled series are favorable, we may not conclude that omission of MBP is better. More powerful randomized clinical trials are needed. Such a large multi-center trial with patient oriented outcome is presently being conducted in the Netherlands.
We conclude that mechanical bowel preparation is not a *sine qua non* for safe colorectal surgery. Healing of the loaded bowel is more than feasible.

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-Chapter III

The effect of mechanical bowel preparation with polyethylene glycol on surgical outcome in elective open colon surgery

A randomized multi-center trial

A condensed form of this chapter has been published

Mechanical bowel preparation or not? Outcome of a multi-center randomized trial in elective open colon surgery

Diseases of the Colon and Rectum
2005 aug; 8:1509-16.

Abstract

Background: Mechanical bowel preparation is common practice in elective colon surgery. In recent literature the value of this procedure is under discussion. In order to verify the value of mechanical bowel preparation in elective open colon surgery, a randomized clinical trial was conducted.
Methods: During a prospective, multi-center, randomized study, 250 patients undergoing elective open colon surgery were randomized between receiving mechanical bowel preparation with polyethylene glycol (PEG group, 125 patients) and having a normal meal preoperatively (NMP group, 125 patients). Outcome parameters were wound infection with bacterial results of peroperative swabs and anastomotic leak.
Results: In the PEG group there were a total of nine wound infections (7.2%) and seven anastomotic leaks (5.6%) in comparison with seven wound infections (5.6%)(p=0.61) and six anastomotic leaks (4.8%)(p=0.78) in the NMP group. Bacterial results showed 52% sterile subcutis swabs in the PEG group and 63% sterile subcutis swabs in the NMP group (p=0.11).
Conclusion: In the present study we could not detect a difference in outcome parameters between patients receiving mechanical bowel preparation in elective open colon surgery and patients without preoperative treatment of the bowel. The present study, although underpowered, did not show a difference in the primary outcome of bacterial wound cultures between patients receiving preoperative mechanical bowel preparation and patients receiving no preoperative bowel treatment. We conclude that there may be no need to continue the use of mechanical bowel preparation in elective open colon surgery.

Introduction

In most surgical centers preoperative bowel preparation is still considered to be a prerequisite in elective open colon surgery. Since the publication of Nichols and Condon it has been thought to reduce the risk of wound infection and anastomotic leakage in colorectal surgery[1 2 3 4 5]. The rigid regimen of whole bowel irrigation has nowadays been replaced by less discomforting methods of bowel preparation, mainly by the use of agents that act as osmotic and contact laxatives, such as polyethylene glycol, sodium picosulphate and sodium phosphate. Previous studies demonstrate that these agents can induce osmotic disturbances in the elderly, and may prolong hospital stay. Moreover in animal studies, there is indication that these substances may lead to colonic tissue damage and impaired healing of the bowel anastomosis[6,7,8,9,10]. There have been a number of non-randomized and randomized trials that show no additional protective effect of mechanical bowel preparation in elective colorectal surgery in the presence of an adequate systemic antibiotic prophylaxis[11-16].
Since the benefit of preoperative bowel preparation has never been unequivocally proven in previous studies, Platell et al. in a meta-analysis of 3 randomized trials on the value of mechanical bowel preparation concluded that it is discomforting to the patient and probably unnecessary in addition to adequate systemic antibiotic prophylaxis in elective colorectal surgery[11].
The criticism on the trials included in the meta-analysis was the omission of well-defined inclusion and exclusion criteria and the relative small sample sizes with resulting lack of statistical power[11]. More recently, Miettinen and Zmora presented results of randomized trials with well-defined designs[17,18]. The results of these trials prompted the same conclusion as the meta-analysis of Platell et al. However, the problem of small inclusion numbers and heterogeneity of the inclusion group persists in these trials. In response, we conducted a randomized trial in 5 surgical centers with patients undergoing only colon resections with an intraperitoneal anastomosis, thus excluding rectal cancers. The aim of this trial was to investigate whether preoperative mechanical bowel preparation with polyethylene glycol has any additional value in the prevention of wound infection and anastomotic leakage in elective open colon surgery.

Patients and Methods

Eligibility, Randomization, and Surgical procedures

Between October 1st of 1998 and October 1st of 2002 a total of 250 patients who underwent elective colon surgery were enrolled in the study. Patients who underwent previous radiotherapy and/or chemotherapy, patients with idiopathic inflammatory bowel disease, patients with obstructive tumors, patients undergoing an emergency laparotomy and those receiving mechanical bowel preparation for diagnostic reasons up to one week prior to surgery, were excluded from the study. Included surgical procedures varied from right hemicolectomies to sigmoid resections excluding ileocecal resections and resections below the peritoneal reflection. In the 5 participating centers, patients were randomized between receiving 4 litres of polyethylene glycol preoperatively (PEG group) and a normal meal up to 10 hours prior to surgery without additional bowel cleaning procedures (NMP group). Randomization was performed at the central trial office and was based on permuted blocks of eight with stratification according to center. Antibiotic prophylaxis was administered according to the guideline for prevention of surgical site infection issued by the national center for infectious diseases of the U.S. Department of Health[19]. All patients received systemic antibiotic prophylaxis by way of cefazoline 2 grams and metronidazole 1.5 grams or gentamicin 240 milligrams and metronidazole 1.5 grams within 30 minutes prior to surgery. Semi-quantative bacterial swabs for aerobic and anaerobic cultures were taken intraoperatively of the subcutis after closing the abdominal fascia. The bacterial swabs were cultured into a Stuart medium and the cultures were performed on different media: blood agar, McConkey, CNA-agar (colistine and nalidixine acid) and Streptococcus selective supplement. Cultures were incubated aerobic and anaerobic at 37º Celsius for 48 hours. The microorganisms were identified by standard laboratory procedures (i.e. VITEK, API, MICROSCAN).

All procedures were done by open surgery through a midline incision; colectomies were performed for colonic malignancy or for recurrent diverticular disease. Additional procedures consisted of restoration of a Hartmann procedure or colectomy for a benign lesion or stricture. Anastomoses were performed according to the preference of the surgeon or surgical trainee. No additional antibiotic irrigation took place during the operations. The trial was approved by the medical ethics committees of all five participating hospitals.

Definition of outcome parameters and Follow-up

The primary outcome parameters were wound infection, the bacteriological results of peroperative swabs and anastomotic leakage. Wound infection was defined as a clinically significant infection of the skin for which the wound had to be evacuated. Semi-quantative bacterial results of a swab taken peroperatively of the subcutis, after closure of the abdominal fascia, were compared. Anastomotic leakage was defined as major when leakage was clinically significant leading to a relaparotomy and minor when leakage was subclinical, verified by radiographic examination, and treated conservatively.

Secondary outcome parameters were duration of ileus, total hospital stay and number of relaparatomies. Duration of ileus was defined as the number of days before signs of restoration of the bowel function appeared (bowel movement, flatus and stool) after which oral intake was restarted. Total hospital stay was defined as the number of days from date of surgery until hospital discharge.
There was a follow-up period through the outpatient clinic of 3 months and this was executed by surgeons and surgical residents unaware of the randomization procedure.

Statistical Analysis
Case report forms were sent to the central trial office, where information was entered into a database (Excel for Windows) and analysed with SPSS statistical software (version 9.0 for Windows, SPSS, Chicago). Pearson's chi-square test was used to compare frequencies between the two treatment groups. For comparison of continuous outcome measures the Student t-test was used for outcomes with a normal distribution and the Mann-Whitney test for non-parametric outcomes. Quantitative results are reported as mean (+/-SD) for normally distributed outcomes or as median (range) for non-parametric outcomes. A two-sided p-value of 0.05 was considered statistically significant.
The sample size was calculated with an α of 0.05 and test power of β 0.10, respectively. Detecting a difference in wound infection rate by halving the incidence (from 12 to 6%) it was determined that each group would require 472 patients. Since in a previous study we found the bacterial swab to be a good predictor of ultimate wound infection development[20] we set the expected difference between groups for bacterial cultures at 20% (from 50 to 30% sterile swabs). Thus each group would need 121 patients. For halving the anastomotic leakage from 10 to 5% each group would need 577 patients. Based on the above assumptions, we decided to perform an interim analysis after 250 patients were included. With such a number, results of bacterial swabs would most probably deliver enough information to decide whether continuing the trial was worthwile.

Results

Patient demographics
A total of 125 patients were included in the PEG group and another 125 patients were included in the NMP group. All patients were included as intention to treat and there were no exclusions. Both systemic antibiotic prophylaxis regimens were evenly distributed between the two randomization groups. There were 3 late deaths (defined as death more than 30 days after surgery) in the overall cohort (2 in the PEG, 1 in the NMP group) resulting from severe co-morbidity of these patients in the form of cardiac disease. No electrolyte disbalances were found contributing to the deaths. The characteristics of the included patients, the indication for surgery and the number of procedures performed by a staff surgeon (as opposed to surgical trainees under supervision of a staff surgeon*)* were similar in the two randomization groups (**Table 1**). Operative findings showed that the tumor distribution varied significantly between the two randomization groups with higher pT staging in the NMP group (according to the international TNM classification for colorectal cancer). The intra-operative parameters operation time and blood-loss showed no significant differences between the two randomization groups (**Table 2**).

Primary outcome parameters
Nine wound infections in the PEG group versus seven wound infections in NMP group were detected. Unfortunately, bacterial results were only correctly obtained in a subgroup of 185 patients (90 in the PEG group, 95 in the NMP group) but showed 52% sterile subcutis swabs in the PEG group and 63% sterile subcutis swabs in the NMP group (p=0.11) **(Table 3)**, which was a trend in favor of the NMP group. Wound infections were only seen in patients with a positive bacterial swab, which was in accordance with our previous observations on the predictive value of bacterial swabs[20]. In the PEG group six major and one minor anastomotic leaks were diagnosed. In the NMP group there were six major anastomotic leaks. There was no significant difference in the occurrence of wound infection or anastomotic leak between left and right colectomies or between mechanical and hand-sewn anastomoses.

Secondary outcome parameters
The postoperative ileus lasted a mean of 5.0 days in the PEG group and 4.7days in the NMP group. Median hospital stay was 10 days (range 2-221) in the PEG group and 9 days (range 4-55) in the NMP group. Patients who developed an anastomotic leak and/or a wound infection had a significant longer hospital stay than those with an uncomplicated course: median 31 days (range 6-55) versus median 9 days (range 2-221)($p<0.001$) with reference to anastomotic leak and median 17 days (range 7-55) versus median 9 days (range 2-221)(p=0.002) with reference to wound infection. There were 11 patients with one or more relaparatomies in the NMP group versus 13 patients with one or more relaparatomies in the PEG group **(Table 4)**.

DEMOGRAPHICS	PEG	NMP	P VALUE
Age in years Median (range)	68.3(27.7-86.5)	70.7(28.8-89.0)	0.38
Sex No. (%)			0.80
Male	58(46)	56(45)	
Female	67(54)	69(55)	
Indication for operation No. (%)			0.41
Recurrent Diverticular disease	19(15.2)	23(18.4)	
Colon malignancy	90(72.0)	92(73.6)	
Other	16(12.8)	10(8.0)	
First Surgeon No. (%)			0.20
Surgeon	52(41.6)	62(49.6)	
Surgical trainee	73(58.4)	63(50.4)	

Table 1 *Baseline characteristics of patients, indication for surgery and number of procedures performed by a trained surgeon*
PEG=Patients receiving mechanical bowel preparation with polyethylene glycol preoperatively; NMP= Patients receiving a normal meal preoperatively.

OPERATION PARAMETERS	PEG	NMP	P VALUE
Type of operation No. (%)			0.54
Right colectomy	65 (52.4)	53 (42.1)	
Tranverse colectomy	3 (2.4)	3 (2.4)	
Left colectomy	10 (8.1)	10 (7.9)	
Sigmoid resection	41 (33.1)	54 (42.9)	
Additional procedures	6 (4.8)	5 (4.0)	
Type of anastomosis No. (%)			0.81
Handsewn	116 (92.8)	115 (92.0)	
Stapled	9 (7.2)	10 (8.0)	
Operation time (minutes) Median (range)	95 (48-400)	120 (33-240)	0.28
Bloodloss (ml.) Median (range)	300 (0-2300)	300 (0-1650)	0.12
Tumor distribution pT stage No. (%)			0.04
T1	28 (31.1)	17 (18.5)	
T2	20 (22.2)	19 (20.7)	
T3	39 (43.3)	44 (47.8)	
T4	3 (3.3)	12 (13.0)	

Table 2 *Operation-related parameters and tumor distribution*
PEG=Patients receiving mechanical bowel preparation with polyethylene glycol preoperatively; NMP= Patients receiving a normal meal preoperatively.
TNM= International tumor-node-metastasis classification for colorectal cancer.

PRIMARY OUTCOME PARAMETERS	**PEG**	**NMP**	**P VALUE**	**RELATIVE RISK** (95% C.I)
Anastomotic leak No. (%)	7(1 minor) (5.6)	6 (4.8)	0.78	0.86 (0.30–2.48)
Wound infection No. (%)	9 (7.2%)	7 (5.6)	0.61	0.78 (0.30–2.02)
Anastomotic leak and wound infection	3 (2.4%)	2(1.6%)	0.65	0.67 (0.11-3.92)
Sterile bacterial swab No. (%)	49 (52)	57 (63)	0.11	

Table 3 *Primary outcome parameters*
PEG=Patients receiving mechanical bowel preparation with polyethylene glycol preoperatively; NMP= Patients receiving a normal meal preoperatively.

SECONDARY OUTCOME PARAMETERS	**PEG**	**NMP**	**P VALUE**
Duration of Ileus Mean *(+/-SD)*	5.0 (2.7) days	4.7(1.7) days	0.25
Hospital stay Median (range)	10 (2-221) days	9 (4-55) days	0.97
Patients with one or more relaparotomies No. (%)	13(10.4%)	11(8.8%)	0.51

Table 4 *Secondary outcome parameters*
PEG=Patients receiving mechanical bowel preparation with polyethylene glycol preoperatively; NMP= Patients receiving a normal meal preoperatively.

Discussion

In the present study no significant difference in rate of wound infection or rate of anastomotic leak was observed between patients receiving preoperative mechanical bowel preparation by means of polyethylene glycol and patients having a normal meal the evening before surgery. A type II error seems unlikely since there is a trend in favor of patients in whom mechanical bowel preparation was omitted. We found more positive swabs of the subcutis in patients receiving mechanical bowel preparation indicating a higher degree of bacterial contamination of the surgical wounds in this group. In a previous study we showed that a negative bacterial swab of the subcutis has a very strong negative predictive value for wound infection development[20]. Because in the present data the trend (p=0.11) was opposite, increasing the power of the study by including a higher number of patients may not have changed the conclusion that the PEG group is not significantly better than the NMP group (concerning bacterial cultures and thus wound infection rates).

Our study suggests the results of previous studies on the effect of preoperative bowel preparation in elective colorectal surgery. Irving and Scringemour presented a group of 72 patients undergoing elective and emergency colorectal surgery, which were operated without previous bowel preparation[21]. This heterogeneous group presented excellent outcome with no anastomotic leak and a wound infection rate of 8.3 %. As was indicated in this landmark paper of Irving the surgery without mechanical bowel preparation in our group too posed no specific technical problems, prior to opening the bowel the stool was manually manipulated aside and atraumatic bowel clamps were applied to secure a clean operating field. In 1992, Mansvelt et al. presented a consecutive series of 189 patients undergoing an elective colectomy without preoperative bowel preparation with a 0% anastomosis leak and a 2.6% infection rate[22].
van Geldere et al. presented a group of 250 patients undergoing elective colorectal surgery without bowel preparation of any sort and reported an anastomotic leakage rate of 1.2 % and a wound infection rate of 2.8%[23].
Over the past decade a number of controlled trials have been presented comparing patients receiving preoperative bowel preparation with patients receiving no form of bowel cleaning. The results of the trials of Santos et al., Brownson et al., Burke et al., Miettinen et al. and Zmora et al[12,13,14,17,18]. demonstrated that patients receiving preoperative bowel preparation fared no better and sometimes even worse than those receiving no preoperative bowel preparation before surgery.
An excellent meta-analysis of three of the above-mentioned trials was published by Platell et al[11]. Their conclusion was that no additional value could be attributed to preoperative bowel preparation in elective colorectal surgery. However, as mentioned before, the randomized trials that were included in the meta-analysis of Platell et al. had a debatable study design and lacked statistical power. The more recent trials of Miettinen and Zmora have well defined trial designs but have the persisting problem of statistical lack of power and heterogeneity of the inclusion group. Recent meta-analysis of Slim et al (that included abstract data of the

present trial) and Bucher et al. even show that there are significantly more anastomotic leakages after MBP compared to a no preparation regimen[24,25]. Other endpoints like wound infection also favored the no-preparation groups.

In the present trial, in contrast to previous trials, selection bias was minimized by including only colon surgery with an intraperitoneal anastomosis. Low anterior resections were excluded because previous studies demonstrate that the anastomotic leakage rate in these low anastomoses is higher due to poor anastomosis vascularisation and several other surgical aspects[26,27,28].

By restricting the inclusion criteria the problem of statistical lack of power persists also in the present trial. In this era of evidence based medicine, proponents of invasive procedures like mechanical bowel preparation should actually provide convincing data to show the statistical significant advantage of such a procedure. Those who advocate the omission of such a procedure —like us— have the problem of statistical power calculation depending on the a priori assumption of differences between certain endpoints. In case there is no real statistical difference between two intervention groups an endlessly large study population would be needed to proof so.

In the present study we stopped after evaluation of 250 patients. Although we had only 185 bacterial swabs for definitive analysis, the fact that the trend of these results was in favor of the no preparation group led us to conclude that larger numbers of included patients leading to a greater power finally would not change the results and our conclusions.
We believe that since this trial was conducted in five different centers, two of which were university training hospitals, the results are representative of the average surgeon population. In this study the resulting anastomotic leakage rate was 5.6% in the PEG group and 4.8% in the NMP group. This is comparable with previously published rates in heterogeneous groups which vary widely from 0 to 15% but average 5%[11,21,29,30,31,32,33,34]. This also applies for the wound infection rate, which in our study was 7.2% in the PEG group and 5.6% in the NMP group. A previous review of the wound infection rate in elective open colorectal surgery reported an 11% rate[35]. The results of the semi-quantative bacterial swabs taken of the subcutis after closure of the abdominal wall showed a trend towards a higher bacterial contamination rate of the surgical wound in the PEG group. To our knowledge this is the first study measuring the impact of mechanical bowel preparation on bacterial flora. This argument is important, since lowering bacterial load has in fact been suggested to be one of the major reasons for performing mechanical bowel preparation in elective open colorectal surgery. With reference to the secondary outcome parameters such as postoperative duration of ileus, hospital stay and number of relaparotomies, no significant difference could be found between the two randomization groups. For the operation-related parameters such as bloodloss, duration of the procedure, surgical technique or resection level, no significant differences could be found between the two randomization groups. There was a significant difference in tumor distribution between the two randomization groups with higher pT staging in the NMP group. This result is in

favor of our conclusion since this difference possibly predisposed the patients in the NMP group to postoperative complications. In contrast, we found a trend in favor of the NMP group in all primary and secondary endpoints.

Previous authors have suggested that leaving faecal material in the preoperative bowel increases the risk of mechanical disruption of the fresh anastomosis and impairs bowel manipulation preoperatively[36,37]. In our study patients with obstructive tumors were excluded. Moreover, the surgeons encountered no problems in manipulating solid faecal mass during operation; it was even appreciated more than the sometimes uncontrollable liquid faecal material. The results of the present study demonstrate no additional protective effect of preoperative mechanical bowel preparation with polyethylene glycol in the prevention of wound infection and anastomotic leakage in elective open colon surgery. On the contrary, recent studies show that there may well be a negative effect of preoperative bowel preparation. Animal studies show damage of the colonic tissue when treated with polyethylene glycol, while sodium phosphate is known to cause aphtous lesions in human colonic tissue, which may lead to false positive findings at colonoscopy[38,39,40,41]. This damage is thought to be caused directly by fluid shifting and inflammation leading to oxidative stress, and indirectly by depriving the colonic mucosa of short chain fatty acids, which are washed away with faeces. These fatty acids probably play a crucial role in energy delivery and homeostasis of the colonic mucosa. Deprivation of short chain fatty acids causes damage mostly in the mucosa, which forms an important barrier against bacterial translocation in the peri-operative phase of colorectal surgery[42,43,44,45]. Furthermore, by reducing solid stool to liquefied debris, which by its physical characteristics is more likely to leak through the fresh anastomosis, mechanical bowel preparation may cause problems instead of preventing them. Indeed, in the present study the level of bacterial contamination of the subcutis was highest in patients receiving mechanical bowel preparation. Finally, mechanical bowel preparation remains distressing to the patient. Although the available products are sweetened nowadays, they still taste bad and vomiting and abdominal cramping are not unusual side-effects[46,47].
Considering these side-effects, the nursing staff is burdened with controlling the patients to whom mechanical bowel preparation is being administered. In several surgical centers the sole reason for early entry of the patient, and subsequent prolonged hospital stay, is the procedure of preoperative mechanical bowel preparation. The results of the present multi-center randomized trial prompt us to conclude that, since we could not demonstrate an additional protective effect of preoperative mechanical bowel preparation with polyethylene glycol in the prevention of anastomotic leakage and wound infection in elective open colon surgery, there seems to be no evidence to continue this invasive practice with potentially negative side-effects.

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-Chapter IV.I

Bacteriological results of abdominal wounds in elective open colon surgery: a prospective descriptive study of 100 surgical wounds

A condensed form of this chapter has been published

Bacteriological results of abdominal wounds in elective open colon surgery: a prospective descriptive study of 100 surgical wounds

Clin Microbiol Inf 2005; 11:155-7.

Abstract

Background: In order to assess the value of peroperative bacterial sampling in elective open colon surgery, a prospective bacteriological study of 100 surgical wounds was conducted.
Methods: Bacteriological samples of the subcutaneous tissue were taken peroperatively after closing the abdominal fascia in 100 patients during elective colon surgery.
Results: Of the 100 samples taken, 52 were sterile with no resulting wound infection, ten of the 48 contaminated samples resulted in a wound infection. Bacteriological results of the wound infections revealed colonic pathogens and nosocomial micro organisms.
Conclusion: Peroperative bacterial sampling seems a useful method to predict wound infection in elective colon surgery.

Introduction

One of the persisting problems in colorectal surgery is the occurrence of wound infections. The infection rate of the laparotomy wound varies from 10 to 15%[1]. Wound infection prolongs wound healing, increases the risk of poor cicatrisation and the duration of hospitalization and subsequent costs of medical care [2, 3, 4].
Prevention of wound infection in elective open colorectal surgery consists of antibiotic prophylaxis and mechanical bowel preparation. The advantages of the latter preventive measure are currently under discussion[5]. Antibiotic prophylaxis in colorectal surgery consists of an antimicrobial regimen directed at the endogenous flora of the large intestines, which are mainly Gram-negative and Gram-positive aerobes and anaerobes[6]. In order to better understand the dynamics of abdominal wound infection after colon surgery, a prospective bacteriological study of abdominal wounds was performed in 100 patients undergoing elective open colon surgery.

Patients and Methods

In the period of October 1998 through May 2000 one hundred patients who underwent elective open colon surgery were included. Indications for surgery were recurrent diverticular disease or colon malignancy. All patients underwent colorectal resection with primary anastomosis without a deviating stoma. All surgical interventions were classified as clean-contaminated, according to the National Research Council of the U.S. department of health[7].

Antibiotic prophylaxis was given to all patients 30 minutes prior to operation by means of 2 grams of cefuroxim and 1.5 grams of metronidazole intravenously.
In 43 patients mechanical bowel preparation with 4 litres of polyethylene glycol orally was given prior to surgery.
After closing the abdominal fascia and just before closing the skin a bacteriological sample was taken of the subcutaneous tissue of each abdominal wound. Postoperative follow-up was performed by surgeons and surgical residents unaware of the bacteriological results of the swabs taken during operation. The occurrence of wound infection was documented during hospital stay and up to 4 weeks postoperatively in the outpatient setting.
Infection was defined as discharge of pus from the wound, or a clinical suspicion of wound infection based on inflammatory signs like raised temperature, redness and tenderness of the wound. When it was deemed necessary to open the infected wound a separate bacteriological sample was taken of the drained area. The study was approved by the local hospital ethical committee.

Bacterial swabs were cultured into a Stuart medium and the cultures were performed on different media: blood agar, McConkey, CNA-agar (colistine and nalidixine acid) and Streptococcus selective supplement. Cultures were incubated aerobic and anaerobic at 37º Celsius for 48 hours.
The microorganisms were identified by standard laboratory procedures (i.e. VITEK, API, MICROSCAN).

Results

Of the 100 bacteriological swabs taken, a total of 52 swabs were sterile.
The remaining 48 swabs revealed 21 contaminations with facultative aerobic bacteria only, 13 contaminations with anaerobic bacteria only, while 14 swabs were contaminated with a mixture of anaerobic and facultative aerobic bacteria.
The most prominent aerobic bacteria were *Escherichia coli* (n=18) and the *Streptococcus species (spp.)* (n=10).
The most prominent anaerobe bacterium was *Bacteroides fragilis*, which was present in 17 of the contaminated swabs. The 43 patients receiving mechanical bowel preparation preoperatively were equally distributed in the groups with positive and negative preoperative bacterial sampling.
There were no wound infections in the 52 patients with a sterile peroperative swab. In the group of patients with a contaminated peroperative swab, ten of the 48 patients developed a clinical relevant wound infection. All ten patients had a positive bacteriological swab growing *Bacteroides fragilis, Escherichia coli* or *Streptococcus spp*. In six of the ten swabs *Bacteroides fragilis* was present.
In seven of the ten patients with a clinical wound infection a swab of the opened wound was taken. Four of the seven swabs corresponded with at least one species found in the original peroperative taken swab. All seven swabs were contaminated with potentially pathogenic micro organisms (ppm) (*Pseudomonas aerogunosa, Enterobacter cloacae, Escherichiae coli, Morganella morganii* and *Candida albicans*). **Table 1** presents the isolated organisms.

ISOLATED ORGANISM	NO. OF POSITIVE PEROPERATIVE SWABS	NO. OF POSITIVE WOUND INFECTION SWABS
Streptococcus viridans	5	2
Escherichiae Coli	18	4
Bacteroides fragilis	17	2
Bacteroides uniformis	1	0
Streptococcus, beta-hematolytic group C	2	0
Actomyocines viscosus	2	0
Enterococcus faecalis	3	3
Endobacterium lentum	4	0
Staphylococcus species	3	0
Corynebacterium species	2	0
Peptostreptococcus	2	1
Lactobacillus species	1	0
Actinomyces Israeli	3	0
Bacteroides vulgatus	1	0
Bacteroides ovatus	1	0
Enterobacter aerogenes	1	0
Klebsiella pneumoniae	1	0
Bacteroides melaninogenicus	1	0
Streptococcus bovis	1	0
Proteus mirabilis	1	0
Corynebacterium species	2	0
Stenostrophomonas maltophilia	1	0
Propioni bacterium	1	0
Bacteroides buccae	1	0

Table 1 *Results of bacteriological swabs in patients after elective open colon surgery.*

Discussion

The present study demonstrates that a positive preoperative bacteriological swab of the surgical wound seems to be a valuable predictor for a possible subsequent clinical infection in elective open colon surgery. With 10 of the 48 contaminated wounds resulting in a clinical infection. Moreover, the negative predictive value of a negative peroperative bacterial swab proved to be 100% in this study.

In abdominal surgery the wound infection rate is probably the highest after colorectal operations. It has been suggested that in colorectal surgery there is an increased bacterial load prior to wound closure in comparison with other abdominal operations. This is mainly due to the high concentration of aerobic and anaerobic intestinal species such as *Escherichia coli* and *Bacteroides fragilis* that are released upon opening the abdominal viscera [8, 9]. In the present series we used a culture from the subcutaneous fat after fascial closure because it has been suggested that this may be the best predictor of abdominal wound infection with organisms likely to cause the subsequent infection[10,11].
The reported bacteria to cause abdominal wound infections in colorectal surgery are endogenous micro organisms, namely *Escherichia coli, Bacteroides fragilis* and other potentially pathogenic micro organisms like *Proteus* spp. and *Klebsiella* spp.[12,13,14]. The present study confirms these pathogens to be the main causative pathogens of wound infections in elective open colon surgery.
However, nosocomial potentially pathogenic micro organisms were also causative agents in all seven wound infections. It seems that peroperative contamination of the surgical wound with colonic flora may cause a polymicrobial infection caused by commensals and potentially pathogenic micro organisms. When systemic antibiotic prophylaxis was not common practice, peroperative bacterial swabs seemed to have the best predictive value in assessing wound infection[15,16]. The present data demonstrate that the predictive value of peroperative bacterial swabs for wound infection assessment remains high even when systemic preoperative antibiotic prophylaxis and mechanical bowel preparation in a subgroup is given. These findings raise the question whether there may be a place for targeted antibiotic treatment in those cases where peroperatively taken swabs of the surgical wound grow colonic-, or potentially pathogenic flora.

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-Chapter IV.II

Bacteriological results in patients receiving mechanical bowel preparation with polyethylene glycol in elective open colon surgery

A descriptive bacteriological study

A condensed form of this chapter has been published

Bacteriological results in patients receiving mechanical bowel preparation with polyethylene glycol in elective open colon surgery

Clin Microbiol Inf 2005; 11:158-60.

Abstract

Background: Mechanical bowel preparation is common practice in elective colon surgery. In order to verify the effect of mechanical bowel preparation on the colonic flora, a randomized study was conducted.
Methods: A total of 185 patients undergoing elective open colon surgery were assigned to receive mechanical bowel preparation [PEG group, n=90] or not [NMP group, n=95]. Peroperatively a bacteriological swab of the anastomosis and of the subcutis was taken. In the occurrence of a wound infection a swab was taken of the surgical wound.
Results: There was a tendency towards more sterile subcutaneous swabs in the NMP group (p=0.11).
Conclusion: Mechanical bowel preparation does not reduce the contamination of the peritoneal cavity or the subcutis during open colon surgery

Introduction

Since the introduction of preoperative bowel preparation in elective colorectal surgery in the seventies, it has been believed to reduce the risk of wound infection and anastomotic leakage[1,2,3]. These benefits have been challenged during the last decade [4,5,6]. Recent animal studies indicate histological damage of the colonic bowel and healing impairment of the colonic anastomosis due to preoperative bowel preparation [7,8,9]. The data concerning the effect of osmotic laxatives like polyethylene glycol on the bacteriological ecology of the colonic content are scarse. It is thought that these effects cause a bacteriological overgrowth which may increase the risk of subsequent postoperative wound infection after elective colorectal surgery [10,11]. The present trial was conducted to determine the impact of preoperative bowel preparation on the colonic bacterial flora of patients undergoing elective open colon surgery.

Patients and Methods

Between October 1998 and May 2002, a total of 185 patients who underwent elective open colon surgery for malignancy or recurrent diverticular disease were included in the study. Patients were randomized between a group of 90 patients receiving preoperative bowel preparation with 4 litres polyethylene glycol (PEG) and a group of 95 patients that had a normal meal up to 10 hours before elective surgery (NMP).
All patients received routine systemic antibiotic prophylaxis (cefazoline and metronidazole) thirty minutes prior to surgery.
Peroperatively 2 bacteriological swabs were taken of each patient. One swab was taken at the outside of the colonic anastomosis, a second swab was taken of the subcutis after closure of the abdominal fascia.

Postoperatively, the wounds were observed by surgeons and surgical residents unaware of the randomization groups. A clinical wound infection was defined as discharge of pus from the wound or a clinical suspicion of wound infection based on inflammatory signs like raised temperature, redness and tenderness of the wound. In those cases in which it was deemed necessary to open the infected wound, a separate bacteriological sample of the drained area was taken.
Bacterial swabs were cultured into a Stuart medium and the cultures were performed on different media: blood agar, McConkey, CNA-agar (colistine and nalidixine acid) and Streptococcus selective supplement. Cultures were incubated aerobic and anaerobic at 37º Celsius for 48 hours.
The microorganisms were identified by standard laboratory procedures (i.e. VITEK, API, MICROSCAN).

Bacteriological results were compared between the two groups and between the two samples per patient, as were the results of the wound infections.
The study was approved by the ethical committees of the including centers.

Statistical analysis
Data of the two groups were compared using Pearson's chi square test for trend. A two-sided P-value of 0.05 was considered statistically significant.

Results

In the PEG group a total of 14 patients had a sterile swab of the anastomosis, 49 patients had a sterile swab of the subcutis and 11 patients had both swabs sterile. In the NMP group 14 patients had a sterile swab of the anastomosis, 57 patients had a sterile swab of the subcutis and in 13 patients both swabs were sterile. In the PEG group a positive correlation with at least one bacteriological species between the samples taken of the anastomosis and those species cultured in the subcutis was found in 43 of the 95 patients. In the NMP group this correlation was positive in 42 of the 90 patients.

In the PEG group there were nine clinical wound infections in comparison to seven wound infections in the NMP group. In the PEG group in five of the nine wound infections a bacteriological swab was taken, while in the NMP group a bacteriological swab was taken in three of the seven wound infections. In all eight swabs the causative agents of the wound infections were either intestinal flora or potential pathogenic micro organisms (ppm). There was a positive correlation with at least one of the bacteriological species found peroperatively in six of the eight swabs. (**Table 1**)

PT. NR	RANDOM. GROUP	ANASTOM. SWAB	SUBCUT. SWAB	WOUND INFECTION SWAB
1	**NMP**	*Escherichia coli, Moraxella* species, *Pseudomonas aerogunosa, Bacteroides fragilis*	*Bacteroides fragilis*	*Bacteroides fragilis*
2*	**NMP**	*Bacteoides fragilis, Actinomyces viscosis*	*Bacteroides fragilis*	*Enterococcus faecalis, Pseudomonas aerogunosa*
3	**NMP**	*Enterococcus faecalis, Streptococcus viridans, Bacteroides fragilis*	*Bacteroides fragilis*	*Enterococcus faecalis, Escherichia coli*
4*	**PEG**	*Escherichia coli*	*Streptococcus species*	*Morganella morganii, Enterococcus faecalis, Peptostreptococci, Bacteroides capillosus, Gemella hemolysans*
4*	**PEG**	*Escherichia coli*	*Streptococcus species*	*Morganella morganii, Enterococcus faecalis, Peptostreptococci, Bacteroides capillosus, Gemella hemolysans*
5	**PEG**	*Citrobacter freundii*	*Streptococcus. viridans*	*Escherichia coli, Enterobacter. cloacae, Streptococcus viridans*
6	**PEG**	*Escherichia coli, Bacteroides fragilis*	*Bacteroides fragilis*	*Escherichia coli, Bacteroides fragilis, Streptococcus viridans*
7	**PEG**	*Escherichia coli, Streptococcus viridans, Corynebacterium species*	*Bacacteroides fragilis*	*Escherichia coli, Enterobacter faecalis*
8	**PEG**	*Escherichia coli, Streptococcus Viridans*	*Bacteroides fragilis*	*Proteus vulgaris, Morganella morganii, Enterobacter faecalis, Bacteroides fragilis*

Table 1 *Results of the bacteriological species cultured in both perioperative swabs and in the wound infections.*

PEG=*polyethylene glycol,* **NMP**= *normal meal prior to surgery,* *spp.=species*

**No correlation between causative specimens cultured in the wound infections and the bacteriological spp. cultured intraoperatively.*

Discussion

This study shows that mechanical bowel preparation does not reduce the contamination of the peritoneal cavity or the subcutis during surgery. Furthermore, mechanical bowel preparation does not alter the correlation between bacteria cultured at the colonic anastomosis and the flora cultured at the subcutis after closure of the abdomen. Finally, mechanical bowel preparation does not alter the correlation of bacteriological species found in wound infections and peroperative cultured micro organisms.

Although systemic antibiotic prophylaxis is commonly accepted to prevent anastomotic leakage and wound infection after elective colorectal surgery, the value op preoperative bowel management has not been unequivocally accepted [12].

In the present study the most encountered bacteriological species were *Escherichiae Coli* and *Bacteroides Fragilis.* The bacterial flora in human stool is a stable ecologic environment, with anaerobic *Bacteroides* predominating at a concentration of 10^9 colony forming units (CFU) to 10^{10} CFU per gram of stool and aerobic coliforms with 10^6 to 10^8CFU per gram of stool. After spillage or perforation of the colon, more than 400 bacterial species may contaminate the peritoneal cavity[13]. It has long been thought that cleaning the bowel preoperatively reduced the amount of bacteriological species. However, while reducing faecal mass, preoperative bowel preparation does not alter the concentration of faecal organisms intraluminally. Previous studies showed that a vigorous 72-hour mechanical cleansing regime produces only a significant reduction in coliforms while the residual colonic microflora remains unchanged [14,15]. Moreover, mechanical bowel preparation seems to reduce solid stool to less manageable liquefied debris which can more readily protrude the fresh anastomosis. This observation may facilitate the translocation and/or invasion of bacteria into the peritoneal space and the abdominal layers[16]. Besides wound infections this outflow of colonies can also lead to local infection of the anastomosis causing leakage and subsequent fistulous tracts [17, 18].

The results of this study demonstrate that preoperative mechanical bowel preparation apparently does not reduce the amount of bacterial contamination intra-operatively, nor does it have an impact on the correlation between the micro organisms cultured peri-anastomotically, subcutaneously or in subsequent wound infections.

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-Chapter V.I

The effect of mechanical bowel preparation on human colonic tissue in elective open colon surgery

A microscopic comparative study

A condensed form of this chapter has been published

The effect of mechanical bowel preparation on human colonic tissue in elective open colon surgery: A microscopic comparative study.

Dis Colon and Rectum 2004; 47:948-9

Abstract

Background: Preoperative mechanical bowel preparation with osmotic laxatives is common practice in elective colorectal surgery. However, little is known about the side effects of osmotic laxatives on the intestinal tissue. We conducted a microscopic study to further evaluate the spectrum of the effects of bowel preparation.
Methods: Forty patients who underwent elective open colon surgery were included in the study. Twenty of the patients received mechanical bowel preparation with polyethylene glycol (MBP group) and twenty patients received a normal meal the night before surgery (ND group).
Colonic full-thickness biopsies taken at surgery were examined microscopically with scoring for five damage criteria; *epithelial damage* (vacuolar degeneration, dedifferentiation, lifting), *non specific lamina propria damage* (edema, congestion, hemorrhage), *presence of polymorphonuclear cells, presence of eosinophilic cells* and *presence of pigmented macrophages*.
Results: In a univariate analysis of the five damage criteria there was no statistical significant difference in microscopic damage of the colonic tissue between patients who received polyethylene glycol preoperatively and those who did not. There was a statistically non-significant tendency towards increased damage in the lamina propria in patients receiving polyethylene glycol preoperatively (p=0.096).
Conclusions: In our series preoperative mechanical bowel preparation with polyethylene glycol caused no significant additional tissue damage in comparison with patients receiving a normal meal the night before surgery.

Introduction

Preoperative mechanical bowel preparation is common use in elective colorectal surgery.
It is believed to reduce the risk of wound infection and anastomotic leakage and is supplemental to antibiotic prophylaxis in most surgical centers [1-5].
Although the clinical benefits are currently under debate, the reason to continue this procedure is that it is believed to be safe, reliable, effective and well tolerated [6-10].
There is, however, little information available on the histopathologic alterations that mechanical bowel preparation exerts on the human colonic tissue in a surgical setting and the potential negative impact on clinical outcome.

The most commonly used agents for mechanical bowel preparation are osmotic laxatives inducing diarrhea. It has been proven that such agents may cause electrolyte disturbances in the elderly.[11,12]
There are a number of clinical studies comparing different osmotic laxatives for their efficacy and side effects. They indicate polyethylene glycol and sodium phosphate to be the least harmful and most effective agents[13,14].
Polyethylene glycol has been shown to cause microscopic damage in the different layers of the gastrointestinal wall in rats[15,16]**.** One previous study also shows polyethylene glycol given before colonoscopy to cause eosinophilic cell infiltration and increased edema of the lamina propria[17]. There is however, little information on the histopathologic changes after the use of polyethylene glycol or other osmotic agents in patients undergoing elective open colon surgery.

In order to document the effect of polyethylene glycol on the different layers of the human colonic wall we examined the pathologic specimens of forty patients in whom elective open colon surgery for non–obstructive colorectal malignancy was performed.
To our knowledge this is the first study of the effects of an osmotic laxative on the colonic wall in patients undergoing elective open colon surgery

Patients and methods

The study was approved by the hospital ethics committee.
From December 2000 until April 2001 forty patients who were hospitalized for an elective, non-obstructive oncologic colon resection were included in the study. Patients with inflammatory bowel disease were excluded from the study, as were patients with clinical bowel obstruction. Patients who received radiotherapy or chemotherapy up to three weeks prior to surgery and immunocompromised patients were also excluded.
Patients were randomly divided into two groups. Twenty patients received mechanical bowel preparation with 4 litres of polyethylene glycol orally the night before elective surgery (MBP group).
Twenty patients received no preoperative bowel preparation and received a normal meal the night before surgery (NMP group). The surgical procedures included right hemicolectomies, left hemicolectomies and sigmoid resections. Specimens for histologic examination were taken 5 cm distal to the colonic tumors in the freshly resected bowel specimen (approximately 12 hours after the initial polyethylene glycol administration) and fixed in 10% formalin. Routine histology was performed on formaldehyde fixed, parafin embedded material and haematoxilin and eosine stained sections. All specimens were examined by light microscopy by two separate pathologists unaware to which group the bowel specimens belonged.

Before microscopic examination two patients were excluded due to revision of the preoperative diagnosis (lymphoma, endometriosis), one patient was excluded due to sample loss, and one patient was excluded because of a narrow distal resection margin.

Histopathologically the specimens were evaluated for bowel damage and inflammation by means of five criteria including *epithelial damage* (vacuolar degeneration, dedifferentiation, lifting), *non specific lamina propria damage* (edema, congestion, hemorrhage), *presence of polymorphonuclear cells, presence of eosinophilic cells* and *presence of pigmented macrophages*. These criteria have been used in previous studies to evaluate damage of the colonic wall[10 11 12]. Criteria were scored semi-quantitatively as absent(0), mild(1), moderate(2), or severe(3).

Statistical analysis

Association between colonic tissue damage and preoperative mechanical bowel preparation with polyethylene glycol was evaluated by Pearson's chi square test for trend. A two-sided P-value of 0.05 was considered statistically significant.

Results

Thirty-six patients remained in the study, eighteen in each group. The median age was 61 years with a similar distribution for the two groups. The male/female ratio was 1:1.4.
In the MBP group eight right hemicolectomies, three left hemicolectomies and seven sigmoid resections were performed. In the NMP group seven right hemicolectomies, two left hemicolectomies and nine sigmoid resections were performed.
All tumors were T2 or T3 tumors according to the international TNM classification system. There were three T2 and fifteen T3 tumors in the MBP group and two T2 and sixteen T3 tumors in the NMP group.

Histopathologic changes

Analysis of all five criteria for mucosal damage revealed no statistical significant differences between samples of the patients with and without bowel preparation.
In a univariate analysis for the separate criteria, in the MBP group, damage in the lamina propria layer was more pronounced in some patients, indicating a tendency towards increased damage in this group. This difference was not statistically significant in comparison with the NMP group (p=0.096) (**Table 1**).

	Epithelial damage				**Lamina propria damage**				**Polymorfo nuclear cells**				***Eosinophilic* cells**				**Pigmented macrophagic Cells**			
	0	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
MBP	4	9	5	0	12	5	1	0	17	1	0	0	15	3	0	0	6	6	1	5
NMP	5	7	4	2	16	2	0	0	16	2	0	0	17	0	1	0	5	5	5	3
	p=0.70				**p=0.096**				p=0.55				p=0.70				p= 0.88			

Table 1 *Univariate analysis of the histopathologic changes in the two groups.*
Values are presented as the number of samples with scoring of the different criteria in a semi-quantative way as absent(0), mild(1), moderate(2), or severe(3).
MBP=mechanical bowel preparation, NMP=normal diet

Discussion

Little is documented on the histopathologic changes caused by osmotic laxatives on human colonic tissue in a surgical setting.
Previous authors have mentioned damage on a microscopic level in animal studies. In human colonic tissue sodium phosphate and other laxative agents have been shown to induce aphtous lesions that can lead to diagnostic errors in colonoscopy[18] [19] . Other studies describe macroscopic abnormalities with the use of osmotic agents including polyethylene glycol [20-23] .
The purpose of this study was to document this detrimental effect by histopathologic examination of biopsies taken in a surgical setting, as this is most relevant to surgical practice.
Although there was a tendency towards increased damage in the lamina propria in patients receiving polyethylene glycol preoperatively in a univariate analysis for all five microscopic damage criteria there was no statistically significant difference between patients receiving mechanical bowel preparation and those who did not. In accordance with previous studies by Bingol et al[15] and Coskun et al[16], in our study damage was most pronounced in the mucosal layers of the intestinal wall. The barrier formed by these layers is known to be important in the prevention of bacterial translocation[34].

The exact pathways by which bowel preparation with osmotic agents leads to mucosal damage are not clear. Different mechanisms may lead to the eventual damage. There may be a direct damage to the colonic intestinal wall by polyethylene glycol due to oxidative stress. Treatment of the colon with both sodium picosulphate and polyethylene glycol activates oxidants and antioxidants. Free oxygen radicals can react with vital components such as membrane lipids. During this process of lipid peroxidation, malonyldialdehyde is produced, an accepted early indicator of oxidative damage and cell death[24,25]. A high level of malonyldialdehyde has been demonstrated in colonic tissue treated with sodium picosulphate or polyethylene glycol[16]. How mechanical bowel preparation disturbs the oxidant-antioxidant balance is poorly understood. A possible explanation is an inflammatory reaction in which infiltration with activated neutrophilic cells produces oxygen free radicals[26,27]. In a colonoscopy setting, edema of the lamina propria and eosinophilic influx have been observed 4 hours after polyethylene glycol administration, although polyethylene glycol caused less histopathologic changes (such as flattening of epithelial cells and depletion of goblet cells) in the colonic bowel than conventional laxatives (48 hours of clear liquid diet, magnesium citrate and a senna derivative)[17]. In the present study the degree of infiltration of polymorphonuclear cells, eosinophilic cells and activated macrophages was analyzed as a sign of inflammation and possible cause of oxidative stress and mucosal damage in patients being treated with preoperative polyethylene glycol. No significant difference in the level of influx and activation of these cells could be found in our series of patients treated with preoperative mechanical bowel preparation.

An increase of pigmented macrophages is described in chronic laxative abuse[28]. It is plausible that mechanical bowel preparation with osmotic agents exerts a similar damage as is inflicted by chronic laxative abuse. The chronic use of laxatives was excluded in the history taking of the patients included in our study. Since our study was done in a surgical setting, the time interval between administration of polyethylene glycol and tissue biopsy was approximately 12 hours as is normal in clinical practice. This differs from previous studies with human colon in a colonoscopy setting and animal studies in surgical setting which had much shorter intervals between polyethylene glycol administration and tissue biopsy[15,16,17].
Secondly, it is postulated that bowel preparation leaves the mucosa depleted of essential nutrition in the form of short fatty acids, in particular butyrate and proprionate. These short chain acids are normally present in the faeces that is washed out with bowel preparation. Butyrate has a number of characteristics and functions that are not fully understood. It is seen as a main nutrient of the colonic mucosa without which damage to the tissue occurs.
Diversion colitis has been treated successfully with short chain fatty acids and there are animal reports suggesting a higher anastomosis strength with the addition of butyrate[29-33].

Strict inclusion criteria were applied to reduce the risk of confounding factors to a minimum in this study. Confounders such as the effect of radiotherapy, chemotherapy, idiopathic inflammation and immune suppression were ruled out. Only surgery for colon malignancy was included, thus excluding two patients in whom the diagnosis changed during or after surgery. By selecting only non-obstructive tumors and taking a sample at a distance of 5 cm distally from the tumor possible interference of tumor related mucosal damage by venous congestion and ischaemia was ruled out. The level of colectomy did not alter the level of mucosal damage in our series.
In the present study, using five microscopic damage criteria previously used in animal and human studies to measure bowel tissue damage, we found no significant damage to the colonic tissue due to the use of polyethylene glycol. Although in a univariate analysis for separate criteria we found a tendency towards increased damage in the lamina propria, this may well be an incidental finding. Possibly the relative small number of patients explains having found a mere tendency instead of statistically significant differences. Further research with greater numbers and possibly alternative damage criteria is warranted to verify the tendency of a detrimental effect of polyethylene glycol on human tissue. In the discussion about the additional effect of preoperative bowel preparation in prevention of clinical complications such as wound infection and leakage of the bowel anastomosis, these possible negative histopathologic changes should be taken into account as valid arguments.

Bowel preparation is common practice in elective open colon surgery, little is known about the detrimental effects of this practice on human colonic tissue. We examined the microscopic effects on the human intestinal wall of polyethylene

glycol, a commonly used osmotic laxative for mechanical bowel preparation, in a surgery setting.

In our series there could be found no statistically significant differences between patients receiving preoperative mechanical bowel preparation with polyethylene glycol or not. There was a statistically non-significant tendency towards increased damage of the lamina propria of the colonic wall in patients receiving preoperative polyethylene glycol.

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- Chapter V.II

The effect of polyethylene glycol and butyrate on anastomotic healing in the rat colon
An experimental study

A condensed form of this chapter has been submitted for publication as an original article

Abstract

Background: Negative histopathologic effects on colonic tissue have been observed after polyethylene glycol (PEG) administration. In this study the effects of PEG, with or without single dose butyrate, on colon anastomotic healing were studied.
Methods: In a group of 20 Spraque-Dawley rats, 10 with and 10 without bowel preparation, the bursting pressure of an intact colon segment was measured.
In a separate group of 50 rats a colectomy with primary anastomosis was performed. Of this group 20 rats received PEG 24 hours before operation (PEG group), 20 rats had PEG bowel preparation and a single dose of 3.0mM (1,5mM intraluminally, 1,5mM intraperitoneally) butyrate at operation (BUT group), 10 rats served as controls. Histopathologic damage was scored 24 hours after administration of PEG. The anastomotic bursting pressure was measured on the fifth postoperative day.
Results: In rats without a colectomy, the mean bursting pressure was 159.2 mmHg (18.9 SD) after PEG and 116.7 mmHg (27.5 SD) in controls ($p = 0.001$).
In the rats with a colectomy the mean anastomotic bursting pressure was 90.4 mmHg (45.9 SD) in the PEG group, 108.0 (31.9 SD) in the BUT group, and 102.7 (44.7 SD) in controls ($p = 0.44$). No significant differences in histopathologic scores were observed between the rats treated with PEG and the control group.
Conclusion: Bowel preparation with PEG does not significantly interfere with colon anastomotic healing in rats. No benefit of a single dose of butyrate after PEG pre-treatment was observed.

Introduction

Leakage of the anastomosis and wound infection are complications in colorectal surgery leading to considerable morbidity. In the prevention of these complications mechanical bowel preparation and antibiotic prophylaxis are part of most surgical practices[1-5].
The additional value of bowel preparation in elective colorectal surgery has been disputed in several studies [6-16]. Moreover, studies indicate that polyethylene glycol (PEG) and other agents used for bowel preparation might well have negative effects on the histopathologic constituency of colonic tissue [17 - 20]. Little is known about the effect of PEG on the mechanical properties of the colon and on anastomotic healing. In this experimental study we wanted to explore whether bowel preparation with PEG would negatively affect the colonic wall and anastomotic healing. While there seems to be a detrimental effect of osmotic agents used for bowel preparation on colonic tissue, a beneficial effect of butyrate has been reported [21-28]. This short chain fatty acid is produced through bacterial fermentation in the large bowel and is reported to have a hypertrophic and healing promoting effect on colonic tissue in animal and human studies. Previous studies have shown a beneficial effect of continuous irrigation with this agent on the healing of colon anastomoses in rats [21- 23]. In our study, we analysed the effect of a single dose of intra-operatively administered butyrate on colonic anastomotic healing as this would be the most feasible way of administration in human colon surgery.

Methods

The study was approved by the local hospital ethics committee. Seventy immunocompetent, female Spraque-Dawley rats, 12-16 weeks of age, weighing 250-300 grams were used.
To examine the acute effect of PEG on intact colonic tissue, a group of 20 rats was divided into 10 rats receiving PEG 24 hours before operation and a control group receiving no bowel preparation. After being sacrificed a laparotomy was performed. The decending colon was freed of the mesocolon 5cm above the pubis, ligated and pressure measurements were performed using a 16-gauge pressure catheter which was inserted transanally. The anus was sealed with a purse string using polyglactin 2.0. Sodium chloride 0.9% was then infused intraluminally at a constant rate of 2 ml/minute until bursting of the bowel. Pressures were measured using a disposable pressure transducer and the Menuet urodynamic pressure instruments (Menuet petite, Medtronic Inc. division Belgium).
In these rats no histopathogical examinations were performed.
To evaluate the delayed effect of PEG on the strength of anastomotic healing in 50 rats a segmental colectomy was performed. In this group 20 of the rats received preoperative bowel preparation with PEG orally during 24 hours prior to surgery (**PEG group**). Another 20 rats received preoperative PEG and in addition, a single dose of 3.0mM butyrate (10 ml of a 300 mM/L sodium butyrate solution) was administered intraluminally (1.5 mM) and intraperitoneally (1.5 mM) after the colectomy was performed (**BUT group**).
The remaining 10 rats received no bowel preparation and were starved for food 24 hours before surgery while offered water ad libitum, serving as a control group. In this control group the proximal fecal pellets were cautiously removed manually after the colectomy and before performing the anastomosis. All rats underwent a laparotomy under general anaesthesia with ether. A colectomy of a 0.5 cm segment was done at the level of the descending colon at a uniform height of 2½ cm above the pubis. The anastomosis was single layered and performed with non-resorbable polypropylene 5.0 separate stitches.
To evaluate histological changes the resected bowel segments were examined microscopically and scored for 1) mucosal damage, 2) lamina propria damage (edema, loosening), and 3) serosal inflammation. Each criterium was scored semi-quantitatively by a blinded pathologist as absent (0), moderate (1) or severe (2). These criteria have been used in previous studies to evaluate damage of the colonic wall[11, 13, 14].
The rats were starved for food postoperatively, with water offered ad libitum and were sacrificed on the fifth postoperative day. After relaparotomy, the decending colon was dissected free of its mesocolon starting 5 cm above the pubis where the colon was ligated, down to the peritoneal reflection. Pressure measurements were then performed as described above. The parameters used to measure anastomotic strength were bursting pressure of the anastomosis, and pressure rise, depicted by the slope of intraluminal pressure over time until anastomotic bursting.

Statistical Analysis

Data on quantitative variables are presented as mean (standard deviation) or median (range) as indicated. Differences between treatment groups were evaluated with one-way ANOVA and independent samples t-test, after testing for normality. Differences in histologic damage criteria were evaluated using Pearson's chi-squared test for trend.

Results

Bursting pressures
In the group of 20 rats used to study the acute effect of PEG (no anastomosis performed) there were no exclusions. In the group of 50 rats used to study the delayed effect of PEG
(anastomosis performed) seven rats were excluded. One rat allocated to the PEG group died at induction and there were a total of six spontaneous bursts (no intraluminal pressure build-up because of immediate leakage at the anastomosis); two in each of the subgroups. Thus, the results of 43 rats were included for statistical analysis (8 controls, 17 **PEG group**, 18 **BUT group**). In the group of 20 rats without an anastomosis the bursting pressure and the pressure rise were significantly higher in the rats receiving PEG (**Table 1**). In the 50 rats in which an anastomosis was performed, no significant difference was observed between the bursting pressure or pressure rise between the three subgroups
(**Table 2**).

Microscopy
At 24 hours after PEG administration no significant difference in transmural damage between the control group and the rats receiving PEG could be found in univariate analysis of the different criteria studied (**Table 3**).

	PEG (N=10) MEAN (SD)	**CONTROL** (N=10) MEAN (SD)	P VALUE
Bursting pressure (mmHg)	159.2 (18.9)	116.7 (27.5)	0.001
Pressure rise (mmHg/s)	1.56 (0.36)	0.98 (0.39)	0.003

Table 1 Bursting pressure and pressure rise in an intact colon segment within 24 hours after polyethylene glycol (PEG) administration and in a control group.

	CONTROL (N=8) MEAN (SD)	**PEG** GROUP (N=17) MEAN (SD)	**BUT** GROUP (N=18) MEAN (SD)	P VALUE
Bursting pressure (mmHg)	102.7 (44.7)	90.4 (45.9)	108.0 (31.9)	0.44
Pressure rise (mmHg/s)	1.28 (0.56)	1.23 (0.71)	1.81 (1.02)	0.11

Table 2 Anastomotic bursting pressure and pressure rise in the control group, the group receiving preoperative polyethylene glycol (PEG) and the group receiving preoperative PEG and intra-operative butyrate (BUT).

Group	**Control**			**PEG**			**P VALUE**
Semi-quantitative scoring	**0**	**1**	**2**	**0**	**1**	**2**	
Mucosa	8	0	0	31	4	0	0.74
Lamina propria	8	0	0	26	7	2	0.27
Serosal inflammation	8	0	0	33	1	1	0.79

Table 3 *Comparison of histopathologic findings at surgery 24 hours after PEG administration between the group receiving preoperative polyethylene glycol (PEG; n=35) and the control group(n=8). Numbers indicate the number of specimens presenting the features of the different criteria scored in a semi-quantitative way as absent(0), moderate(1), or severe(2).*

Discussion

To prevent anastomotic leaks mechanical bowel preparation became part of common surgical practice. Bowel preparation using PEG or other agents has been reported to have negative histopathologic effects on colonic tissue[17-20]. This detrimental effect of PEG was observed in the human colonic mucosa in a colonoscopy setting with biopsies taken within a few hours after bowel preparation [17 18]. Histopathologic damage was also observed in rat colonic tissue 4-8 hours after PEG administration[19, 20]. Finally, the value of mechanical bowel preparation in elective colorectal surgery as assessed in different randomized clinical trials remains controversial [6–16]. In the present study, we evaluated the effect of PEG on histology and on the mechanical properties of the rat colon before and after an anastomosis was performed .

In our study the acute effect of treatment with PEG induced positive changes of the mechanical properties of the intact colon, with a mechanically significant 'stiffer and stronger' rat colon 24 hours after PEG administration as compared with untreated control animals. At the first laparotomy, the colon of rats treated with PEG macroscopically appeared to be more swollen and hypervascularized. However, this observation was not supported by microscopic examination, although there was a trend towards more submucosal swelling.

When examining the delayed effect of PEG, our findings indicate that bowel preparation with PEG had no detrimental effect on anastomotic healing in rats. Bursting pressure and pressure rise were not significantly different between treated and untreated groups.

The percentage of spontaneous bursts that we observed at the second laparotomy, 5 days after construction of a colonic anastomosis, was low for all groups in comparison with other studies[21 22]. Considering spontaneous bursts as failed anastomotic healing (covered leaks) would not change this conclusion, since they occurred in 20% of untreated animals and in 10% after bowel preparation. Thus, in the present study we could not document any detrimental effect of preoperative bowel preparation with PEG on colon anastomotic healing in rats. Shortage of short chain fatty acids may be a factor contributing to suboptimal healing of a colonic anastomosis. We imposed a five-day postoperative starvation period, potentially depriving the colon of butyrate through feeding. Such a period is common in human colonic surgery due to postoperative ileus. Rolandelli and others reported a positive effect of butyrate on the healing of colonic anastomoses in rats, although not in addition to preoperative bowel preparation with PEG [21-23]. In our study we analysed the effect of a single dose administration of butyrate intraluminally and intraperitoneally on anastomotic healing. In contrast to a continuous intraluminal or intravenous infusion in rats as reported in the above mentioned studies a single administration would be the most feasible and preferred way of butyrate administration in human colon surgery. Intraluminal administration of butyrate has been examined in previous studies [21 28], to our knowledge this is the first study examining the effect of intraperitoneal administration of butyrate.

Our results showed no significant benefit of a single dose of butyrate on colonic anastomotic healing in rats after PEG pre-treatment.

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-Chapter VI

The effects of mechanical bowel preparation with polyethylene glycol on patient well-being

A questionnaire study of patients undergoing elective open colon surgery

A condensed form of this chapter has been published

Meta analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation.

Br J Surg 2005;91:1125-30

Abstract

Background: Recent literature indicates that mechanical bowel preparation in elective colorectal surgery offers little additional effect in the prevention of anastomotic leakage and wound infection. In order to quantify patient satisfaction, nursing staff workload and total cost of the procedure of mechanical bowel preparation a multi-center, consecutive, questionnaire study was conducted
Methods: Fifty-eight adult patients were asked to fill-out a questionnaire after receiving mechanical bowel preparation prior to elective open colon surgery concerning their satisfaction with the procedure, time spent (with the procedure) and discomfort due to the procedure. Additionally the nursing staff was asked to fill-out a questionnaire concerning the amount of time spent on the patient receiving mechanical bowel preparation and the result of the bowel preparation.
Results: Only 12% of the patients indicated mechanical bowel preparation with polyethylene glycol as not imposing. Patients spent over 6 hours with the procedure while the bowel residue remained fecal in 34%. The nursing staff, on the other hand, spent a mean of 2 hours surveying a patient receiving mechanical bowel preparation.
Conclusion: Mechanical bowel preparation with polyethylene glycol is poorly tolerated by patients and is a time-consuming and ineffective procedure for both the patient and nursing staff.

Introduction

In many surgical centers preoperative bowel preparation is used in elective colorectal surgery. In the past decade there has been much discussion over the clinical benefits and possible negative effects of this procedure[1-5].
From the patient's point of view, preoperative bowel preparation is still believed to be a burden. Nowadays rigid regimes as whole gut irrigation have been abandoned and replaced by less discomforting methods like osmotic laxatives such as sodium phosphate and polyethylene glycol. Still, preoperative bowel preparation is ill-received by older patients in whom it can cause electrolyte and fluid disturbances[6,7,8]. However, although patient discomfort has been described in the form of abdominal pain and vomiting little is known about the patient's subjective appreciation of this procedure in a surgical setting[9,10].
With the known side effects of preoperative bowel preparation, the nursing staff is burdened with surveying the patient who is undergoing preoperative bowel preparation.
In order to quantify how the patient experiences preoperative bowel preparation we conducted a multi-center questionnaire study. In addition we conducted a questionnaire for the nursing staff to quantify the working load involved with preoperative bowel preparation.

Patients and Methods

Fifty-eight patients who received preoperative bowel preparation before undergoing elective open colon surgery were asked to fill out a questionnaire on the effects of the procedure of mechanical bowel preparation. Patients were included in four different surgical centers. The questionnaire contained four sections. The first section was a subjective evaluation of the procedure. Patients could evaluate as A: *not imposing*, B: *somewhat imposing*, *but an acceptible part of the whole hospitalization,* C: *very imposing*, D: *unbearable.*
The second section was to document discomfort. Patients could answer *yes* or *no* to the occurrence of nausea, vomiting and abdominal pain.
The third part was for the evaluation of the general state of the patient after the procedure.
Patients could answer A: *same as before*, B: *worse then before* or C: *better then before.* (**Table 1**)
The final section of the patient questionnaire was a quantification of the total time in hours spent on the procedure of mechanical bowel preparation.
Additionally the nursing staff was asked to fill out an additional segment for each patient.
In this segment the total time spent on the procedure by the nursing staff was documented. Also the total amount of polyethylene glycol solution administered and the quality of the rectal fluid (clear or fecal) at the end of the procedure was documented (**Table 2**).

Results

A total of 58 patient and nursing staff questionnaires were completely filled out. The median age of the patients was 67 years and the male/female ratio was 1:1.7. Indication for operation was either a colectomy for recurrent diverticular disease or colon malignancy in all patients. None of the patients was severely debilitated at the time of the mechanical bowel preparation.
In the evaluation of mechanical bowel preparation as a preoperative procedure 7 of the 58 (12%) patients found it not to be imposing, 34 found it somewhat imposing, 15 found it very imposing and 2 patients found the procedure unbearable. In the documentation of vagal reactions 24 of the 58 patients (41%) had either abdominal pain, nausea or vomiting (12 abdominal pain, 17 nausea, 5 vomiting).
Twenty-two of the 58 patients (37%) felt worse after the procedure of mechanical bowel preparation, none of them felt better.
In total the patients spent a median of 6 hours undergoing the procedure.

The nursing staff spent a median of 2 hours per patient for the procedure of mechanical bowel preparation. In 24 patients, less then the prescribed 4 litres was administered either because rectal fluid was clear or because the procedure was stopped due to patient distress, which was the case in 10 patients (17%). In 20 of the 58 patients (34%) the residual fluid at the end of mechanical bowel preparation was still fecal. (**Fig.1**).

What do you think of the procedure of bowel preparation?	A: Not imposing B: Somewhat imposing C: Very imposing D: Unbearable		
During the procedure of bowel preparation did you experience			
	Nausea	YES	NO
	Vomiting	YES	NO
	Abdominal pain	YES	NO
How do you feel after the procedure of bowel preparation?	A: Same as before B: Worse then before C: Better then before		
How long has the procedure of bowel preparation taken?	----------HOURS		

Table 1 *A sample of the patient questionnaire.*

How long did you spent on the procedure of bowel preparation (incl. preparation, administration, surveying the patient)?	
	1Hour/2 Hours/3Hours
How much of the 4 litres of polyethylene glycol did the patient drink?	
	----------Litres
What is the reason for drinking less then 4 litres of polyethylene glycol?	

Is the rectal fluid clear?	
	YES/ Still fecal fluid / Plain faeces
Has the patient been nauseous?	
	YES NO
Did the patient vomit?	
	YES NO
Has the patient experienced abdominal discomfort?	
	YES NO
Did the patient require medical attention due to the procedure of bowel preparation?	
	YES NO

Table 2 *A Sample of the questionnaire for the nursing staff.*

Patient Satisfaction	Not Imposing	Somewhat Imposing	Very Imposing	Unbearable
	7 patients	34 patients	15 patients	2 patients
Discomfort	Nausea	Vomiting	Abdominal pain	
	17 patients	5 patients	12 patients	
Time spent with procedure	Nursing staff	Patient		
Median (range)	2 hours (1-3)	6 hours (2-48)		

Fig 1. *Results of mechanical bowel preparation in 58 patients prior to elective open colon surgery.*

Discussion

Preoperative bowel preparation is still used in many surgical centers to reduce the risk of anastomotic leakage and postoperative wound infection in elective colorectal surgery. Although its benefits are currently under discussion this procedure continues to be used because it is thought to have little negative effects[2-5].Recent studies show that there are specific negative effects such as bacterial overload leading to an increased risk of infection and damage of the colonic tissue both by inflammation as by depletion of short chain fatty acids[11-15]. From a patient oriented view there is a common sense that patients dislike the taste of osmotic laxatives. They experience discomfort in the form of abdominal pain and vagal reactions [9,10].
There has been little validation of this common sense of patient discomfort in a surgical setting. Oliveira et al. compared sodium phosphate and polyethylene glycol in a large randomized trial in a surgical setting. Their results indicate significant patient discomfort such as abdominal pain, bloating and fatigue in both randomization groups with only 25 % of patients receiving polyethylene glycol willing to repeat the procedure[16]. In our study we aimed at quantifying patient dissatisfaction with preoperative mechanical bowel preparation by ways of a questionnaire for the patients undergoing this procedure. Additionally we issued a questionnaire for the nursing staff surveying the patients undergoing the preparation to quantify the amount of time and working load involved with preoperative bowel preparation.

The results of our study show that patients spent a considerable time (median of 6 hours) on the procedure of mechanical bowel preparation and have significant vagal reactions with 41% having some sort of discomfort. In 12% the discomfort even prompted the patient to abort the procedure. There were only 12 % of the patients who did not seem to mind the procedure.
To our knowledge no previous analysis of nursing staff workload for the procedure of mechanical bowel preparation has been made. The nursing staff spent a median of 2 hours per patient undergoing mechanical bowel preparation in our study. Finally, the cost of every bowel preparation is 20 Euro in addition to the extra day of preoperative hospital stay which is upheld in many surgical centers.

While the value of preoperative bowel preparation is clearly shown in diagnostic procedures such as colonoscopy[17,18], in elective colorectal surgery it seems not to have an additional value in protecting against anastomotic leak and postoperative wound infection[19,20]. In previous literature it has been postulated that the claim that mechanical bowel preparation totally clears bowel content does not hold true. In the present study the administration of preoperative polyethylene glycol was no guarantee for a clean peroperative bowel as in 34% of the patient the residual rectal fluid after the procedure was not clear but still fecal.

In this era of evidence based medicine and economic crisis in health care the flaws and merits of a procedure, embracing significant healthcare cost and workload for the nursing staff should be well documented. In the present study, we found the patient to be dissatisfied with the procedure of preoperative bowel preparation. Mechanical bowel preparation induced a significant amount of patient discomfort and was no guarantee for a clean preoperative bowel.

Our study shows that preoperative bowel preparation in elective open colon surgery is ill accepted by patients and does not guarantee a clean preoperative bowel. Furthermore it is an extra burden of for the nursing staff. Since the advantages of this procedure are doubtful and currently under debate, the question is raised if there still is a place for this regimen in patients undergoing elective open colon surgery.

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-Chapter VII

Conclusion

Conclusion

MBP or not in elective open colon surgery?

The results of the clinical trials conducted in this study reveal no additional value of mechanical bowel preparation in elective open colon surgery. In the randomized trial presented in Chapter 3 we opted for a homogenous surgical group of intraperitoneal anastomoses, as mentioned before, a drawback of this approach being a smaller inclusion number. This paradox has previously been depicted and was again brought to attention by Zmora et al. in the presentation of their randomized study on the value of mechanical bowel preparation in 2003. They presented a power-analysis which showed a total of 1540 patients to be needed to detect a difference of 5% in infection rate (with a 10% infectious complication rate assumption, alpha level 0.05, power 90%).[1] The question remains if a definitive conclusion may be drawn from our data, with a certain underpower persisting in our randomized trial.
Nevertheless, the results of our trial presented in Chapter 3 are the results of a clinically relevant homogenous surgical group and as such present powerful data against the background of a decade of important controlled and uncontrolled trials referenced and tabulated in Chapter 1. None of these trials has ever produced data suggesting an additional value of preoperative mechanical bowel preparation in elective open colon surgery[2-14]. Therefore the results of our randomized trial may lead to definitive conclusions in our view. In addition, our study adds relevant data; a homogenous group is examined separately for the first time and bacteriological results are used for the first time to evaluate the effect of mechanical bowel preparation. Also, experimental studies are conducted on the detrimental effect of polyethylene glycol (a commonly used agent for mechanical bowel preparation) and short chain fatty acids (washed away with mechanical bowel preparation) on colonic tissue.

In discussing the problem of underpower it is clear that the benefit of a homogeneous surgical cohort is the prevention of structural bias. The results of the study presented in Chapter 3 therefore are clear for the group of patients with an intraperitoneal anastomosis. The subsequent question is what conclusions can be drawn for the group of colectomies with an extraperitoneal anastomosis (anterior resections, low anterior resections). Is automatic extrapolation of the results for the intraperitoneal applicable for the extraperitoneal anastomosis?

The extraperitoneal anastomosis

Previous studies on anastomosis dynamics clearly show different results in overall anastomotic leak rate for the extraperitoneal anastomoses. The higher rate of anastomotic leak for these extraperitoneal anastomoses is attributed to a variety of factors including anastomotic vascularization, anastomotic tension and technical surgical difficulty [15-22].
Another factor in the opinion of the author is the actual absence of serosa (being the visceral peritoneum) beyond the peritoneal lining [23,24]. This absence of serosa reduces the amount of sturdy material in the (distal) suturing plane, possibly leading to a higher chance of tissue tear and leakage. Secondly, once (microscopic) leakage occurs extraperitoneally, it will be encased directly by loose, fatty tissue in the perirectal plane in contrast to a smooth, delineated and sturdy peritoneal sac. Hypothetically this loose, fatty tissue can be a better environment for massive infection (and consequent anastomotic necrosis and leakage) than peritoneal tissue; the peritoneal sac thus functioning as a protective buffer against anastomotic infection, -necrosis and -leak.

Having established that the extraperitoneal anastomosis has a higher leakage rate (and is therefore a totally different type of anastomosis to be examined) the question remains what the impact of mechanical bowel preparation is in the prevention of anastomotic leak in these anastomoses. Although the extraperitoneal anastomoses were not examined in the study in Chapter 3
they were included in the consecutive series presented in Chapter 2 alongside the intraperitoneal anastomoses.
Also in 7 of the 8 randomized trials (7 published, 1 presented orally to date) on the value of mechanical bowel preparation in open colon surgery, the extraperitoneal anastomoses were compared along with the intraperitoneal anastomoses [1,2,5,6,7,8,11,12] . All these trials concluded that there is no additional value of mechanical bowel preparation in open colon surgery. Three meta analyses of the most prominent randomized trials on the value of mechanical bowel preparation also conclude the same [9,13,14].

The problem of course remains heterogeneity of all the trials including extraperitoneal anastomoses. When comparing the subgroup of extraperitoneal anastomoses separately within the trials, the numbers are just too low for statistically significant results. In definitely answering the question for the extraperitoneal anastomoses a randomized trial as presented in Chapter 3 with a homogenous group of extraperitoneal anastomoses or a meta-analysis of the extraperitoneal subgroup of all randomized trials run to date would possibly yield more information.

Detailed effects of polyethylene glycol in colon surgery

In this study different aspects of polyethylene glycol (PEG), the most used agent for mechanical bowel preparation in the Netherlands, were examined. Aspects such as the detrimental effect of PEG on human colonic tissue and anastomotic strength, effect on bacteriological load due to PEG and patient satisfaction with PEG have been examined.

In Chapter 4.2 the results indicate that treatment of the bowel with PEG preoperatively does not significantly reduce bacterial load. This finding supports the lack of effect of PEG in reducing clinical complications such as anastomotic leak and wound infection in elective open colon surgery.

The study in Chapter 4.1 also showed the peroperative subcutaneous swab to be a good (and cheap) negative predictor of a postoperative wound infection. This may be an important finding in trying to isolate the risk group of patients in need of (longer) antibiotic prophylaxis, thus significantly cutting medical costs through patient selection by possible reduction of prophylaxis for patients with a negative preoperative swab. Of course direct-result bacteriologic tests and further study would be needed for this.

Although this study showed no beneficial effects of mechanical bowel preparation in elective open colon surgery, the experimental work presented in Chapter 5.1 and 5.2 was inconclusive on the detrimental effects of PEG on human colonic tissue and anastomosis strength in rats. Further study is warranted to clarify these effects.

The healing and trophic effect of butyrate (which is a short chain fatty acid in stool, washed away by mechanical bowel preparation) on colonic tissue has been established through previous experimental studies [25-32]
Converting experimental steps to clinically useful data warrants study, in which negative results are just as important. Previous studies have shown beneficial effects of continuous irrigation with butyrate in animal studies. In our experimental animal study presented in Chapter 5.2 we examined the effect of a single dose of 3.0 mM butyrate as this is a feasible gift modus in human surgery. Our results showed no significant healing effect on anastomotic healing.
Finally, as presented in Chapter 6, patient discomfort with the use of PEG was significant in our study mirroring previous presented results on this subject [33].

No more MBP, definitive and always?

The results of this thesis are clear, there is no beneficial effect of preoperative mechanical bowel preparation in elective open colon surgery, and it should therefore be omitted. There are, however cases and developments that may dictate otherwise.

The obstructed colon

As the result of the experience during the clinical trials conducted in this study, in our opinion the sole reason for decompressing a loaded bowel in elective open colon surgery should be a massively loaded bowel with signs of obstruction, when there is not opted for palliative stenting but for operation. In these cases preoperative mechanical bowel preparation is a contra-indication in order to prevent blow out, therefore on table lavage or a Hartmann procedure should be considered [34,35,36]. The reason for decompression, or choice not to perform an anastomosis in these cases is, in our opinion, mandatory and purely for mechanical reasons, the outward force of massive obstructed faecal material against the anastomosis of distended, ischaemic bowel defies any scientific reasoning. There exists no evidence in literature to support performing a primary anastomosis without faecal unloading in such cases.
A surgeon should always use common sense in his informed,-evidence based-, and -experience based-, substantiated, decision making. These massive obstructed bowels when encountered in our clinical studies presented in Chapter 2 and 3 were excluded from the studies.

Laparoscopic surgery

As colorectal surgery is rapidly moving towards new approaches such as laparoscopic surgery and robotics, with laparoscopic colectomy rapidly becoming the gold standard [35-50], the question on the value of mechanical bowel preparation is renewed. This thesis aims at elective open colon surgery, so no conclusions are to be drawn for laparoscopic colon surgery. However, in our anectodal experience in operating loaded bowel laparoscopically, mechanical problems may be encountered in the endoscopic maneuvering of the bowel. Also, when constructing an intracorporal anastomosis, placement of the anvil for the circular stapler is complicated and potentially unsafe when omitting preoperative mechanical bowel preparation. Future trials will have to evaluate the value of mechanical bowel preparation in laparoscopic colon surgery.
In conclusion, the use of mechanical bowel preparation in elective open colon surgery has to be considered as obsolete in this era of evidence-based medicine. Further study with greater numbers will not add to this conclusion as the past decade has produced a number of controlled and uncontrolled studies with heterogenic as well as homogenic cohorts all leading to the same conclusion. A number of meta-analyses have sustained the same conclusion, even favoring unprepared bowel. Certain cases, such as obstructing tumors will always need unloading of the bowel before performing an anastomosis based on sound

reasoning. Further studies will have to determine the place of mechanical bowel preparation in a future world of laparoscopic colon surgery.

Conclusions of this thesis

- Mechanical bowel preparation in elective open colon surgery does not reduce the rate of anastomotic leak or wound infection nor does it reduce peritoneal bacterial contamination. It is however poorly tolerated by patients and the total workload for the nursing staff and health care costs are considerable. Therefore, it is superfluous in elective open colon surgery and should be abandoned.

-The intraoperative subcutaneous bacterial swab is a powerful negative predictor of a postoperative wound infection in elective open colon surgery.

- Mechanical bowel preparation with polyethylene glycol causes no significant additional histopathologic damage of colonic tissue, in comparison with patients receiving a normal meal the night before open colon surgery.

- Mechanical bowel preparation with polyethylene glycol does not significantly interfere with colon anastomotic healing in rats.

-There is no significant benefit of a single dose of intraluminal 3.0 mM n-butyrate on colon anastomotic healing in rats after polyethylene glycol bowel preparation.

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Summary

Preoperative bowel preparation or mechanical bowel preparation is a long standing practice in elective open colon surgery dating from the 1970's.
It has always been believed to reduce the rate of postoperative complications in the form of anastomotic leakage and wound infection.

In this thesis we broadly and thoroughly examine the various aspects and the value of mechanical bowel preparation in elective open colon surgery.

In the first chapter which is an introduction to the rest of the thesis a review of the history of agents used in the practice of mechanical bowel preparation as well as the most used current agents is given. In this chapter we also depict the current practice of mechanical bowel preparation in the Netherlands and other fields of surgery. The discussion on the value of preoperative bowel preparation as a profylactic against anastomotic leakage and wound infection in elective open colon surgery is introduced. Furthermore, in this chapter a review of the different cardinal septic aspects with regard to our clinical studies (as given by the guideline for prevention of surgical site infection of the National Center for Infectious Diseases of the U.S. Department of Health) is given. This chapter also deals with detrimental non-septical effects of mechanical bowel preparation on colonic tissue. The important fueling and healing functions of fecal constituents such as short chain fatty acids which are washed away during mechanical bowel preparation are discussed.

In the second chapter the results of a prospective trial of 250 patients undergoing elective colorectal surgery without mechanical bowel preparation are presented. The anastomotic leakage rate of this cohort is 1.2% and the wound infection rate is 2.8 %, which are excellent results in comparison with the 5% anastomotic leakage rate and 15% wound infection rate known for elective colorectal surgery with preceding bowel preparation. Although it is conducted in a single surgeon, single center setting this trial proves that elective colorectal surgery without mechanical bowel preparation is very feasible.

Chapter III presents the results of a multi-center, prospective, randomized trial conducted in the Netherlands. A total of 250 patients undergoing elective open colon surgery are randomized to receive 4 liters of polyethylene glycol as mechanical bowel preparation or no means of bowel preparation with a normal meal the night before surgery.
The results show no additional protective effect of mechanical bowel preparation in elective open colon surgery.

In chapter IV.I the value of the peroperative bacterial swab as a predictor of surgical wound infection is studied by ways of a prospective study of 100 patients undergoing elective open colon surgery. In this study, a peroperative bacterial swab of the subcutis after closing the abdominal fascia has a negative predictive value of 1.0 and a positive predictive value of 0.25. This study shows that a

peroperative bacterial swab of the subcutis could possibly identify the subgroup of patients least prone to a postoperative surgical wound infection.

Chapter IV.II presents the results of a multi-center, prospective study of 185 randomized patients undergoing elective open colon surgery. In these patients the correlation between microorganisms surrounding the anastomosis and microorganisms in the subcutis is studied for patients receiving mechanical bowel preparation and patients receiving no preoperative bowel cleaning. The results show that mechanical bowel preparation does not reduce peritoneal contamination in elective open colon surgery.

In chapter V.I a microscopic study of human bowel treated with polyethylene glycol in an elective open colon surgery setting is presented. The results of this study show that mechanical bowel preparation with polyethylene glycol has a statistically non-significant tendency towards increased damage in the lamina propria, however, mechanical bowel preparation with polyethylene glycol caused no significant additional tissue damage in comparison with patients receiving a normal meal the night before surgery.

Chapter V.II presents an experimental study in a total of 70 rats in which the characteristics of the bowel tissue are examined after treatment with preoperative polyethylene glycol before receiving a uniform colectomy and single layer anastomosis. In addition the effect of adding a single dose of 3.0 mM intraluminal n-butyrate is measured. The outcome parameters are anatomopathologic results and pressure measurements. The results indicate that bowel preparation with polyethylene glycol does not significantly interfere with colon anastomotic healing in rats. No benefit of a single dose of 3.0 mM n-butyrate after polyethylene glycol pre-treatment was observed.

Chapter VI deals with the issue of mechanical bowel preparation in elective open colon surgery from a patient oriented point of view. In a study of 58 consecutive patients receiving 4 liters preoperative polyethylene glycol, patient satisfaction, workload of the nursing staff and macro-economical concerns are discussed.
In the Netherlands patient satisfaction with preoperative bowel preparation with the most common agent is poor, total workload of the nursing staff and total cost in healthcare are considerable.

In Chapter VII a discussion of the results of this thesis is presented

Conclusions of this thesis

- Mechanical bowel preparation in elective open colon surgery does not reduce the rate of anastomotic leak or wound infection nor does it reduce peritoneal bacterial contamination. It is however poorly tolerated by patients and the total workload for the nursing staff and health care costs are considerable. Therefore, it is superfluous in elective open colon surgery and should be abandoned.

-The intraoperative subcutaneous bacterial swab is a powerful negative predictor of a postoperative wound infection in elective open colon surgery.

- Mechanical bowel preparation with polyethylene glycol causes no significant additional histopathologic damage of colonic tissue, in comparison with patients receiving a normal meal the night before open colon surgery.

- Mechanical bowel preparation with polyethylene glycol does not significantly interfere with colon anastomotic healing in rats.

-There is no significant benefit of a single dose of intraluminal 3.0 mM n-butyrate on colon anastomotic healing in rats after polyethylene glycol bowel preparation.

Samenvatting

Preoperatieve darmvoorbereiding of mechanische darmvoorbereiding is een al langer bestaande handeling in de electieve open colon chirurgie, daterend uit de jaren zeventig. Er werd altijd verondersteld dat deze handeling het risico op postoperatieve complicaties zoals naadlekkages en wondinfecties zou verlagen

In dit proefschrift onderzoeken en belichten wij uitgebreid de verschillende aspecten van de darmvoorbereiding met polyethylene glycol. Uiteindelijk bepalen wij hierbij de waarde van preoperatieve darmvoorbereiding in de electieve open colon chirurgie.

In het eerste hoofdstuk, wat een introductie is op de rest van de thesis, wordt er een historisch overzicht gegeven van de gebruikte middelen voor darmvoorbereiding, alsook de meest gebruikte middelen heden ten dage. Tevens wordt de huidige situatie met betrekking tot de gebruikte middelen in Nederland beschreven, alsmede het gebruik van preoperatieve darmvoorbereiding op ander chirurgisch gebied. De discussie omtrent de waarde van preoperatieve darmvoorbereiding in de preventie van naadlekkages en wondinfecties in de electieve open colon chirurgie wordt in dit hoofdstuk geintroduceerd. Dit hoofdstuk geeft een overzicht van de verschillende, belangrijke, septische aspecten met betrekking tot de klinische studies van deze thesis (zoals die zijn bepaald in the guideline for prevention of surgical site infection of the National Center for Infectious Diseases van de U.S. Department of Health). Dit hoofdstuk behandelt tenslotte ook de negatieve non-septische effecten van preoperatieve darmvoorbereiding op colon weefsel. De belangrijke voedende- en helende functies van faecale stoffen zoals de korte keten vetzuren (die worden weggespoeld bij de preoperatieve darmvoorbereiding) voor het colon weefsel worden besproken.

In het tweede hoofdstuk worden de resultaten gepresenteerd van een prospectieve studie van 250 patienten die electieve colorectale chirurgie zonder preoperatieve darmvoorbereiding hebben ondergaan. Het naadlekkage percentage is 1.2% en het wondinfectie percentage is 2.8%. Dit zijn uitstekende resultaten vergeleken met de gekende cijfers van 5% naadlekkage en 15% wondinfectie bij electieve open colon chirurgie met preoperatieve darmvoorbereiding. Alhoewel de resultaten afkomstig zijn van een enkele chirurg in een enkel ziekenhuis bewijst deze studie dat electieve open colon chirurgie zonder preoperatieve darmvoorbereiding heel goed mogelijk is.

Hoofdstuk III handelt over de resultaten van een multi centrische, prospectieve, gerandomiseerde Nederlandse studie. In totaal werden er 250 patienten gerandomiseerd die allen electieve open colon chirurgie ondergingen. De ene groep patienten kreeg 4 liter preoperatief oraal polyethyleen glycol en de andere groep patienten kreeg geen enkele vorm van darmvoorbereiding met een normale maaltijd de nacht voor de ingreep.

De resultaten van de studie tonen dat er geen additioneel preventief effect is te verwachten van preoperatieve darmvoorbereiding in de electieve open colon chirurgie.

In hoofdstuk IV.I wordt de waarde van de peroperatieve bacteriele kweek als voorspeller van een chirurgische wondinfectie bepaald via een prospectieve studie van 100 patienten die electieve open colon chirurgie ondergaan. In deze studie heeft een peroperatieve bacteriele kweek van de subcutis na het sluiten van de abdominale fascia een negatieve predictieve waarde van 1.0 en een positief predictieve waarde van 0.25. De studie toont dat een intra operatieve bacteriele kweek van de subcutis mogelijks de subgroep van patienten kan identificeren die geringe kans maakt op een wondinfectie.

Hoofdstuk IV.II geeft de resultaten weer van een multi centrische, prospectieve studie van 185 gerandomiseerde patienten die electieve open colon chirurgie ondergaan. Bij patienten met of zonder darmvoorbereiding wordt de correlatie bekeken tussen de microorganismen die de anastomose omringen en de microorganismen in de subcutis. De resultaten tonen dat preoperatieve darmvoorbereiding de peritoneale contaminatie niet verminderd in de electieve open colon chirurgie.

In hoofdstuk V.I wordt een microscopische studie gepresenteerd. Bij patienten die electieve open colon chirurgie ondergaan wordt het colon weefsel microscopisch onderzocht op histologische schade tengevolge van darmvoorbereiding met polyethyleen glycol. De resultaten van deze studie tonen dat patienten die preoperatieve darmvoorbereiding kregen -behoudens een statistisch non-significante tendens tot toegenomen schade in de lamina propria- verder geen significante weefselschade hadden bij microscopisch onderzoek.

Hoofdstuk V.II presenteerd een experimentele studie van 70 ratten waarin de eigenschappen van darmweefsel dat is behandeld met preoperatief polyethyleen glycol wordt onderzocht. Aanvullend wordt het effect van het toevoegen van intralumineel n-butyraat onderzocht op het helen van de anastomose. De onderzochte parameters zijn anatomopathologische uitslagen en drukmetingen. De resultaten tonen dat preoperatieve darmvoorbereiding met polyethyleen glycol niet significant interfereert met het helen van de colon anastomose in ratten. Er was verder geen positief effect van een enkele dosis 3.0 mM intralumineel n-butyraat na polyethyleen glycol behandeling.

Hoofdstuk VI handelt over preoperatieve darmvoorbereiding in electieve open colon chirurgie vanuit de patient. Een studie van 58 patienten die preoperatief 4 liter polyethyleen glycol krijgen wordt beschreven waarbij patient tevredenheid, werkbelasting voor de verpleging en macro-economische aspecten worden bekeken.
In Nederland is de patient tevredenheid met het meest toegepaste middel voor preoperatieve darmvoorbereiding matig. De totale werkbelasting en kosten voor de gezondheidszorg zijn aanzienlijk.

Hoofdstuk VII is een discussie van de resultaten van dit proefschrift.

Conclusies van dit proefschrift

- Preoperatieve darmvoorbereiding bij electieve open colon chirurgie voorkomt geen naadlekkages of wondinfecties.
  Derhalve dient deze handeling in de electieve open colon chirurgie als overbodig beschouwd, en daarmee verlaten te worden.

- De intraoperatieve subcutane bacteriele kweek is een goede negatieve voorspeller van een postoperatieve wondinfectie in de electieve open colon chirurgie.

- Preoperatieve darmvoorbereiding met polyethyleen glycol veroorzaakt geen histopathologische schade aan het colonweefsel.

- Preoperatieve darmvoorbereiding met polyethyleen glycol interfereert niet met de genezing van de colon anastomose in ratten.

- Er is geen voordeel van een enkele dosis van 3.0 mM intralumineel n-butyraat bij de genezing van de colon anastomose in ratten na behandeling met polyethyleen glycol.

Resúmen

Labamentu di tripa preoperativo den sirugia colorektal ta un akto ku ta data for di añanan setenta. Semper a suponé ku e akto akí lo baha e rísiko di komplikashonnan di despues di oprashon, manera lèk di anastomosis i infekshon di herida.

Den e tésis akí nos a eksplorá i enfoká ekstensivamente riba e diferente aspektonan di labamentu di tripa preoperativo ku polyethylene glycol. Finalmente nos a fiha e balor di labamentu di tripa den surigia elektivo habrí di colon.

Den e promé kapítulo, ku ta un introdukshon di e tésis, ta duna un bista histórico di produktonan ku a yega di uza i tambe di esnan ku ta uza awendia pa labamentu di tripa. Ta deskribí tambe e situashon aktual na Hulanda relashoná ku produktonan uzá i huntu ku esaki ta deskribí labamentu di tripa riba otro tereno sirurgiko. Ta introdusí den kapítulo akí e diskushon tokante e balor di labamentu di tripa preoperativo pa prevenshon di lèkmentu di anastomosis i infekshon di herida den un operashon elektivo habrí di colon.
E kapítulo aki ta duna un bista di e diferente aspektonan séptiko importante relashoná ku estudionan klíniko di e tésis akí (manera ta stipulá den The guideline for prevention of surgical site infection of the National Center for Infectious Diseases van de U.S. Department of Health).
Finalmente e kapítulo akí ta trata e efektonan negativo no séptiko di labamentu di tripa riba e tehido di colon. Ta trata e funshonnan importante nutritivo i kurativo di substanshanan fekal manera e 'short chain fatty acids' ku ta wordu kita ora ku laba tripa promé ku operashon.

Den e di dos kapítulo ta presentá e resultadonan di un estudio prospektivo di 250 pashènt ku a hasi operashon colorektal elektivo sin labamentu di tripa promé ku operashon. E porsentahe di lèkmentu di anastomosis ta 1.2% i e porsentahe di infekshon di herida ta 2.8%. Esakinan ta resultadonan ekselente kompará ku sifranan konosí di 5% di lèk di anantomosis i di 15% di infekshon di herida na momentu di sirugia colorectal elektivo ku labamentu di tripa preoperativo. Maske e resultadonan ta bini di un solo siruhano di un solo hòspital e estudio akí ta prueba ku sirugia elektivo colorectal sin labamentu di tripa preoperativo ta bien posibel.

Kapítulo III ta trata resultado di un estudio hulandes prospektivo randomisa multi séntriko. 250 pashènt a wordu inklui pa hasi un operashon elektivo habrí di colon. Un grupo di pashènt a haña labamentu di tripa preoperativo ku 4 liter di polyethyleen glycol, e otro grupo di pashènt no a haña niun sorto di labamentu di tripa I a kome normal e anochi promé ku operashon.
E resultado di estudio ta mustra ku no por spera efekto preventivo adishonal di e labamentu di tripa promé ku operashon den sirugia elektivo habrí di colon.

Den kapítulo IV.I ta trata e determinashon di e balor di krio bakterial komo prognóstiko di un infekshon di herida via di un estudio prospektivo di 100 pashènt

ku a hasi sirugia elektivo habrí di colon. Den e estudio akí e kultivo bakterial intra-operativo di e subkutis despues di sera e fasia abdominal tin un balor prediktivo negativo di 1.0 i un balor prediktivo positive di 0.25.
E estudio ta proba ku un krio di bakteria intra-operativo di e subkutis por identifiká e supgrupo di pashènt ku tin tiki chèns di haña un infekshon di herida.

Kapítulo IV.II ta duna e resultadonan di un estudio prospektivo multi séntriko di 185 pashènt ku a hasi un operashon elektivo habrí di colon. Serka pashèntnan ku a risibi labamentu di tripa of no a opservá e korelashon entre e mikro-organismonan ku ta rondoná e anastomosis i e mikro-organismonan den subkutis. E resultadonan ta mustra ku labamentu di tripa promé ku operashon no ta baha e kontaminashon peritoneal den operashon elektivo habrí di colon.

Den kapítulo V.I ta presentá un estudio mikroskópiko. Serka pashèntnan ku a hasi un operashon elektivo habrí ta studia e tehido di colon mikroskópikamente riba daño histológiko kousá pa labamentu di tripa ku polyethyleen glycol. E resultadonan di e estudio akí ta mustra ku pashèntnan ku a laba tripa – aparte di un tendensha no-signifikante di daño den 'lamina propria' , mas aleu no ta tin mas daño signifikante di e tehido di colon den e saminashon mikroskópiko.

Kapítulo V.II ta presentá un estudio eksperimental di 70 djaka den kual ta eksaminá e karakterístikanan di e tehido di tripa ku ta tratá ku polyethylene glycol promé ku operashon. Tambe a eksaminá e efekto riba kura di anastomosis ora ta agregá n-butyrate intraluminal. E parametronan eksaminá ta resultadonan anatomopatológiko i midimentu di preshon.
E resultadonan ta mustra ku labamentu di tripa ku polyethylene glycol promé ku operashon no ta interferí signifikantemente den kura di anastomosis di colon serka djaka. Mas aleu no tabatin efekto positivo di un solo dosis di 3.0 mM n-butyrate intraluminal despues di tratamentu ku polyethylene glycol.

Kapítulo VI ta trata labamentu di tripa den sirugia elektivo habrí di colon salí for di bista di pashènt. A eksaminá e satisfashon di 58 pashènt ku a haña 4 liter di polyethylene glycol promé ku operashon, e peso di trabou den enfermeria i e aspektonan makro ekonómiko.
Na Hulanda e satisfashon, ku e produkto mas uzá den labamentu di tripa, ta poko. E peso di trabou i e kosto pa salubridat ta konsiderabel.

Kapítulo VII ta un diskushon riba resultadonan di e tesis akí.

Konklushonnan di e tesis aki

-Labamentu di tripa preoperativo den sirugia elektivo habrí di colon no ta prevení lèkmentu di anastomosis ni infekshon di herida sirúrgiko. Pa e motibunan akí mester mira e tratamentu akí komo di mas i mester bandona e tratamentu akí den sirugia elektivo habrí di colon.

-E kultivo bakterial preoperativo di subkutis ta un bon hèrmènt prognóstiko negativo den identifikashon di infekshon di herida despues di sirugia elektivo habrí di colon.

-Labamentu di tripa preoperativo ku polyethylene glycol no ta kousa daño na e tehido di colon riba nivel mikroskópiko.

-Labamentu di tripa preoperativo ku polyethylene glycol no ta interferí den kura di anastomosis di colon di djaka.

-No tin niun benefisio di un solo dosis di 3.0mM n-butyrate den kura di anastomosis di colon di djaka despues di tratamentu ku polyethylene glycol.

Dankwoord

Dit proefschrift is tot stand gekomen dankzij de hulp van velen.
Ik wil bij deze een ieder bedanken die mij door de jaren hebben gesteund.
Zonder deze mensen zou dit wetenschappelijk werk simpelweg nooit zijn voltooid.
Mijn dank aan de familie, die altijd klaarstond in Nederland en Curacao. Met name Clinton, zonder (en soms met) jou niets mogelijk man!
Henkie, Tante Rieke , Humph de rust gevonden bij jullie thuis en jullie hulp was onbetaalbaar, (de borden was ik wel als ik uit Italie kom! Headers and Footers!) Pa en Ma, zie je wel dat mijn ogen niet dicht vallen! (toch bedankt om altijd even te checken of ze wel open zijn)
Dank aan de naaste vrienden, Ronchi, Carlos, Arjen, Lyan, jullie constante steun en interesse (ook in de kleine uurtjes tussen de biertjes door) was voor mij een grote stimulans, helemaal omdat het voor jullie eigenlijk volstrekt onbekend en saai materiaal was (geef toe)!
Don't forget Felix, die de drukke jaren in Belgie altijd aangenaam hield.

Aan mijn begeleiders en collega's in Veldhoven en Leuven dank, met name Dr. Croiset van Uchelen en prof.dr. Broos die mij de kans hebben gegeven dit mooie en nobele vak te mogen uitoefenen en mij geleerd hebben wat het betekent om chirurg te zijn. Dank aan Dick van Geldere die voor mij nog altijd de man is die het concept van opereren 'in de poep' in Nederland vatbaar heeft gemaakt. Mijn dank tevens aan de afdeling abdominale heelkunde van de Katholieke Universiteit van Leuven voor het geloof in- de steun, en kritiek van de verschillende projecten, zonder dit zou de uitkomst zeker niet van dezelfde kwaliteit zijn. Prof. Aerts, Andre, Tom, Pieter, Frank Kroeze, Kathelijne en allen die hebben geincludeerd in de verschillende klinieken en zij die in de kleine uurtjes hebben geholpen in het lab en met de ratjes in de barakken, bedankt voor jullie tijd. Baki; prof. Pirenne, prof. Verwaest dank voor de kunde en wijze woorden! Mijn dank gaat verder uit naar het datacenter van de Leidse Universiteit en met name Elma Klein-Kranenbarg. Erg dankbaar ben ik voor de leerzame ervaringen op de afdeling medische statistiek van de Leidse Universiteit, bedankt Hein, voor het statistisch hard maken van de klinische vermoedens. Ik zou willen besluiten met een dankbetuiging aan de Curacaosche collega's 'snijdend en beschouwend' die met hun stille trots, interesse en steun de laatste loodjes des te lichter maakten. Dank aan Ashley Duits en Nouel van Leeuwen voor de laatste correcties, Elsje Statius-Muller voor de zo belangrijke definitieve spellingscorrecties (het is toch Amices!) en Joceline Cijntje pa e bon papiamentu.
Last but not least Kiki und Max...jullie kwamen pas later, edoch… dank voor zoveel meer!

Curriculum Vitae

De auteur van dit proefschrift is geboren te Groningen op 21 februari 1971 en reemigreerde met zijn ouders naar Curacao in 1975.
Hij heeft zijn middelbare school opleiding gevolgd aan het Peter Stuyvesant College te Curacao en behaalde zijn VWO diploma in 1989.
Zijn opleiding geneeskunde genoot hij te Leiden alwaar hij in oktober 1995 zijn artsexamen behaalde. In deze periode behaalde hij tevens zijn propadeuse Psychologie.

In het jaar 1996 was de auteur werkzaam als waarnemend huisarts en arts-assistent gynaecologie op Curacao. In 1997 werd begonnen met de vervolgopleiding heelkunde.
Het perifeer gedeelte van zijn opleiding heelkunde volgde hij van 1997 tot 2000 in het Sint Joseph Ziekenhuis te Veldhoven (opleider: dr.F.A.A.M. Croiset van Uchelen) alhier werd gestart met de eerste fasen van het promotieonderzoek onder begeleiding van Dr. R.M.H.Roumen, Dr F.A.A.M. Croiset van Uchelen en prof.dr.C.J.H. van de Velde. Het academisch gedeelte van zijn opleiding werd gevolgd aan de Universitaire Ziekenhuizen van de Katholieke Universiteit van Leuven (opleider: prof.dr.P.Broos) alwaar hij de specialisatie en tevens de laatse fasen van zijn promotieonderzoek in 2003 voltooide. Sinds oktober 2003 is hij werkzaam als algemeen chirurg in het Sint Elisabeth Hospitaal te Curacao.